Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CADTH Therapeutic Review

July 2010*

*An amendment was made in November 2010

Clinical and Economic Overview: Biological Response Modifier Agents for Adults with Rheumatoid Arthritis

Therapeutic Review
CLINICAL AND ECONOMIC OVERVIEW

Biological Response Modifier Agents for Adults with Rheumatoid Arthritis

July 2010*

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Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

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ABBREVIATIONS

ABAT	abatacept
ACR	American College of Rheumatology
ADAL	adalimumab
AE	adverse event
ANAK	anakinra
CEA	cost-effectiveness analysis
CERT	certolizumab pegol
CHF	congestive heart failure
CI	confidence interval
CrI	credible interval
CRP	C-reactive protein
CUA	cost-utility analysis
DMARD	disease-modifying antirheumatic drug
ESR	erythrocyte sedimentation rate
ETAN	etanercept
GOL	golimumab
HAQ-DI	Health Assessment Questionnaire – Disability Index
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IFX	infliximab
IL	interleukin
ITT	Intention to treat
IV	intravenous
MD	mean difference
MG	milligram
MI	myocardial infarction
MTC	mixed treatment comparison
mTSS	modified Total Sharp Score
MTX	methotrexate
NSAID	non-steroidal antiinflammatory drug
PM	product monograph
QALY	quality-adjusted life-year

RA	rheumatoid arthritis
RCT	randomized controlled trial
RP	radiographic progression
RTX	rituximab
SAE	serious adverse event
SC	subcutaneous
SJC	swollen joint count
STC	standard care
SULF	sulfasalazine
TJC	tender joint count
vdHS	van der Heijde Sharp score
WDAE	withdrawal due to adverse event

REVIEW IN BRIEF

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects approximately 1% of Canadians.[1] Goals of therapy for RA include slowing of disease progression and pain control. During the past decade, the approval of biologic drug therapies has led to an increase in therapeutic options for patients with RA. Biologic therapies available include tumor necrosis factor (TNF) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), interleukin-1 antagonists (anakinra), CD28 co-stimulatory modulators (abatacept), and CD20+ B-lymphocyte inhibitors (rituximab). In addition to efficacy and harms, factors that influence treatment selection include the frequency of dosing, route of administration, and the Health Canada indication.

Clinical Effectiveness

The key clinical research question for the therapeutic review was: What is the comparative efficacy and harms for the available biologic agents (especially TNF-alpha inhibitors) in the treatment of adults with RA? A total of 35 randomized controlled trials (RCTs) were included in this Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review.

Biologic Agents for Rheumatoid Arthritis in Methotrexate-Experienced Patients:

Of the 35 randomized controlled trials (RCTs) included in the CADTH systematic review, 25 were conducted in disease-modifying antirheumatic drugs (DMARD)-experienced patients. All trials were placebo-controlled. Thirteen RCTs were homogenous enough to allow pooling in a mixed treatment comparison (MTC) meta-analysis. These 13 RCTs were conducted in patients receiving concomitant methotrexate at mean or median doses of ≥ 15 mg/week and evaluated a biologic agent plus methotrexate compared with placebo plus methotrexate.

- Three trials evaluated adalimumab (ARMADA 2003, Keystone 2004, Kim 2007).
- Two trials evaluated etanercept (TEMPO 2004, Weinblatt 1999).
- One trial evaluated golimumab (GO-FORWARD 2009).
- Two trials evaluated infliximab (ATTRACT 2000, ATTEST 2008).
- Three trials evaluated abatacept (Kremer 2003, AIM 2006, and ATTEST 2008).
- Two trials evaluated anakinra (Cohen 2002, Cohen 2004).
- One trial evaluated rituximab (DANCER 2006).

The remaining trials were not included in the MTC meta-analysis for the following reasons: use of a biologic agent with no concomitant DMARD, background DMARD therapy may not have consistently included methotrexate, or low concomitant methotrexate doses were noted.

The trial evidence was limited by the following factors: unclear allocation concealment for some trials; blinding procedures inadequately described; high and differential proportions of withdrawals between groups in some of the trials; exclusion of patients with significant concomitant medical conditions, which may limit the generalizability of the studies; changes over time in treatment strategies, patient populations and inclusion and exclusion criteria of RCTs; small sample sizes leading to imprecise results; short trial durations; heterogeneity in trial designs and populations; low doses of concomitant DMARDs; and potential publication bias due to reliance on published literature. Of all the biologic agents, the quality of evidence was considered lowest for certolizumab pegol. In the certolizumab pegol trials, withdrawals were highest (up to 87% in the control group of one trial).

Efficacy

- Statistically significant differences between biologic agents could not be detected based on estimates of the American College of Rheumatology (ACR) 50 response obtained through the CADTH MTC meta-analyses (Table 1). Similar trends were observed for ACR 70, except that the proportion of patients achieving a response was lower for ACR 70 compared with ACR 50.

Table 1: MTC Results for ACR 50 Comparing Biologic Agents plus Methotrexate versus Placebo plus Methotrexate				
Intervention	**Number of Trials**	**Number of patients**	**MTC Estimate OR (95% CrI)**	**Direct Estimate OR (95% CI)**
TNF-alpha Inhibitors				
Adalimumab	3	664	7.03 (3.64 to 14.39)	6.72 (3.93 to 11.48)
Etanercept	2	548	3.83 (2.03 to 11.95)	5.62 (0.99 to 31.83)
Golimumab	1	222	3.79 (1.26 to 11.66)	3.76 (1.95 to 7.26)
Infliximab	2	449	2.6 (1.18 to 6.09)	2.52 (1.56 to 4.08)
T-Cell (CD28) Co-Stimulatory Modulators				
Abatacept	3	1,138	3.34 (1.84 to 6.25)	3.28 (2.44 to 4.41)
Il-1 Antagonists				
Anakinra	2	654	3.04 (1.4 to 8.15)	2.95 (1.37 to 6.36)
CD20+ B-lymphocyte Inhibitors				
Rituximab	1	244	3.41 (1.14 to 10.42)	3.35 (1.76 to 6.40)

ACR = American College of Rheumatology; CI = confidence interval; CrI = credible interval; MTC = mixed treatment comparison; OR = odds ratio; TNF = tumor necrosis factor.

- Meta-regression and sensitivity analyses were conducted to explore the impact of potentially influential sources of heterogeneity on ACR 50 (Table 2). Adjustments for disease duration did not alter MTC results considerably. Adjustments for control group response rate did not greatly change the estimates of efficacy for biologics from the primary MTC meta-analysis, with the exception of etanercept, that had its estimate, compared with control, changed from 3.83 (95% CrI 2.03 to 11.95) to 12.18 (95% CrI 3.98 to 56.36). Sensitivity analyses excluding studies with > 30% withdrawal in the control group and studies with data reported beyond 24 weeks were both associated with an increased likelihood of effectiveness for etanercept. Regarding adalimumab, exclusion of studies with a control group withdrawal rate of > 30% was associated with an increased likelihood of ACR 50 response relative to the primary MTC analysis. Estimates of all other biologic therapies were relatively unchanged in both sensitivity analyses.
- Absolute mean differences in Health Assessment Questionnaire-Disability Index (HAQ-DI) (range of scores: 0 to 3) were reported for seven of the 13 trials, representing data on adalimumab, etanercept, anakinra, and rituximab. The mean treatment difference was statistically significant in all seven of these trials, favouring the biologic group over the control group. The mean treatment difference was lowest in one of the trials evaluating anakinra (Δ = –0.11, 95% confidence interval [CI] –0.19 to –0.03). All other estimates ranged from –0.30 (95% CI –0.48 to –0.12) to –0.35 (95% CI –0.14 to –0.56). A difference of 0.22 is considered the minimal clinically important difference for the HAQ-DI. In studies where different methods of reporting HAQ-DI results were used, statistically significant differences were observed, with the exception of the second study evaluating anakinra.
- Data describing radiographic outcomes were available for five of the 13 trials, representing data on adalimumab, etanercept, infliximab, golimumab, and abatacept. Statistically significant differences favouring biologic over control were observed for all biologic agents except golimumab. In the golimumab trial, differences between golimumab and control could not be detected as there was no progression observed in the control group.
- There were three certolizumab pegol trials included in the CADTH systematic review but not in the MTC meta-analysis. While ACR 50, HAQ-DI, and radiographic progression results appeared to be within the range of efficacy estimates for other biologic agents, interpretation of these data is limited by high withdrawal rates.

Table 2: Summary of Sensitivity Analyses for ACR 50 in MTX-Experienced Patients — MTC Estimate of Effect versus Control								
Analysis	**Adalimumab**	**Abatacept**	**Infliximab**	**Anakinra**	**Etanercept**	**Rituximab**	**Golimumab**	**Certolizumab**
Primary MTC analysis	7.03 (3.64 to 14.39)	3.34 (1.84 to 6.25)	2.6 (1.18 to 6.09)	3.04 (1.4 to 8.15)	3.83 (2.03 to 11.95)	3.41 (1.14 to 10.42)	3.79 (1.26 to 11.66)	NA
Meta-regressions adjusting for:								
Control group response rate	5.09 (2.77 to 9.73)	3.41 (2.18 to 5.38)	2.6 (1.34 to 4.98)	1.81 (0.8 to 4.24)	12.18 (3.98 to 56.36)	2.87 (1.21 to 7.05)	3.35 (1.4 to 8.09)	NA
Baseline duration of disease (years)	6.02 (3.13 to 12.66)	3.47 (1.96 to 6.44)	2.68 (1.22 to 6.01)	2.79 (1.34 to 7.63)	4.44 (2.24 to 12.74)	2.93 (0.97 to 8.79)	5.86 (1.78 to 21.45)	NA
Sensitivity analyses with removal of studies with:								
> 30% withdrawal in the control group	15.04 (5.68 to 49.04)	3.09 (2.24 to 4.32)	2.37 (1.36 to 4.27)	2.82 (1.71 to 4.83)	26.14 (4.35 to 723.2)	NA	3.82 (2 to 7.53)	NA
Data reported beyond 24 weeks	6.86 (4.55 to 10.57)	3.31 (2.47 to 4.48)	2.37 (1.37 to 4.25)	2.82 (1.7 to 4.82)	26.45 (4.24 to 806.5)	3.41 (1.81 to 6.7)	3.82 (1.99 to 7.51)	NA

MTC = mixed treatment comparison; NA = not applicable.

Harms

- Serious harms were considered for all 35 trials included in the therapeutic review. Interpretation of the harms data was limited by the short duration of trials, different definitions of serious adverse events (SAEs), high and differential proportions of withdrawals between treatment groups with inadequate follow-up in those patients, and differences across trials in concomitant therapies.
- Mortality was less than 1% in all treatment groups. Deaths were most frequently due to infection, cardiovascular causes, or malignancy, with no clear differences between biologic and control groups.
- The proportions of patients experiencing an SAE were low and details on the types of SAEs were often lacking.
- For all the biologic agents, the proportion of patients reporting a serious infection or malignancy was low and there were no clear differences between biologic and control. Autoimmune diseases and congestive heart failure were inconsistently reported but appeared to be infrequent when information on these events was provided.

Biologic Agents for Rheumatoid Arthritis after Failure of a TNF-alpha Inhibitor

Three RCTs were included in the CADTH therapeutic review that evaluated biologic agents in patients failing an initial TNF-alpha inhibitor (Table 3). The trial evidence was limited by the following factors: lack of head-to-head trials, the small number of trials conducted in patients failing TNF-alpha inhibitors, a less severe patient population evaluated in the golimumab trial, and limitations of data from trial subgroups.

Table 3: RCTs Evaluating Biologic Agents for Rheumatoid Arthritis After Failure of a TNF-alpha Inhibitor			
Study	**ACR 50, OR (95% CI)**	**HAQ-DI***	**Radiographic Outcomes**
ATTAIN 2005 **ABAT versus PL** patients who had failed or were intolerant to IFX or ETAN (N = 393) 24 weeks	6.5 (2.5 to 16.8)	Patients with a ≥ 0.3-point improvement in HAQ-DI: ABAT versus PL: 47% versus 23% P <0.001	Not measured
REFLEX 2006 **RTX versus PL** patients who had failed or were intolerant to IFX, ETAN, or ADAL (N = 520) 54 weeks	7.0 (3.5 to 13.9)	Mean Difference: –0.30	Statistically significant improvement versus PL at 54 weeks
GO-AFTER 2009 **GOL versus PL** patients exposed to ≥ 1 dose of a TNF-alpha inhibitor (N = 461) 24 weeks	2.8 (1.3 to 6.1)	Mean Difference: –0.14	Not measured

ABAT = abatacept; ACR = American College of Rheumatology; ADAL = adalimumab; CI = confidence interval; ETAN = etanercept; GOL = golimumab; HAQ-DI = Health Assessment Questionnaire-Disability Index; IFX = infliximab; OR = odds ratio; PL = placebo; RCT = randomized controlled trial; RTX = rituximab; TNF = tumor necrosis factor.
* The minimal clinically important difference for HAQ-DI is considered 0.22 in patients with RA.

One additional RCT was identified that evaluated the effect of switching from etanercept to infliximab compared with remaining on etanercept in patients with an incomplete response on etanercept; no statistically significant differences in efficacy were observed at week 16 (N = 28). The quality of this trial was limited.

A summary of a National Institute for Health and Clinical Excellence (NICE) technology appraisal evaluating biologic agents (with the exception of golimumab, certolizumab pegol, and anakinra) after failure of a TNF-alpha inhibitor was also considered. In addition to RCTs, there were 31 observational studies included. According to the NICE technology appraisal, in patients failing a TNF-alpha inhibitor there is a lack of good quality evidence directly comparing the effectiveness of biologic agents and observational studies show a different TNF-alpha inhibitor may have some benefit, although the magnitude of the benefit is uncertain.

Cost and Cost-effectiveness

The costs of biologic agents included in the CADTH therapeutic review are provided in Table 4. At the lowest Health Canada recommended doses, the annual cost of biologic agents is relatively similar. Increased costs are associated with dose escalation of biologic agents.

Table 4: Cost Comparison					
Drug	**Price**	**Health Canada Recommended Doses**		**First Year Annual Cost ($)**	**Subsequent Year Annual Cost ($)**
Adalimumab	$707.22 per 40 mg syringe or pen*	40 mg sc every 2 weeks		18,388	18,388
Certolizumab pegol†	$664.51 per 200 mg syringe	400 mg sc at weeks 0, 2, and 4, then 200 mg every 2 weeks		19,271	17,277
Etanercept	$364.28 per 50 mg syringe or pen*	50 mg sc once weekly		18,943	18,943
	$196.98 per 25 mg vial	25 mg sc twice weekly		20,486	20,486
Golimumab†	$1,447.00 per 50 mg syringe or pen	50 mg sc once monthly		17,364	17,364
Infliximab‡	$978.00 per 100 mg vial	3 mg/kg IV infusions at weeks 0, 2, and 6 then **3 mg/kg** every **8 weeks**	70 kg patient	23,472	17,604
			100 kg patient	23,472	17,604
		DOSE ESCALATION **5 mg/kg** every **6 weeks** in subsequent years§	70 kg patient	NA	31,296
			100 kg patient	NA	39,120
Rituximab	$471.90 per 100 mg vial	1,000 mg IV at weeks 0 and 2 (first course). Can be repeated 5 to 6 months after previous treatment		9,438 (1 course) to 28,314 (3 courses)	9,438 (1 course) to 28,314 (3 courses)
Abatacept	$477.40 per 250 mg vial	500 mg every 4 weeks IV	< 60 kg patient	12,412	12,412
		750 mg every 4 weeks IV	60 kg to 100 kg patient	18,619	18,619
		1,000 mg every 4 weeks IV	> 100 kg patient	24,825	24,825
Anakinra	$50.99 per 100 mg syringe	100 mg sc daily		18,611	18,611

IM = intramuscular; IV = intravenous; NA = not applicable; sc = subcutaneous.
Note: Costs presented in this table do not include the costs of administration.
Source: Saskatchewan Drug Benefit (February 2010).
*Ontario Drug Benefit (February 2010).
†Provided by manufacturer.
‡ Costs assume wastage of partially used vials. Where wastage does not occur, the annual cost for a 70 kg patient would be $12,323 at a maintenance dose of 3 mg/kg every 8 weeks.
§Based on expert opinion, usual dose escalation of infliximab in clinical practice is approximately 5 mg/kg every 6 weeks and rarely reaches 10 mg/kg every 4 weeks. At a maintenance dose of 10 mg/kg every 4 weeks, annual costs would be $88,998 for a 70 kg patient and $127,140 for a 100 kg patient.

An economic evaluation was conducted to examine the relative cost-effectiveness of biologic agents (abatacept, adalimumab, etanercept, infliximab, and golimumab) in patients who had failed treatment with traditional DMARDs, such as methotrexate. The clinical inputs for the economic evaluation were based on the results of the MTC meta-analyses, in which clinically meaningful differences in ACR between the biologic agents were not observed (Table 1). Consequently, the Therapeutic Review Panel focused their deliberations on the cost of biologics rather than the cost-effectiveness estimates derived from the MTC meta-analyses and economic model. A summary of the economic evaluation has been provided in Appendix 6.

Additional Research

Additional research is summarized for:

- Switching Between Biologic Agents in Appendix 3
- Dose Escalation of TNF-alpha Inhibitors in Appendix 4
- Discontinuation of TNF-alpha Inhibitors in Patients Achieving Remission in Appendix 5
- Additional Harms Information in Appendix 5
- Efficacy of Biologic Agents Compared with Combination DMARD Therapy in Appendix 5

CLINICAL REVIEW SUMMARY

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects approximately 1% of Canadians; it is therefore estimated that approximately 300,000 Canadians have RA.[2,3] Disease onset is typically between the ages of 25 and 50, though it can occur at any age. Women are approximately three times more likely than men to develop RA.[2]

For patients with RA, treatment goals include decreasing disease activity, preventing irreversible joint damage, alleviating pain, and improving quality of life. These goals are achieved by a combination of interventions that include both non-pharmacologic interventions and drug therapy.

Pharmacologic treatment options for RA include non-steroidal anti-inflammatory drugs (NSAIDs); corticosteroids; disease-modifying antirheumatic drugs (DMARDs), such as methotrexate; and more recently, biologic agents, including TNF-alpha inhibitors (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol). Initial treatment for RA is NSAIDs, which reduce joint pain, stiffness, and swelling, but there is little evidence to demonstrate that they inhibit the destruction of joints. They are also associated with important gastrointestinal adverse events.

Methotrexate is the preferred DMARD. The maximum dose of 20 mg to 30 mg per week is to be achieved within a month, and meaningful control of disease is expected by three months. The majority of patients with active RA often receive an NSAID and at least one DMARD, with or without low-dose oral corticosteroids. If disease remission is observed, regular NSAID or systemic steroid treatment may no longer be needed. DMARDs control RA, but do not cure the disease.[2]

Better knowledge of the disease process in the recent decade has led to the development of biologic agents that directly interfere with pathologic pathways underlying the inflammatory processes in RA. To date, eight biologic agents (including five TNF-alpha inhibitors) have been approved for use in patients with RA in Canada. Following failure of methotrexate, the addition of a biologic agent is now seen as the next step in therapy. Which of the biologic agents to select as initial therapy is unclear, as to date there have been no head-to-head randomized controlled trials (RCTs) comparing different biologic agents. Other current questions in clinical practice include whether or not to initiate biologic therapy earlier, whether or not biologic agents can be temporarily stopped in patients achieving disease remission, how biologic agents compare with combination DMARD therapy, and best treatment strategies in non-responders or partial responders to initial therapy.

In addition to efficacy and harms, factors that influence treatment selection include the frequency of dosing, route of administration, and the Health Canada indication (Table 5).

Table 5: Drugs Included in the Therapeutic Review		
Generic Name (brand name; manufacturer)	**Health Canada Rheumatoid Arthritis Indications**	**Dose and Route of Administration**
TNF-alpha Inhibitors		
Adalimumab (Humira; Abbott)	For reducing signs and symptoms, inducing major clinical response and clinical remission, inhibiting progression of structural damage, and improving physical function in adult patients with moderately to severely active RA; can use alone or in combination with MTX or other DMARDs. When used as first-line treatment in recently diagnosed patients who have not been previously treated with MTX; should be given in combination with MTX; can give as monotherapy in case of intolerance to MTX or when MTX treatment is contraindicated.	40 mg **SC** every 2 weeks*
Certolizumab pegol (Cimzia; UCB)	In combination with MTX for reducing signs and symptoms, inducing major clinical response, and reducing the progression of joint damage as assessed by x-ray, in adult patients with moderately to severely active RA. It may be used alone for reducing signs and symptoms in adults with moderately to severely active RA who do not tolerate MTX.	400 mg **SC** weeks 0, 2, 4, then 200 mg every 2 weeks or 400 mg **SC** every 4 weeks
Etanercept (Enbrel; Amgen Wyeth Immunex)	For treatment of moderately to severely active RA in adults. Treatment is effective in reducing the signs and symptoms of RA, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function; can be initiated in combination with MTX in adult patients or used alone	25 mg **SC** bi-weekly or 50 mg **SC** weekly
Golimumab (Simponi; Schering-Plough Canada)	For reducing signs and symptoms in adult patients with moderately to severely active RA, in combination with MTX.	50 mg **SC** monthly
Infliximab (Remicade; Schering-Plough Canada)	For use in combination with MTX for reduction in signs and symptoms, inhibition of progression of structural damage, and improvement in physical function in adults with moderately to severely active RA.	3 mg/kg **IV** at weeks 0, 2, 6, then 3 mg/kg **IV** every 8 weeks†
T-cell (CD28) Co-Stimulatory Modulators		
Abatacept (Orencia; Bristol-Myers Squibb)	For reducing signs and symptoms, inducing clinical responses, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs or to TNF-alpha antagonists or to both; may be used as monotherapy or in combination with DMARD therapy; first-line treatment in recently diagnosed patients who have not been previously treated with MTX (should be given in combination with MTX).	Body weight: < 60 kg, 500 mg **IV**; 60 kg to 100 kg, 750 mg **IV**; > 100 kg, 1 gram **IV** given at weeks 0, 2, 4, and then every 4 weeks
IL-1 Antagonists		
Anakinra (Kineret; Amgen)	For reducing the signs and symptoms of active RA in patients $\geq$ 18 years of age; inhibiting the progression of structural damage by reducing erosions and cartilage; degradation in patients with active RA despite treatment with stable doses of MTX; can be used alone or in combination with other DMARDs, particularly MTX.	100 mg **SC** daily

Table 5: Drugs Included in the Therapeutic Review		
Generic Name (brand name; manufacturer)	**Health Canada Rheumatoid Arthritis Indications**	**Dose and Route of Administration**
CD20+ B-Lymphocyte Inhibitors		
Rituximab (Rituxan; Hoffmann-La Roche)	In combination with MTX, is indicated to reduce signs and symptoms in adult patients with moderately to severely active RA who have had an **inadequate response or intolerance to one or more TNF-alpha inhibitor** therapies.	1,000 mg **IV** on weeks 0 and 2.

DMARD = disease-modifying antirheumatic drug; IV = intravenous; MTX = methotrexate; SC = subcutaneous; RA = rheumatoid arthritis; TNF = tumor necrosis factor-alpha.
*When treated with adalimumab as monotherapy, some patients with RA, who experience a decrease in their response to adalimumab 40 mg every other week, may benefit from an increase in dose intensity to 40 mg adalimumab every week.
†For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg and/or treating as often as every 4 weeks.

Objective

The key clinical research question for the therapeutic review was: What is the comparative efficacy and harms for the available biologic agents (especially TNF-alpha inhibitors) in the treatment of adults with RA?

a) Trial Characteristics

A total of 35 placebo-controlled RCTs were included in this Canadian Agency for Drugs and Technologies in Health (CADTH) therapeutic review of biologic agents for RA, many of which were identified based on a recently published systematic review.[4,5] Only treatment groups evaluating Health Canada-approved doses of biologic agents and their control group were included in the analysis. A total of eight trials evaluated adalimumab,[6-13] six evaluated abatacept,[14-19] five evaluated infliximab,[18,20-23] three evaluated anakinra,[24-26] five evaluated etanercept,[27-31] three evaluated rituximab,[32-34] three evaluated golimumab,[35-37] and three evaluated certolizumab pegol.[38-40] No head-to-head trials evaluating biologic therapies for RA were identified, although there was one placebo-controlled trial, ATTEST 2008,[18] evaluating abatacept that also included an infliximab reference group and was counted as both an abatacept and an infliximab study.

All studies were double-blinded, but methods for allocation concealment, treatment scheme generation, and blinding were inconsistently reported across trials. Most trials were multicentred and conducted in multiple countries. There were two trials conducted only in Asian countries, both of which evaluated adalimumab.[10,11]

At trial enrolment, patients were considered to have early RA in six trials (mean disease duration < 2 years), established RA in 11 trials (mean disease duration between two to 10 years), late RA in 10 trials (mean disease duration > 10 years), and a mix of established and late RA in seven trials; one trial did not report disease duration at enrolment (see Tables 11 and 12 for a summary of trial characteristics). Disease stage is sometimes reflective of prior treatment experience, which varied across trials:

- There were 25 trials conducted in DMARD-experienced patients. Of these 25 trials, 17 were six months in duration, seven were one year in duration, and one was two years in duration.
- One trial was conducted in DMARD-naive patients and six trials were conducted in methotrexate-naive patients. Of these seven trials, one was six months in duration, five were one year in duration and one was two years in duration.

- Three trials were conducted in patients who were TNF-alpha inhibitor experienced. In two of these trials patients were required to have had an inadequate response to a TNF-alpha inhibitor; in the third trial patients were only required to have been exposed to a TNF-alpha inhibitor. All three trials were six months in duration.

In the 25 trials conducted in DMARD-experienced patients, there was considerable heterogeneity with respect to concomitant medications that were used during the trials:

- There were 17 trials in which patients received concomitant methotrexate.
- There were three trials in which patients received background DMARD therapy, which may or may not have included methotrexate.[6,17,26]
- There was one trial in which patients received concomitant sulfasalazine.[31]
- There were four trials where biologic monotherapy was evaluated with no concomitant DMARD therapy. In these trials, it was required that DMARDs, including methotrexate, be discontinued at study enrolment.[9,11,29,38]

In trials where patients received concomitant methotrexate, mean or median doses ranged from 7.5 mg/week to 19.6 mg/week across studies and treatment groups; methotrexate doses were generally balanced between treatment groups within a study, but differed across studies. The route of methotrexate administration was not commonly reported; however, when this information was provided, oral was the most common route of administration. Current clinical practice guidelines suggest that methotrexate doses should be initiated at 10 mg to 15 mg/week, with rapid escalation to 20 mg to 30 mg/week.[41] Considering that these are methotrexate-experienced patients with established disease, in some trials, methotrexate dosing may have been low. Currently, the maximum methotrexate dose approved by Health Canada is 20 mg/week.[42] Trials also varied with whether or not patients were inadequate responders to methotrexate and how this was defined.

In order to reduce the impact of clinical heterogeneity associated with the 35 trials included in the CADTH therapeutic review, three populations were specified for meta-analyses:

- Methotrexate-experienced patients receiving concomitant methotrexate at doses ≥ 15 mg/week (n = 13)
- Methotrexate-naive patients (n = 7)[12,13,19,21,28,35]
- Patients who are TNF-alpha inhibitor experienced (n = 3).[16,34,36]

The use of concomitant methotrexate at doses ≥ 15 mg/week in the methotrexate-experienced analysis population was established in order to further reduce heterogeneity within the DMARD-experienced population. This excluded four trials where low concomitant methotrexate doses were used.[23,32,39,40] The methotrexate cut-off dose of ≥ 15 mg/week was selected based on the factors discussed previously, including recent clinical practice guidelines, Health Canada-approved dosing, and clinical expert input.

Individual trial level results are presented in the CADTH therapeutic review for all trials, including those excluded from meta-analyses, in order to maximize available information on biologic agents and to permit comparisons with pooled meta-analysis results.

Baseline characteristics such as gender, age, mean number of tender and swollen joint counts, functional capacity (measured using the Health Assessment Questionnaire-Disability Index, [HAQ-DI]) varied across studies.

Trials included in the CADTH therapeutic review have been conducted over a 10-year period (1998 to 2009). During this time there have been changes in treatment strategies, RA patient populations, as well as changes to the inclusion and exclusion criteria of RCTs. The latter have changed as experience has been gained with biologic agents and contributed to identifying the types of patients who respond best to biologic therapy and those who should not receive biologic agents. Etanercept and infliximab were the first TNF-alpha inhibitors approved for use in RA in Canada (in approximately 1999 and 2000 respectively) while certolizumab pegol and golimumab are the most recently approved TNF-alpha inhibitors (2009 for both).

b) Patient Disposition

In most trials, data were analyzed using an intention-to-treat (ITT) approach or a modified ITT approach. There were a total of 11,706 patients available for efficacy analyses in the CADTH therapeutic review. There were also a few abatacept and rituximab trials where a large number of patients were enrolled but not randomized (Appendix 2).

The frequency of withdrawals in the control group varied considerably across studies (Figure A8). For example, proportions of withdrawals in the control group were as low as 0% (versus 10% for the infliximab group in Quinn 2005)[22] and as high as 87% (versus 29% for the certolizumab pegol group in RAPID2).[40] The variability in withdrawals may be associated with control group therapy (where low doses of concomitant therapy may have increased withdrawals due to lack of efficacy), disease stage, availability of other therapeutic options, and trial design. In the majority of trials, withdrawals were statistically significantly higher in the control group compared with the biologic group. In the individual trials, approaches such as non-responder imputation and last observation carried forward were frequently used to account for missing data, which limits confidence in the interpretation of results. Withdrawals reported at one year did not necessarily appear to be greater than withdrawals reported at six months, although, heterogeneity of trials and evaluation of different biologic agents makes cross-trial comparisons difficult; no one trial reported withdrawals at both six months and one year to permit within-trial comparisons.

There were nine RCTs that offered rescue therapy or an early escape option prior to 24 weeks if a pre-defined clinical response was not achieved (six adalimumab trials, two golimumab trials, and one rituximab trial). Twenty-four weeks was the earliest time point assessed in this CADTH therapeutic review.[6-9,11,12,34,36,37] Criteria for assessing patients' eligibility to receive rescue therapy included ACR 20 responses, swollen and tender joint counts, and investigator clinical judgment. Options for rescue therapy were variable but included switching concomitant DMARDs, adjusting doses of DMARDs, entering an open-label extension to receive active therapy, and dose escalation of the biologic agent. In five of these trials, which evaluated either adalimumab or golimumab, patients who met early escape or who were rescued may not have been counted as withdrawing due to lack of efficacy, resulting in an underestimation of withdrawal rates.[8,11,12,36,37] Given the differences in trial design and the potential misclassification of some withdrawals, estimates of patient withdrawals must be interpreted with caution and may be underestimated in some trials.

Table 6: Proportion of Patients Not Completing Randomized Treatment (Includes Both Patients Withdrawing and Those Meeting Early Escape)

		Biologic Group	Control Group
Adalimumab			
CHANGE 2008	Withdrawals	7/87 (8.0)	16/91 (17.6)
	Meeting early escape	44/87 (50.6)	16/91 (17.6)
MTX-experienced patients	**Total**	**51/87 (58.6)**	**32/91 (35.2)**
KEYSTONE 2004	Withdrawals	48/207 (23.1)	60/200 (30.0)
	Meeting early escape	NR	NR
MTX-experienced patients	**Total**	**Unknown**	**Unknown**
PREMIER 2006	Withdrawals	65/268 (24.2)	88/257 (34.2)
	Meeting early escape	29/268 (11)	52/257 (20.2)
MTX-naive patients	**Total**	**94/268 (35.1)**	**140/257 (54.5)**
Golimumab			
GO-FORWARD 2009	Withdrawals	17/89 (19.1)	49/133 (36.8)
	Meeting early escape	15/89 (16.9)	41/133 (30.8)
MTX-experienced patients	**Total**	**32/89 (36.0)**	**90/133 (67.7)**
GO-AFTER 2009	Withdrawals	12/153 (7.8)	31/155 (20.0)
	Meeting early escape	41/153 (26.8)	72/155 (46.4)
Patients who are TNF-alpha inhibitor experienced	**Total**	**53/153 (34.6)**	**103/155 (66.4)**

MTX = methotrexate; TNF = tumor necrosis factor.

c) Outcomes

Table 7 provides a summary of the outcomes reported by the studies included in the therapeutic review. Whenever possible and for consistency, efficacy outcomes reported in the CADTH therapeutic review were those measured at 24 weeks after randomization. In some trials, outcomes were only reported at one or two years.

ACR response: Thirty-one studies reported each of the ACR responses; ACR 20, ACR 50, and ACR 70. The ACR 20 is defined as a ≥ 20% improvement in the swollen joint count (66 joints), the tender joint count (68 joints), and at least three of the following assessments: patient assessment of pain, patient global assessment of disease activity, physician global assessment of disease activity, the HAQ-DI, and either the c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) levels. The ACR 50 and ACR 70 are defined analogously, but with corresponding 50% and 70% improvements.

HAQ-DI: Thirty-one studies reported HAQ-DI, although different methods of reporting results were used in different trials. Nineteen studies reported absolute mean treatment differences. The HAQ-DI is a self reported measure of functional status. The questionnaire assesses the difficulty patients incur in the performance of eight tasks: dressing, arising, eating, walking, maintaining hygiene, reaching, griping, and carrying out other common activities. Each component of the HAQ-DI can be answered using one of four choices as follows: 0 (no difficulty), 1 (some difficulty), 2 much difficulty, and 3 (unable to do). The mean of the category scores is subsequently calculated to provide an overall disability index that ranges between 0 and 3 (with 0 representing no disability and 3 representing severe disability). The minimum clinically important difference for HAQ-DI is 0.22.[43]

Radiographic progression: Fourteen studies measured changes in radiographic progression. This outcome was assessed using the modified Total Sharp Score (mTSS), also known as the van der Heijde (vdH) Sharp score, in trials of TNF-alpha inhibitors and using the Genant modified version of the Sharp score in abatacept and rituximab trials. The mTSS quantifies progression based on both articular erosion and joint space narrowing, and is based on x-rays taken of specific joints in the hands and feet before treatment begins and during the course of treatment. Scores range from zero to 440, with higher scores indicating greater disease severity. The van der Heijde version of the total Sharp score is the most commonly used outcome measure; while a range of clinically relevant differences have been suggested, an established minimal clinically important difference for this measure does not exist. A panel of experts in 2002 identified a value of 4.6 units based on consensus and on the premise that it appears to be equal to the smallest detectable difference and is the smallest estimate in literature. It has been suggested that a 10-point change is associated with an irreversible loss in function.[44] The minimal clinically important difference of the modified Genant has not been determined. In patients who withdrew from studies or for whom radiographic measures were unavailable at the end of the study, linear extrapolation was often used to handle missing data. The extent to which this practice may have biased study findings is unclear.

Withdrawals due to adverse events: There were 34 and 32 trials reporting data on withdrawals due to adverse events (WDAEs) and withdrawals for any reason, respectively. Details of the reasons for withdrawals and types of adverse events resulting in withdrawals were inconsistently reported across trials.

Serious adverse events: Harms such as mortality and serious adverse events (SAEs) were reported to some extent in all trials. There were 27 trials reporting the proportion of patients with SAEs that could be meta-analyzed. SAEs of interest in this CADTH therapeutic review included hospitalizations, serious infections, malignancies, lupus and other autoimmune disorders, and congestive heart failure). Definitions of SAEs and types of SAEs varied across trials and were inconsistently reported across trials. No trial reported hospitalization as an outcome, although patients who were hospitalized were sometimes referred to when SAEs were described.

Table 7: Reporting of Outcomes in RCTs Included in the CADTH Therapeutic Review										
Drug	**Study**	**Meta-Analysis Population**	**ACR 20**	**ACR 50**	**ACR 70**	**WDAE**	**WD**	**HAQ-DI***	**RP**	**SAE**
TNF-alpha Inhibitors										
Adalimumab	ARMADA 2003[7]	MTX-experienced	X	X	X	X		X		
	Keystone et al. 2004[8]	MTX-experienced	X	X	X	X	X	X	X	
	Kim et al. 2007[10]	MTX-experienced	X	X	X	X	X	X		X
	STAR 2003[6]	—	X	X	X	X	X			X
	Van de Putte et al. 2004[9]	—	X	X	X	X	X	X		X
	CHANGE 2008[11]	—	X	X	X	X	X	X		X
	PREMIER 2006[12]	MTX-naive	X	X	X	X	X	X	X	
	Bejarano et al. 2008[13]	MTX-naive	X	X	X	X	X	X		
Certolizumab pegol	RAPID1 2009[39]	—	X	X	X	X	X	X	X	X
	RAPID2 2009[40]	—	X	X	X	X	X	X	X	X
	FAST4WARD 2009[38]	—	X	X	X	X	X	X		X
Etanercept	TEMPO[27]	MTX-experienced	X	X	X	X	X	X	X	X
	Weinblatt et al. 1999[30]	MTX-experienced	X	X	X	X	X	X		
	Moreland et al. 1999[29]	—	X	X	X	X	X	X		
	Combe et al. 2009[31]	—				X	X	X		X
	COMET 2008[28]	MTX-naive	X	X	X	X	X	X	X	X
Golimumab	GO-FORWARD 2009[37]	MTX-experienced	X	X	X	X	X	X	X	X
	GO-BEFORE 2009[35]	MTX-Naive	X	X	X	X	X	X	X	X
	GO-AFTER 2009[36]	TNFi-experienced	X	X	X	X	X	X		X
Infliximab	ATTRACT 2000[20]	MTX-experienced	X	X	X	X	X	X	X	X
	ATTEST-a 2008[18]	MTX-experienced	X	X	X	X	X	X		X
	Maini et al. 1998[23]	—								
	ASPIRE 2004[21]	MTX-naive	X	X	X	X	X	X	X	X
	Quinn et al. 2005[22]	MTX-naive	X	X	X	X	X	X	X	

Table 7: Reporting of Outcomes in RCTs Included in the CADTH Therapeutic Review										
Drug	**Study**	**Meta-Analysis Population**	**ACR 20**	**ACR 50**	**ACR 70**	**WDAE**	**WD**	**HAQ-DI***	**RP**	**SAE**
T-CELL (CD28) Co-Stimulatory Modulators										
Abatacept	Kremer et al. 2003[14]	MTX-experienced	X	X	X	X	X	X		X
	AIM 2006[15]	MTX-experienced	X	X	X	X	X	X	X	X
	ATTEST-b 2008[18]	MTX-experienced	X	X	X	X	X	X		X
	Weinblatt et al. 2006[17]	—				X	X	X		X
	AGREE 2009[19]	MTX-naive		X	X	X	X	X	X	X
	ATTAIN 2005[16]	TNFi-experienced	X	X	X	X	X	X		X
IL-1 Antagonists										
Anakinra	Cohen et al. 2002[24]	MTX-experienced	X	X	X	X	X	X		
	Cohen et al. 2004[25]	MTX-experienced	X	X	X	X		X		X
	Fleischmann et al. 2003[26]	—				X	X			X
CD20 + B-lymphocyte Inhibitors										
Rituximab	DANCER 2006[33]	MTX-experienced	X	X	X	X	X	X		X
	Edwards et al. 2004[32]	—	X	X	X	X	X			X
	REFLEX 2006[34]	TNFi-experienced	X	X	X	X	X	X	X	X
Total Number of Studies			31	31	31	34	32	17	14	27

ACR = American College of Rheumatology; CADTH = Canadian Agency for Drugs and Technologies in Health; HAQ-DI = Health Assessment Questionnaire-Disability Index; MTX =methotrexate; RCT = randomized controlled trial; RP =radiographic progression ; SAE = serious adverse event; TNFi = tumor necrosis factor-alpha inhibitor; WD = withdrawals; WDAE = withdrawal due to adverse event.

*HAQ-DI reported as the absolute mean change from baseline with standard error. Trials reporting per cent changes from baseline in HAQ-DI or the proportion of patients achieving a minimal clinically important difference are not included in this accounting.

Key Results and Interpretation

Outcomes that were considered in the CADTH therapeutic review included ACR 20, ACR 50, ACR 70, change in HAQ-DI, radiographic progression, mortality, SAEs (including hospitalizations, malignancies, serious infections, autoimmune disorders, and congestive heart failure), WDAEs, and all-cause withdrawals.

- Both direct and indirect estimates of effect were considered:
  - Meta-analyses pooling direct estimates from placebo-controlled trials were conducted by CADTH for ACR responses, SAEs, WDAEs, and all-cause withdrawals. Direct estimates from individual trials were also considered for all outcomes.
  - In the absence of head-to-head trials evaluating biologic agents, the comparative efficacy and harms of biologic agents were explored by CADTH through indirect mixed treatment comparison (MTC) meta-analyses of the following outcomes: ACR 20, ACR 50, ACR 70, and WDAEs.
- Details as to how prior treatment experience (e.g. MTX-experienced) was categorized can be found in Appendix 1, Table 1 (pages 27-29).
- In the methotrexate-experienced analysis, subgroup analyses and meta-regressions were conducted for factors that could introduce variability and bias into results, such as control group response rates, high proportions of withdrawals, disease duration, and trial duration. Because of the small number of trials included in the methotrexate-naive and TNF–alpha inhibitor-experienced analyses, meta-regressions and sensitivity analyses were not conducted for these populations and heterogeneity was explored at an individual trial level.

Efficacy

a) ACR 50 Response (Figure A4)

Methotrexate-experienced patients: When considering only trials conducted in methotrexate-experienced patients receiving concomitant methotrexate at doses ≥ 15 mg/week (n = 13), data were available for all biologic agents with the exception of certolizumab pegol. In all 13 trials, comparisons were made between a biologic agent plus methotrexate and placebo plus methotrexate. In the CADTH meta-analyses of direct estimates based on ACR 50 response, odds ratios (ORs) comparing each biologic agent with control ranged from 2.52 (95% confidence interval [CI] 1.56 to 4.08) for infliximab (based on two trials) to 6.72 (95% CI 3.93 to 11.48) for adalimumab (based on three trials). Based on these CADTH pooled meta-analyses, all biologic agents were statistically significantly better than control with the exception of etanercept (OR = 5.62, 95% CI 0.99 to 31.83, based on two trials). However, in the two etanercept trials that were pooled, individual trial estimates were both statistically significantly better than control (OR = 2.99, 95% CI 2.04 to 4.39 for TEMPO 2004 and OR = 18.53, 95% CI 2.36 to 145.51 for Weinblatt 1999).

- Response rates in the control group were as low as 3% (versus 39% for etanercept in Weinblatt 1999) and as high as 43% (versus 69% for etanercept in TEMPO 2004).
- In ATTEST 2008, which was a placebo-controlled trial evaluating abatacept that also included an infliximab reference group, ORs for ACR 50 responses were similar for each biologic agent compared with control at six months (OR = 2.71, 95% CI 1.54 to 4.77 for abatacept and OR = 2.35, 95% CI 1.33 to 4.12 for infliximab).[18]
- Although none of the certolizumab pegol trials conducted in methotrexate-experienced patients were included in this CADTH meta-analysis (two because of low concomitant methotrexate doses and one because it evaluated certolizumab pegol monotherapy), ORs from individual certolizumab pegol trials were within the range of ACR 50 OR estimates observed in other individual trials included in the meta-analysis. ORs may be higher than expected in trials with low control group response rates as was observed with certolizumab pegol trials and in a few trials evaluating other biologic agents (e.g., Weinblatt 1999 evaluating infliximab, Moreland 1999 evaluating etanercept). Unlike with certolizumab pegol, these other trials do not represent the entire body of evidence for the biologic agent. There are additional concerns regarding the high proportion of withdrawals observed in certolizumab pegol trials (up to 87% in the control group of RAPID2) and interpretation of these results.
- Of the 13 trials included in the methotrexate-experienced analysis population, six had withdrawals greater than or equal to 30% in the control group, which may decrease confidence in the

interpretation of results from these trials (Kremer 2003 evaluating abatacept, Keystone 2004 and Kim 2007 evaluating adalimumab, TEMPO 2004 evaluating etanercept, ATTRACT 2000 evaluating infliximab and DANCER 2006 evaluating rituximab). In GO-FORWARD 2009 evaluating golimumab and in ARMADA 2003 evaluating adalimumab, patients who met early escape criteria and began receiving rescue therapy part way through the trial were not counted as withdrawals due to lack of efficacy; therefore, withdrawals may be underestimated in these two trials.

- **Methotrexate-naive patients:** When only trials conducted in methotrexate-naive patients (n = 7) were considered, there were two evaluating adalimumab, two evaluating infliximab, and one each for golimumab, etanercept, and abatacept. There is no RCT evidence for the use of certolizumab pegol, anakinra, or rituximab in methotrexate-naive patients. ACR 50 response rates in the control group ranged from 29% (versus 40% for golimumab in GO-BEFORE 2009) to 49% (versus 71% for etanercept in COMET 2008). In five of the seven trials, the biologic agent was statistically significantly better than the control, one trial for each biologic agent evaluated. Direct estimates from meta-analyses of adalimumab (two trials) and infliximab (two trials) were OR = 1.81 (95% CI 1.33 to 2.45) and OR = 1.85 (95% CI 1.34 to 2.56) respectively, based on ACR 50 response. ORs from the individual trials were of a similar magnitude, ranging from 1.62 (95% CI 1.02 to 2.58) for golimumab to 2.51 (95% CI 1.74 to 3.63) for etanercept when compared with control. Withdrawals were greater than or equal to 30% in the control group for three of the seven trials (COMET 2008 evaluating etanercept; PREMIER 2006 and Bejarano 2008 evaluating adalimumab)[12,13,27] and may have been underestimated in GO-BEFORE 2009, which did not count patients entering early escape as withdrawals due to lack of efficacy.[35]

- **Patients who are TNF-alpha inhibitor experienced**: When only trials conducted in patients with TNF-alpha inhibitor experience (n = 3) were considered, there were data available for golimumab, rituximab, and abatacept. ACR 50 response rates in the control group ranged from 4% (versus 20% for abatacept in ATTAIN 2005) to 7% (versus 16% for golimumab in GO-AFTER 2009); the low control group response rates compared with the higher response rates more frequently observed in methotrexate-experienced and methotrexate-naive populations likely reflect a more difficult to treat population. In these three trials, the magnitude of the point estimates for ACR 50 responses were similar in the abatacept (OR = 6.53, 95% CI 2.54 to 16.77) and rituximab (OR = 7.01, 95% CI 3.53 to 13.91) placebo-controlled trials, but lower for the golimumab placebo-controlled trial (OR = 2.83, 95% CI 1.31 to 6.12), although consideration should be given to the overlap in CIs. Withdrawals were greater than 30% in the control group of REFLEX 2006, evaluating rituximab, which may limit confidence in the interpretation of these results.

When the CADTH MTC meta-analyses were conducted on ACR 50 response, compared with control, the magnitude of the ORs obtained through indirect MTC estimates were similar to ORs obtained through meta-analyses of direct estimates. When biologic agents were compared with each other based on indirect MTC estimates, statistically significant differences between biologic agents could not be detected for any of the three analysis populations considered (methotrexate-naive, TNF-alpha inhibitor experienced, or methotrexate-experienced [Table A10]).

Meta-regression and sensitivity analyses were conducted to explore the impact of potentially influential sources of heterogeneity on ACR 50 results. Meta-regression analysis conducted in the methotrexate-experienced population on baseline disease duration did not alter MTC conclusions considerably. Adjustment for control group response rate did not greatly change estimates of efficacy for biologics from the primary MTC meta-analysis, with the exception of etanercept, which had its estimate, compared with control, changed from 3.83 (95% CrI 2.03 to 11.95) to 12.18 (95% CrI 3.98 to 56.36). This change was related to characteristics of the TEMPO trial, in which the control group demonstrated an increased rate of ACR 50 response (43%) relative to the control groups in other included trials (range 3.3% to 20%), likely due to the inclusion of a proportion of patients who were methotrexate-naive in addition to those who were methotrexate-experienced. Sensitivity analyses excluding studies with > 30% withdrawal in the control group and studies with data reported beyond 24 weeks were also associated with increased likelihood of efficacy for etanercept because both criteria eliminated the TEMPO study from the analysis, leaving only one study of etanercept (n = 89) with a control group ACR 50 response rate of 1 of 30

(3.3%). Regarding adalimumab, exclusion of studies with a control group withdrawal rate of > 30% was associated with an increased likelihood of ACR 50 response relative to the primary MTC analysis. This exclusion criteria eliminated two of three included adalimumab trials, leaving one study (n = 129) for analysis with a control group response rate of 5 of 62 (8.1%). Estimates of all other biologic therapies were relatively unchanged in both sensitivity analyses.

Similar trends were observed for results of CADTH direct and indirect analyses based on ACR 20 and ACR 70, except that the proportion of patients achieving a response was highest for ACR 20 and lowest for ACR 70 when compared with ACR 50 (Figures 4 and 6 for more details on ACR 20 and ACR 70).

b) HAQ-DI (Table A8)

The HAQ-DI is a measure of functional status and, while data on HAQ-DI were available from 31 trials, different methods of reporting results were used in different trials and CADTH meta-analyses were not conducted. The most frequent method of reporting HAQ-DI was the absolute mean treatment difference (n = 19); other methods included the median treatment difference, the mean or median per cent change from baseline, and the proportion of patients achieving an improvement in HAQ-DI with different cut-offs used in trials to establish improvement in functional status.[43,45] The mean or median baseline HAQ-DI in the 31 trials ranged from 1.3 to 2.0, where scores of 1 to 2 represent some and much difficulty performing selected tasks on a scale ranging from zero to three. A HAQ-DI score of 0.5 has been observed in healthy adults and in published literature, 0.22 has been suggested to be a minimal clinically important difference in patients with RA.[43,45]

- **Methotrexate-experienced patients:** Of the 13 trials included in the methotrexate-experienced analysis population, eight reported mean treatment differences. Of these trials, six reported statistically significant mean treatment differences with individual trial estimates in the range of –0.30 to –0.35. The two exceptions to this were the two trials evaluating anakinra. Cohen 2002, which evaluated anakinra with results that were not statistically significant and Cohen 2004, which evaluated anakinra and reported a statistically significant mean treatment difference of –0.11, which is not considered a clinically relevant difference. When reported, similar mean treatment differences were observed among the 12 trials not included in the meta-analysis population. Estimates were greatest for certolizumab pegol in FAST4WARD 2009 (mean difference = –0.49, $P < 0.001$), although these results should be interpreted with caution given the high proportion of withdrawals in this trial and last observation carried forward methods of imputing missing HAQ-DI data.
- **Methotrexate-naive patients:** Of the seven trials conducted in methotrexate-naive patients, statistically significant improvements in HAQ-DI were not observed in two trials: PREMIER 2006, one of the two adalimumab trials and GO-BEFORE 2009, which evaluated golimumab. For the three trials reporting statistically significant mean differences favouring the biologic agent over control, clinically relevant differences were observed for adalimumab (–0.3), but not for infliximab or abatacept (–0.12 and –0.2 respectively).
- **Patients who are TNF-alpha inhibitor experienced**: All three trials in TNF–alpha inhibitor-experienced patients reported statistically significant improvements in HAQ-DI favouring the biologic agent, but improvements were only considered clinically relevant for abatacept and rituximab, not for golimumab. A mean treatment difference of –0.30 was observed for rituximab in REFLEX 2006 and a mean treatment difference of –0.14 was observed for golimumab in GO-AFTER 2009. In ATTAIN 2005, significantly more abatacept patients reported a 0.3-point improvement in HAQ-DI.

c) Radiographic progression (Table A9)

Controlled data on the inhibition of radiographic disease progression were reported in 14 studies, providing information on all biologic agents except anakinra. Because of the small number of trials reporting radiographic progression and the variety of scales used in its assessment, meta-analyses were not conducted. Statistically significant differences favouring biologic agent over control were reported in all trials, with the exception of GO-FORWARD 2009 evaluating golimumab in methotrexate-experienced patients and Quinn 2005 evaluating infliximab in methotrexate-naive patients. Although all of the biologic agents, with the exception of anakinra and golimumab, have demonstrated statistically significantly less radiographic progression than control, the clinical relevance of these findings is uncertain. The minimal

clinically important difference for the modified Genant scale is unknown, there is a range of minimal clinically important differences reported in the literature for the vdH mTSS scale, and there are limited data demonstrating the prevention of long-term joint damage for either scale.[46] Consideration of longer-term data on radiographic progression from uncontrolled trials was outside the scope of this CADTH therapeutic review.

- **Methotrexate-experienced patients:** Radiographic data were available from five of the 13 trials included in the analysis population, representing data on adalimumab, etanercept, infliximab, golimumab, and abatacept. Statistically significant differences favouring biologic agent over control were observed in all trials except GO-FORWARD 2009, which evaluated golimumab. In GO-FORWARD 2009, the control group did not progress, preventing detection of a treatment difference. All trials measured progression using the vdH Sharp score, with the exception of AIM 2006 evaluating abatacept, which used the Genant modified Sharp score. Although certolizumab pegol trials were not included in this methotrexate-experienced analysis population, statistically significant differences favouring certolizumab pegol compared with control were observed with respect to inhibiting radiographic progression in RAPID1 2009 at 52 weeks and RAPID2 2009 at 24 weeks.[39,40]

- **Methotrexate-naive patients:** Radiographic data were available from six of the seven trials conducted in methotrexate-naive patients, representing data on all of the biologic agents evaluated in this population. Statistically significant differences were observed for all six trials with the exception of Quinn 2005, which evaluated infliximab. This was a small study and was not powered to detect differences.

- **Patients who are TNF-alpha inhibitor experienced:** Of the three biologic agents evaluated in patients who are TNF-alpha inhibitor experienced, only rituximab provided data on radiographic progression. In REFLEX 2006, statistically significant differences were observed at 56 weeks.

Harms

The relatively short duration of most trials limits interpretation of harms associated with biologic therapy in a chronic disease such as RA. In order to maximize information on serious harms, mortality and SAEs were considered for all 35 trials included in the therapeutic review and were not stratified by prior treatment experience (i.e., methotrexate-experienced, methotrexate-naive, TNF-alpha inhibitor experienced).

a) Mortality

When considering Health Canada-approved doses of biologic agents, mortality was less than 2% in all biologic and control groups; estimates ranged from 0% for rituximab to approximately 1.6% for adalimumab patients. Most deaths were due to infection, cardiovascular causes, or cancer. No notable findings were observed when deaths were considered in patients receiving higher than approved doses of biologic agents.

b) SAEs (Figure A6)

The proportion of patients experiencing an SAE was similar between treatment groups, but differed across trials. A CADTH meta-analysis pooling direct estimates of SAEs from trials found no statistically significant differences between each biologic agent and control with the exception of certolizumab pegol. Interpretation of SAE results is limited by factors such as differences in the definitions of SAEs across included trials; the high proportions of withdrawals in some studies; differences in concomitant DMARD therapies, both within trials and across trials; and variations in trial durations and the lack of exposure-adjusted estimates of harms. For example, the higher risk of SAEs associated with certolizumab pegol compared with control may be influenced by the high proportion of withdrawals in the control group of certolizumab pegol trials. Published exposure-adjusted estimates for certolizumab pegol trials have demonstrated that SAEs are similar between certolizumab pegol and control groups. Duration of trials was considered when interpreting harms, but it did not appear that the proportion of patients with SAEs was always greater in trials of one to two years compared with 24-week trials. Hospitalizations were rarely

reported as an outcome in the published literature. Although in some trials SAEs were partially defined as those events requiring hospitalization, numbers and details of events requiring hospitalization were poorly reported.

c) Types of SAEs

Malignancies were observed with all biologic agents, with the exception of rituximab, but with no apparent differences between biologic and control groups. Similarly, serious infections were observed with all biologic agents with no differences detected between biologic and control groups. Types of serious infections were not reported for anakinra, but cases of tuberculosis were observed for all other biologic agents, with the exception of rituximab. There were only a few reports of autoimmune disorders or congestive heart failure across trials. RCTs are limited in their ability to detect SAEs because of the rarity of events and the short duration of trials; therefore, a review of regulatory warnings issued for biologic agents for RA was also conducted by CADTH (Summary of Additional Harms Information, Appendix 5). Most warnings were similar across biologics or were drug class warnings related to serious infections and malignancies, with the exception of a warning for rituximab that was related to the development of progressive multifocal leukoencephalopathy (PML). Longer-term harms from uncontrolled extension studies were outside the scope of this CADTH therapeutic review. Some long-term data and meta-analyses that were summarized as supplemental material did not identify any additional harms signals or differences between biologic agents that have not been previously noted (Summary of Additional Harms Information, Appendix 5).

d) WDAEs (Figure A7)

In individual trials, WDAEs were low. For example, the proportions of WDAEs in the control group were as low as 0% (versus 3% for rituximab in DANCER 2006) and as high as 14% (versus 10% for etanercept in TEMPO 2004). Proportions did not appear greater in trials of longer duration. Only two trials had statistically significant differences between biologic and control groups: Keystone 2004 conducted in methotrexate-experienced patients and evaluating adalimumab at one year (OR = 2.07, 95% CI 1.03 to 4.15) and ASPIRE 2004 conducted in methotrexate-naive patients, evaluating infliximab at one year (OR = 3.17, 95% CI 1.50 to 6.73). Statistically significant differences between biologic agents and control were not observed in direct meta-analyses, with the exception of infliximab, or among biologic agents in MTC meta-analyses for any of the analysis populations considered. Overall, the lack of statistically significant findings may be a result of low event rates in the trials and wide CIs and credible intervals, which may diminish confidence in these estimates. Types of adverse events leading to withdrawal from the studies were not well reported in the published literature.

Limitations and Sources of Bias

Summaries of critical appraisal, quality assessment, and potential sources of bias for the individual studies are detailed in Appendix 2. Key limitations are summarized below.

- While most studies were described as being double blinded, details used to achieve blinding were inconsistently reported and there was potential for unblinding in instances where injection site reactions occurred. Details regarding allocation concealment were also inconsistently reported.
- Withdrawal rates were high in a number of studies and withdrawals were not balanced across treatment groups, with higher withdrawals in the control groups compared with biologic groups. In most included studies, the use of analytic techniques, such as non-responder imputation, last observation carried forward, and linear extrapolation to deal with missing data may be problematic as these techniques have the potential to bias study findings, although the extent and direction of this bias is not always clear.
- Concomitant methotrexate doses used in trials did not always meet currently recommended practices. The Health Canada-approved product monograph for methotrexate recommends doses up to 20 mg/week for the treatment of RA. Current practice guidelines suggest methotrexate be initiated at doses of 10 mg to 15 mg/week with escalation by 5 mg every week up to 20 mg to 30 mg/week, depending on clinical response and tolerability.[41] Mean or median methotrexate doses among included trials ranged from approximately 7.5 mg/week to 20 mg/week, with most being

approximately 15 mg/week. Many trials were conducted prior to these guidelines being introduced or included patients from other countries where methotrexate use may differ and may not adequately reflect current clinical practice; thereby possibly resulting in lower than expected clinical response rates. Trials with low concomitant methotrexate dosing may still provide some relevant information on patients unable to tolerate higher doses of methotrexate, although this was not an inclusion criterion of any of the trials.

- External validity in terms of the patient populations studied may be limited. Most studies excluded patients with other significant medical conditions (e.g., infections and other uncontrolled disease). Furthermore, patients enrolled in initial trials evaluating biologic agents may differ from those enrolled in more recent trials due to changes in clinical trial screening practices, trial inclusion and exclusion criteria, and treatment strategies over time.
- Sample sizes ranged from 20 patients to approximately 1,400 patients. The small sample sizes in some trials resulted in large CIs and imprecise estimates of effect, which may have contributed to the inability to detect differences among biologic agents.
- The duration of trials was either six months or a year in most trials, which is inadequate for assessment of serious harms that have been associated with biologic agents, such as malignancies and serious infections. Further, the length of controlled trials is inadequate to evaluate whether or not there is a survival advantage associated with the use of biologic agents in patients with RA. While data addressing these issues may be available in long-term uncontrolled extension studies or observational studies, interpretation of findings from these types of study designs is limited and was outside the scope of this CADTH therapeutic review.
- Reporting of outcomes varied across trials. Therefore, analysis of outcomes such as HAQ-DI, radiographic progression scores, and types of SAEs are based on less available evidence.
- The considerable heterogeneity of trial designs and patient populations evaluated makes interpretation of pooled results challenging. While conducting meta-analyses in three different patient populations reduced clinical heterogeneity in the patient populations, pooled analyses were based on fewer available trials.
- Because only published literature were included in this CADTH therapeutic review, there is the possibility of publication bias.

Discussion

This CADTH therapeutic review included a total of 35 RCTs that evaluated the efficacy and harms of biologic agents compared with control. Given the paucity of head-to-head trials comparing biologic agents, CADTH MTC meta-analyses were pursued to explore the relative efficacy and harms of biologic agents. Co-medication with methotrexate, patients' prior exposure to DMARDs and biologic therapies, and other factors including gender, age, and tender and swollen joint counts varied among the included RCTs, resulting in clinical and methodological heterogeneity across the included trials. Approaches taken to handling heterogeneity included conducting analyses in separate patient populations based on prior treatment experience, focusing the analysis of DMARD-experienced patients on those receiving concomitant methotrexate at doses ≥ 15 mg/week, and conducting selected meta-regressions and subgroup analyses.

Heterogeneity

Baseline characteristics, such as mean number of tender and swollen joint counts, functional capacity (measured using the HAQ-DI), and treatment duration were variable across studies. Some of this variation may be a result of changing inclusion and exclusion criteria of RCTs over time, as experience has been gained with biologic agents and has contributed to identifying the types of patients who respond best to them, as well as those who should not receive biologic agents. Patient characteristics in trials evaluating the first-approved biologic agents, etanercept and infliximab, might be more similar to each other than to certolizumab pegol and golimumab, the most recently approved biologic agents. For example, tender and swollen joint counts appear higher in infliximab and etanercept trials compared with golimumab and certolizumab pegol trials. Also, inclusion and exclusion criteria for golimumab trials appeared to be less stringent than earlier trials, enrolling patients with less severe disease compared with trials of other TNF-alpha inhibitors (e.g., based on requirements for tender and swollen joint counts).

When assessing harms, the change in trial inclusion criteria and study populations over time should also be considered as these changes may favour newer agents evaluated in trials conducted in a narrower population that is at less risk for serious harms.

Other biases to be considered that may also contribute to heterogeneity of trials include the high and differential proportion of withdrawals between the treatment groups, high control group response rates, and low concomitant methotrexate doses. Some RA trials have early escape designs that limit the number of withdrawals reported, which may contribute to the heterogeneity of reported withdrawal rates. In addition, methods used to handle missing data from early escape patients included potentially problematic approaches, such as last observation carried forward, linear extrapolation, and non-responder imputation. In many of the included studies where patients withdrew their participation or there were missing data for clinical outcomes due to missed visits or losses to follow-up, study investigators employed methods of non-responder imputation, last observation carried forward, and/or linear extrapolation to complete missing data for these patients. There are biases associated with the use of these techniques and the extent to which they bias and misrepresent findings is unclear. Recent research has drawn attention to the potential biases associated with the use of a last observation carried forward approach to analysis.[47,48] The use of this technique is prominent in several areas of clinical research and may be associated with sizable misrepresentations of treatment efficacy. Also, provision of low concomitant methotrexate doses may sometimes be associated with low responses and high withdrawal rates in the control groups, thereby generating misleading estimates of effectiveness of therapy. As most studies reported only mean doses of concomitant methotrexate received, it was sometimes unclear what proportion of patients may have received less than the recommended doses.

ACR Response

This CADTH therapeutic review focused on results obtained for ACR 50 response, as was selected in the Cochrane overview of biologics for RA. ACR 20, often the primary end point in clinical trials, is sometimes viewed as a low threshold to be achieved, and attainment of ACR 50 may represent a more clinically meaningful improvement in disease.[49] While ACR 70 is a higher threshold and is considered by some to indicate disease remission,[50] the low proportions of patients achieving ACR 70 in RCTs leads to variability and reduced confidence in these estimates, particularly when exploring the relative efficacy of therapies. While ACR response is commonly used as an efficacy measure in RA trials, there is some concern that it relies on subjective components, such as tender and swollen joint counts and patient and physician global assessments. As well, it does not provide an assessment of absolute changes in disease activity, but relies on relative changes, based on a patient's baseline disease status.[43] Therefore, when possible, it is important to consider other clinical outcomes when assessing the relative efficacy of biologic therapies in RA.

Radiographic Progression

Inhibiting radiographic progression is an important outcome in RA, but changes in patients take time to occur, and thus six-month controlled trials may be insufficient to demonstrate the benefits of therapy. Baseline levels of disease are also important to consider when interpreting radiographic progression results. For example, in the GO-FORWARD trial in methotrexate-experienced patients, radiographic progression was observed in neither the control group nor the golimumab group, preventing any detection of a treatment difference between groups. This may be related to enrolment of a less severe patient population compared with trials of other TNF-alpha inhibitors in methotrexate-experienced patients. Use of linear extrapolation also makes findings difficult to interpret as radiographic changes may not necessarily be linear, and there are often differential withdrawals between treatment groups, which further complicate the interpretation of results. To date, golimumab is the only TNF-alpha inhibitor that does not have a Health Canada-approved indication for radiographic progression, which may be due to the unavailability of these data at the time that it was approved for use in Canada. Based on radiographic progression results reported in this CADTH therapeutic review, there were no data available on anakinra. Additional radiographic data on these biologic agents may be available from longer-term uncontrolled studies, but only controlled data were considered in the scope of this CADTH therapeutic review.

External Validity of Populations

Meta-analysis of RA research is complicated by the fact that patient populations in related RCTs are continually changing over time. In 2009, Strand and Sokolove[51] highlighted a variety of related factors in a review of developments in RA research in the past decade. The definition of "active disease," a primary inclusion criterion for most trials, has widened over time, as the increasing number of available therapeutic regimens has led to fewer patients whose disease is insufficiently controlled. Consequently, as additional therapies emerge, RCTs assessing their therapeutic value encompass patients with a more broad range of disease. Results from patient populations included in early trials of TNF-alpha inhibitors may not be generalizable to those evaluated in later clinical trials.

The extent of generalizability of findings from clinical trials included in this CADTH therapeutic review to clinical practice is also uncertain. Strand and Sokolove[51] highlighted two recent studies by Sokka et al.[52] and Greenberg et al.,[53] which suggest that patients enrolled in several RCTs of therapies for RA are not reflective of the patients seen in clinical practice. Greenberg et al. reported two principal findings; the first was that patients in their cohort had a less severe disease state than those enrolled in clinical trials, and the second was that response to TNF-alpha inhibitors in the cohort of patients who were ineligible for clinical trials was reduced. Based on their findings, the authors suggested that caution be taken regarding the interpretation of external validity of trials, and drew attention to trial enrolment strategies that attempt to enrich the patient populations used in RA trials (including the exclusion of patients with serious medical comorbidities). A recent systematic review of RCTs of etanercept, infliximab, and adalimumab in patients with RA has noted that compared with data from a prospective biologic agents registry (DREAM, the Dutch Rheumatoid Arthritis Monitoring), efficacy of TNF-alpha inhibitors was lower in clinical practice compared with in clinical trials when assessed based on ACR 20 response.[54] In part, this may be due to the fact that in clinical practice, more patients with lower disease activity are treated with TNF-alpha inhibitors compared with the disease activity of patients in clinical trial populations, which has implications for external generalizability of clinical trial results. As this CADTH therapeutic review is based on synthesis of findings from RCTs, contemplation of these concerns is relevant in the context of interpreting MTC findings. Trials that evaluated biologic agents in combination with background DMARD therapy such as Fleischmann 2003 evaluating anakinra, Weinblatt 2006 evaluating abatacept, and STAR 2003 evaluating adalimumab were included in the CADTH therapeutic review and may offer some insight into real-world experience with biologic agents.

Harms

While no patterns with respect to types of SAEs emerged in regard to any one specific biologic, trends were consistent with the known harms profile of TNF-alpha inhibitors and biologic agents (e.g., reports of malignancies and serious infections). RCTs are often limited in their ability to detect rare but serious outcome measures. Trials were typically of short duration, and thus, many were insufficient for the evaluation of long-term harms. In the meta-analysis of placebo-controlled trials conducted in this CADTH therapeutic review, certolizumab pegol was found to be associated with an increased risk of SAEs that was not observed with any of the other biologic agents when compared with placebo. This increased risk associated with certolizumab pegol may be a result of bias due to differential withdrawals in the related trials where placebo patients were followed for a shorter duration of time than patients receiving certolizumab pegol. Exposure-adjusted analyses of certolizumab pegol trials have demonstrated that SAEs were similar between placebo and certolizumab pegol. For example, in RAPID-1, there were 14.8 SAEs per 100 person-years and 12.0 SAEs per 100 person-years for certolizumab pegol and control respectively. While exposure-adjusted analyses were outside the scope of the CADTH therapeutic review, in assessing harms based on the 35 included trials, the biologic agent evaluated in the largest number of patients and provided the most available harms data was adalimumab. Another consideration is the time frame during which trials included in the therapeutic review were conducted (published 1998 to 2009) and the changing definitions of SAEs over time and across trials. In many trials, hospitalizations were considered an SAE, but attempts to determine the proportion of patients being hospitalized (versus SAEs that did not result in hospitalization) were unsatisfactory as hospitalization data were rarely reported in the published literature. Although analyses of SAEs were not stratified by patients' prior treatment experience, it has been considered that patients who are TNF-alpha inhibitor experienced may have

higher levels of disease activity, which can have impact on the immune system, leading to higher rates of adverse events.

While RCTs represent best levels of evidence for assessing efficacy, limited sample size and study duration serve as limiting factors for the assessment of harms. Identification of rare adverse events associated with emerging therapies may be better addressed through the use of exposure databases and continued post-marketing surveillance, such as registries.[51] Therefore, regulatory warnings were also considered in this therapeutic review (Summary of Additional Harms Information, Appendix 5). A number of warnings were noted for TNF-alpha inhibitors, including those related to a potentially increased risk of lymphoma and reports of serious infections and harms associated with combination biologic therapies. While it is difficult to establish a causal relationship between rare SAEs and biologic agents based on reports from post-marketing surveillance data, these warnings contribute to the development of unique harms profiles associated with each biologic and may be a consideration for clinicians and patients choosing among biologic therapies. For example, there is a black box warning indicating reports of PML in patients receiving rituximab.[55] While only three cases of PML have been identified in patients with RA, at least 57 cases of PML have been identified in HIV-negative patients following rituximab therapy. Cases of PML have also been reported in patients with autoimmune disorders who are not receiving biologic therapy.

In order to supplement data on serious harms reported in the RCTs included in the CADTH therapeutic review, findings from recently published systematic reviews and meta-analyses (some including observational and cohort data) were considered as well as some long-term extension data. In considering these published systematic reviews and meta-analyses, it was noted that there is conflicting evidence on whether or not there is an increased risk of malignancies and serious infections associated with TNF-alpha inhibitors and other biologic agents (Summary of Additional Harms Information, Appendix 5). Long-term extension data that was reviewed did not identify any increased risks associated with adalimumab, etanercept, abatacept, or rituximab that have not already been identified. However, the lack of control groups in these studies, losses to follow-up, and potential biases associated with open-label studies limit conclusions that can be drawn from these data.

Differences between biologic agents were not detected based on MTC analyses of WDAEs, but these results may be limited by the low event rates observed in trials. Interpretation of withdrawals and WDAEs should also be considered in light of the fact that details of allocation concealment were often unclear due to poor reporting and there is the potential for unblinding in instances where adverse events (e.g., injection site reactions) could possibly reveal treatment assignment.

Conclusions

Efficacy

Methotrexate-experienced: Based on direct estimates from pooled meta-analyses and/or individual trials, ACR 50 responses for all biologic agents were statistically significantly better compared with control. Indirect estimates from CADTH MTCs did not detect any statistically significant differences among biologic agents based on ACR 50 response. Although certolizumab pegol trials were not included in pooled meta-analyses, estimates from individual trials were within the range of estimates observed from the individual trials included in this CADTH therapeutic review. Estimates from certolizumab pegol trials should be interpreted with caution because of a high proportion of withdrawals in these trials. Based on the evaluation of functional outcomes using the HAQ-DI scores, efficacy may be less for anakinra than other biologic agents. Data on inhibition of radiographic progression were available for all biologic agents except anakinra. While statistically significant differences in inhibiting radiographic progression were observed for all biologic agents, the clinical relevance of these findings is uncertain.

Methotrexate-naive: Only adalimumab, etanercept, infliximab, golimumab, and abatacept have been evaluated in methotrexate-naive populations. Based on direct estimates from pooled meta-analyses and individual trials, ACR 50 responses for these biologic agents were statistically significantly better compared with control. Indirect estimates from CADTH MTCs did not detect any statistically significant differences among biologic agents based on ACR 50 responses. When the influence of biologic agents on functional outcomes was considered, statistically significant and clinically relevant differences in HAQ-DI scores were only observed for adalimumab and etanercept. Data on inhibition of radiographic progression were available for adalimumab, etanercept, golimumab, infliximab, and abatacept. While statistically significant differences in inhibiting radiographic progression were observed for all biologic agents, the clinical relevance of these findings is uncertain.

TNF-alpha inhibitor experienced: Only golimumab, rituximab, and abatacept have been evaluated in RCTs in TNF-alpha inhibitor experienced populations, although patients who were enrolled in the golimumab trial did not have to be refractory to TNF-alpha inhibitors. Patients failing a TNF-alpha inhibitor constitutes the only population for which rituximab has a Health Canada indication in RA. Based on direct estimates from individual trials, ACR 50 responses for the three biologic agents were statistically significantly better compared with control. While point estimates from individual trials were numerically higher for abatacept and rituximab compared with golimumab, CIs indicated overlap and indirect estimates from CADTH MTCs did not detect any statistically significant differences among the three biologic agents based on ACR 50 responses. Data on HAQ-DI were available for the three biologic agents considered, but statistically significant and clinically significant results were only observed for abatacept and rituximab. Rituximab was the only one of the three biologic agents to report data on inhibiting radiographic progression, and statistically significant results favouring rituximab were observed at one year.

Harms

The proportion of patients reporting an SAE was similar for all biologic agents based on a meta-analysis of placebo-controlled trials, with the exception of certolizumab pegol, although interpretation of data is limited by the lack of exposure-adjusted analyses. Serious infections, tuberculosis, malignancies, congestive heart failure, and lupus did not appear to differ across biologic agents, although event rates were low and information on the type of SAE was missing from some trials. RCTs are limited in their ability to detect SAEs because of the rarity of events and short duration of trials, but a number of regulatory warnings have been issued for biologic agents, including one for the development of PML following exposure to rituximab. In the CADTH MTCs, statistically significant differences between biologic agents with respect to WDAEs were not detected, although estimates are uncertain as, in the majority of RCTs, events were low and the type of adverse event leading to withdrawal was rarely reported.

APPENDIX 1: METHODS

- Expertise of this review team includes pharmacy, epidemiology, pharmacology, biostatistics, health economics and rheumatology.
- The systematic review and indirect comparisons meta-analysis were prepared by a CADTH clinical reviewer in consultation with an external clinical expert specializing in rheumatology, as well as an epidemiologist/biostatistician with content expertise.
- The research questions were developed jointly by jurisdictions, expert committee members, the external clinical expert and CADTH clinical reviewers in consultation with the internal and external pharmacoeconomic reviewers.

Systematic Review Protocol for Primary Research Question

- The objective of this systematic review was to evaluate the relative clinical effectiveness and harms of biologic therapies for the treatment of adult patients with rheumatoid arthritis. Studies were chosen for inclusion in the review based on the criteria outlined below:

Table A1: Study Selection Criteria

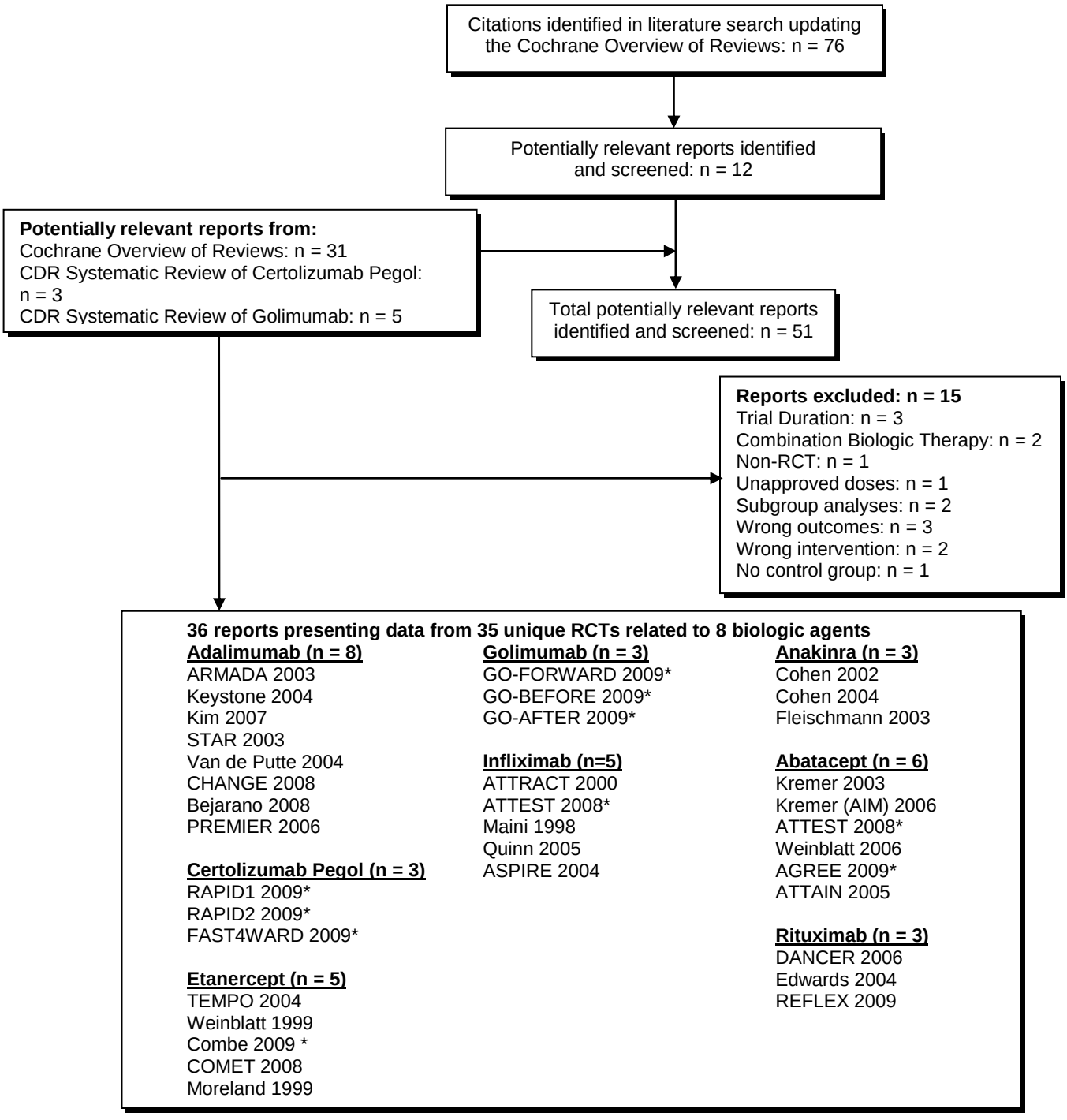
Inclusion criteria	
Study design	Published double-blind randomized controlled trials, parallel group
Population	Adult patients with rheumatoid arthritis
Interventions	Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept, anakinra, rituximab — at Health Canada-approved doses
Comparators	Placebo, DMARDs, biologic agents — alone or in combination (except combination biologic therapy)
Outcomes	**Efficacy:** ACR 20, ACR 50, ACR 70, HAQ-DI, radiographic progression **Harms:** Mortality, serious adverse events (including hospitalizations, serious infections, malignancies, lupus and autoimmune disorders, congestive heart failure), WDAEs, all-cause withdrawals
Exclusion criteria	
• Studies with a duration of less than six months • Non-English publications • Combination biologic therapies	

Literature Search Methods

- A recent Cochrane Overview of Reviews on Biologics for RA (2009)[5] was used to identify randomized controlled trials to be included in the CADTH therapeutic review.
- Additional searches were conducted to identify newly published RCTs not included in the Cochrane Overview. An electronic search covering the months of May to December 2009 was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: BIOSIS Previews, EMBASE and Medline through Ovid; The Cochrane Central Register of Controlled Trials (2009, Issue 4) through Wiley InterScience. An RCT filter was applied.
- The search for RCTs was limited to English language articles published in 2009. Where possible, retrieval was limited to the human population.
- The initial search was completed on November 26, 2009. Regular alerts were established to update the search until therapeutic review recommendations are made.
- Grey literature was obtained by searching the web sites of regulatory agencies, health technology assessment agencies, related technology assessment agencies and clinical trial registries. Google and other Internet search engines were used to search for a variety of web-based information.
- Similar searches, with no date limit, were conducted to identify trials evaluating golimumab and certolizumab pegol as these two TNF-alpha inhibitors were not included in the Cochrane Overview.
- Unpublished data were not included in this therapeutic review.

Figure A1: Finding from the Literature

PRISMA flowchart for inclusion and exclusion of studies



* Trials that were not included in the Cochrane Overview of Reviews.
Note: Three additional trials met the systematic review inclusion criteria but were summarized in the Supplemental Information on Biologics and Combination DMARD Therapy (Appendix 5) as the focus of this CADTH therapeutic review was the relative efficacy and harms of biologic agents: the BeST trial, which evaluated a step-up/step-down treatment strategy after patients were initial randomized to infliximab plus methotrexate; the SWEFOT trial, which evaluated infliximab plus methotrexate relative to combination DMARD therapy and the TEAR trial, which evaluated etanercept plus methotrexate relative to combination DMARD therapy.

Table 1: Summary of Studies Meeting the Therapeutic Review Inclusion Criteria (see Appendix I for more detailed summary tables)									
Study	**TJ count**	**SJ count**	**Duration of RA (years)**	**HAQ-DI**	**MTX naïve?**	**Age; % female**	**N**	**Comparisons**	**Tx duration**
TNF INHIBITORS									
Adalimumab									
Breedveld 2006 (PREMIER)	30.7-32.3	21.1-22.1	0.7-0.8	1.5-1.6	Yes	51.9-52.1; 72.0-77.4%	799	ADA v MTX v ADA/MTX	2 yrs
Keystone 2004	27.8	19.3	10.9	1.44-1.48	No	56.1-57.3; 73.0-76.3%	619	ADA/MTX v PL/MTX	52 wks
Kim 2007	19.2-20.3	12.2-12.8	6.8-6.9	1.3-1.4	No	48.5-49.8; 85.7-95.4%	128	ADA/MTX v PL/MTX	24 wks
Myasaka 2008 (CHANGE)	24.6	19.7	9.8	1.66	No	53.4-56.9; 77.0-82.8%	265	ADA v PL	24 wks
Van de Putte 2004	34.4	19.8	11	1.9	No	51.8-54.4; 72.3%-79.6%	544	ADA v PL	26 wks
Weinblatt 2003(ARMADA)	28.9	17.2	12.3	1.56	No	53.5-57.2%; 74.6-82.3%	271	ADA/MTX v PL/MTX	24 wks
Bejarano 2008	12.8-12.9	9.4-10.4	8 mos	1.3	Yes	47; 53.4-58.4%	148	ADA/MTX v PL/MTX	56 wks
Furst 2003 (STAR)	27.3-27.6	20.9-21.3	9.3-11.5	1.37-1.43	No	55.0-55.8; 79.2-79.6%	636	ADA/SAT v PL/SAT	24 wks
Certolizumab $^{\Sigma}$									
Keystone (RAPID-1) (2008)	30-31	21-22	6.1-6.2	1.7	No	51.4-52.4; 82.4-83.9%	592	CER/MTX v PL/MTX	52 wks
Smolen (RAPID-2) (2009)	30	21-22	5.6-6.1	1.6	No	51.5-52.2; 78-84.3%	371	CER/MTX v PL/MTX	24 wks
Fleischmann (FAST4WARD) (2009)	28-30	20-21	8.7-10.4	1.4-1.6	No	52.7-54.9; 78.3-89%	210	CER v PL	24 wks
Etanercept									
Emery 2008 (COMET)	25.0	17.3	9 mos	1.7	Yes	50.5-52.3; 73-74%	542	ET v ET/MTX	52 wks
Klareskog 2004 (TEMPO)	33.1-35.0	22.1-23.0	6.3-6.8	NR	No*	52.5-53.2; 74-79%	682	ET v MTX v ET/MTX	52 wks
Moreland 1999	33-35	25	11-13	1.6-1.7	No	51-53; 74-84%	234	ET v PL	6 mos
Weinblatt 1999	28	18	13	1.5	No	48-53; 73-90%	89	ET/MTX v PL/MTX	24 wks
Combe 2008	NR	NR	NR	NR	NR	51; NR	254	ET v ET/SUL v SUL	104 wks
Golimumab $^{\Sigma}$									
Emery 2009 (GO-BEFORE)	27-29	15-16	2.9-4.1	1.5-1.6	Yes	48.2-50.9; 79.6-84.9%	637	GO/MTX v GO/PL v PL/MTX	52 wks

Table 1: Summary of Studies Meeting the Therapeutic Review Inclusion Criteria (see Appendix I for more detailed summary tables)									
Study	**TJ count**	**SJ count**	**Duration of RA (years)**	**HAQ-DI**	**MTX naïve?**	**Age; % female**	**N**	**Comparisons**	**Tx duration**
Keystone 2009 (GO-FORWARD)	25-28	15-17	7.3-9.0	1.3-1.4	No	50-52; 78.9-82%	444	GO/MTX v GO/PL v PL/MTX	24 wks
Smolen 2009 (GO-AFTER)	29-31	15-18	10.6-12.4	1.5-1.6	No*	53.7-54.8; 73.9-85.2%	461	GO/DMARD v PL/DMARD	24 wks
Infliximab									
Lipsky (ATTRACT)	31-34	21-24	9-12	1.7-1.8	No	51-54; 73-81%	428	IFX/MTX v PL/MTX	54 wks
Maini 1998	17-33	16-20	7.6-14.3	1.4-2.0	No	47-58.9; 67-86%	101	IFX/MTX v PL/MTX	26 wks
Quinn 2005	NR	NR	6-7.4 mos	Med 1.3	Yes	51.3-53.1; NR	20	IFX/MTX v PL/MTX	12 mos
St Clair 2004 (ASPIRE)	32-34	21-22	0.8-0.9	1.5	Yes	50-51; 68-75%	1049	IFX/MTX v PL/MTX	46 wks
Schiff (ATTEST) (2008)	30.3-31.7	20.1-21.3	7.3-8.4	1.7-1.8	No	49-49.4	431	ABA/MTX v INF/MTX v PL/MTX	24 wks
T-CELL (CD28) CO-STIMULATORY MODULATORS									
Abatacept									
Moreland 2002	25.6-32.9	18.5-26.9	3.0-4.2	NR	No*	45.6-51.5; 69.0-81%	214	PL v CTLA-4Ig v LEA29Y	12 wks
Kremer 2003	28.2-30.8	20.2-21.8	8.9-9.7	NR	No	54.4-55.8; 63-75%	339	ABAT+MTX v PL+MTX	52 wks
Genovese 2005 (ATTAIN)	31.2-32.8	22.0-22.3	11.4-12.2	1.8	No	52.7-53.4; 77.1-79.7%	391	ABAT v PL	24 wks
Kremer 2006 (AIM)	31-32.3	21.4-22.1	8.5-8.9	1.7	No	50.4-51.5; 77.8-81.7%	652	ABAT/MTX v PL/MTX	54 wks
Weiinblatt 2006	NR	NR	9.5-11.3	1.5-1.6	No	52.0-54.6; 75.0%-83.7%	1441	AVAT/SAT v PL/SAT	52 wks
Schiff (ATTEST) (2008)	30.3-31.7	20.1-21.3	7.3-8.4	1.7-1.8	No	49-49.4; 12-87.3%	431	ABA/MTX v INF/MTX v PL/MTX	24 wks
Westhovens (AGREE) (2009)	30.8-31.3	21.9-22.9	6.2-6.7 mos	1.7	Yes	49.7-50.1; 76.6-78.7%	509	ABA/MTX v PL/MTX	52 wks
IL-1 ANTAGONIST									
Anakinra									
Cohen 2002	22.0-28.1	17.4-19.1	6.3-8.8	1.3-1.5	No	49.0-54.1; 62.5-85.1%	419	PL/MTX v ANAK/MTX	24 wks
Cohen 2004	24.5-26.8	20.0-20.1	10-11	1.3-1.4	No	56-57; 75-79%	501	ANAK/MTX v PL/MTX	24 wks
Fleischmann 2003	22.6	18.3-18.8	10.2-10.7	NR	No*	54.6-55.7; 74.6-74.7%	1,399	ANAK v PL	24 wks

Table 1: Summary of Studies Meeting the Therapeutic Review Inclusion Criteria (see Appendix I for more detailed summary tables)									
Study	**TJ count**	**SJ count**	**Duration of RA (years)**	**HAQ-DI**	**MTX naïve?**	**Age; % female**	**N**	**Comparisons**	**Tx duration**
CD20+ B-LYMPHOCYTE INHIBITOR									
Rituximab									
Edwards 2004	32-34	19-23	9-11	NR	No	53-54; 73-83%	161	MTX v RIT +MTX	48 wks
Emery (DANCER) 2006	32-35	21-22	9.3-11.1	NR	No	51.1-51.4; 80-83%	465	PL/MTX v RIT/MTX	24 wks
Cohen 2006 (REFLEX)	33.0-33.9	22.9-23.4	11.7-12.1	1.9	No	52.2-52.8; 81%	517	PL/MTX v RIT/MTX	24 wks

TJ=tender joint; SJ=swollen joint; HAQ-DI=Health Assessment Questionnaire – Disability Index; RA=rheumatoid arthritis; Tx=treatment; MTX=methotrexate; SAT=standard antirheumatic therapy; ADAL=adalimumab; ABAT=abatacept; INFLIX=infliximab; ANAK=anakinra; ETAN=etanercept; INFLIX=infliximab; RIT=rituximab; GOL=golimumab; CER=certolizumab. ' * ' denotes studies where there was prior MTX use for only a portion of patients, or for studies where patients were described as DMARD-experienced. A superscript '∑' is used to denote studies that were not included in the Cochrane overview of reviews. Where ranges of values are presented for tender/swollen joint counts, disease duration and HAQ score, these reflect the range of mean values of the study groups included in each trial.

Table 1 provides a summary of relevant patient baseline characteristics for all of the trials included in this therapeutic review. A more detailed account of these studies, including critical appraisal is provided in tables found in Appendix I including:

- primary study characteristics (intervention regimens, outcomes evaluated, sample size, duration, exposure history);
- study inclusion/exclusion criteria (diagnostic criteria for RA, and permissible past treatment exposures);
- study baseline characteristics (past treatment exposures, tender/swollen joint counts, age, gender, HAQ, and other factors);
- appraisal of quality and potential for biases (including assessments of the presence of blinding, allocation concealment, approach to analysis, and accounting for withdrawals)

Data Analysis

Comparison of the relative effects of the interventions of interest in this therapeutic review would ideally be based strictly on assessment of head-to-head randomized controlled trials providing direct evidence to compare clinical effectiveness and harms. However, in the absence of such data, efforts to determine relative estimates of effectiveness between all active comparators by other means can inform discussion of clinical effectiveness and construction of economic models. Statistical methods for mixed treatment comparisons (MTC) using Bayesian hierarchical modeling techniques as described by Lu and Ades were employed in this review. MTCs are a helpful set of techniques for analysts in situations wherein a collection of studies used to address a hypothesis of interest includes trials comparing different subsets of relevant interventions with a control group, and there exists (a) a primary interest in comparing treatments that have not and may not ever be directly compared; and/or (b) there is a desire to borrow strength from indirect comparisons to strengthen that inferential power associated with direct estimates. Appropriate use of MTC methodology hinges upon the assumption that patient populations and other associated study characteristics, including trial design and control group therapy, are similar. Past empirical studies by Song *et al*.[60] and Vandermeer *et al*.[61] have found that indirect comparisons can arrive at similar conclusions when compared to syntheses of direct comparisons.

Winbugs software was used for all MTC analyses. Posterior densities for all unknown parameters were estimated using Markov Chain Monte Carlo methods. Prior distributions for overall effects of interest and study-specific effect estimates were assigned vague normal prior distributions centered at zero with adequately large variances to allow the collected data to drive the calculation of pooled estimates. Model diagnostics including trace plots, autocorrelation plots, and the Brooks-Gelman-Rubin statistic were assessed to ensure model convergence. Measures of effect were estimated according to the Winbugs routine developed by the Evidence Synthesis Group consisting of experts from the universities of Bristol and Leicester (code is available from their website). Median estimates were reported along with corresponding 95% credible intervals. For comparative purposes, fixed effects MTC meta-analyses were conducted in addition to random effects MTC meta-analyses. Random effects meta-analyses are presented in the report as similar non-significant results were observed even though credible intervals were narrower.

Regarding interpretation of MTC estimates, if a 95% CrI for a risk ratio comparing two interventions did not include the value 1, this was interpreted as an indication that there is a < 5% probability that there was no difference in effect between treatments and results were considered not statistically significant.

Standard random effects meta-analyses of pooled Mantel-Haensel odds ratios using estimates from individual trials were computed using Review Manger 4.2 software (The Cochrane Collaboration) were calculated along with corresponding 95% confidence intervals, and are reported along with all MTC estimates to facilitate comparison with output from a standard approach to analysis.

Heterogeneity

- Heterogeneity of included studies was assessed with respect to trial design and patient populations. Approaches to heterogeneity are outlined in Table A2. In order to reduce heterogeneity, three analysis populations were specified (see Figure A2):
  - Methotrexate-experienced patients.
  - Methotrexate-naive patients.
  - Patients who are TNF-alpha inhibitor experienced.
- In order to further reduce heterogeneity within the methotrexate-experienced population, the analysis population focused on trials evaluating concomitant methotrexate at doses ≥ 15 mg/week. This dose was selected based on recent clinical practice guidelines suggesting that methotrexate doses should be initiated at 10 mg to 15 mg/week with rapid escalation to 20 mg to 30 mg/week based on tolerability and clinical response, Health Canada-approved methotrexate dosing,[42] as well as clinical expert input.

- Heterogeneity was further explored through selected meta-regressions and subgroup analyses based on factors such as disease duration, trial duration and proportions of withdrawals. Meta-regressions were performed when the variable was continuous in order to incorporate the maximum amount of information available from trials. Subgroup analyses were performed when there was a desire to obtain results for subgroups of trials (e.g., higher quality trials that would not be biased by high proportions of withdrawals) or when the variable could be dichotomized (e.g., six-month trials versus one to two year trials). For sensitivity analyses, cut-offs defining the subgroups (e.g., adequate methotrexate doses or acceptable levels of withdrawals) were selected based on currently accepted conventions and clinical expert input.

Table A2: Approach to Addressing Key Areas of Clinical and Methodological Heterogeneity

Variable	Description of Heterogeneity	Approach
Prior treatment experience	Trials included patients who were MTX-naive, MTX-experienced, DMARD-experienced, TNF-alpha inhibitor-experienced and TNF-alpha inhibitor failures.	• Present results and conduct meta-analyses based on 3 populations: MTX-naive, MTX-experienced and patients who are TNF-alpha inhibitor experienced.
Concomitant medications	Trials evaluated biologic monotherapy, biologic agents in combination with MTX, biologic agents in combination with sulfasalazine, and biologic agents in combination with background DMARDs.	• Exclude trials not evaluating MTX as the main concomitant medication from meta-analyses.
Dose of concomitant methotrexate	Trials evaluating biologic agents with concomitant MTX included a range of mean or median MTX doses from 7.5 mg/week to 20 mg/week.	• Exclude trials with an inadequate dose of methotrexate (< 15 mg/week) from meta-analyses. Threshold selected based on practice guidelines and clinical expert input. • Exclude trials evaluating biologic monotherapy from meta-analyses.
Duration of disease	Disease duration at trial enrolment ranged from a few months to 12 to 13 years in some trials.	• Meta-regression • May also be closely associated with prior treatment experience and therefore addressed in the three separate analysis populations.
Swollen and tender joint counts at baseline	Although trial inclusion criteria varied across time with respect joint counts, baseline joint counts in the enrolled populations were similar with the exception of one Asian trial. Trends towards lower joint counts in more recent years may be detectable but are currently uncertain.	• Sensitivity analysis if necessary • Assessed at individual trial level
Control group response rates	There was a range of control group response rates (e.g., ACR 50 control group responses were as low as 2% to 3% and as high as 49%)	• Meta-regression
Proportions of withdrawals	Withdrawals ranged from as low as 0% to as high at 87% across trials.	• Subgroup analyses by removal of trials where withdrawals were > 30% in the control group. The 30% threshold was selected based on maximum acceptable levels of withdrawals (i.e., 20% based on SIGN-50 critical appraisal) and input for clinical experts indicating that 30% withdrawals is commonly observed in RA trials.

Table A2: Approach to Addressing Key Areas of Clinical and Methodological Heterogeneity		
Variable	**Description of Heterogeneity**	**Approach**
Use of early escape and rescue therapy designs	A number of trials evaluating golimumab and adalimumab employed early escape criteria and may have counted withdrawals such that those meeting early escape criteria were not counted as withdrawals due to lack of efficacy.	• Sensitivity analysis if necessary on the outcome of withdrawals by removal of trials not counting patients meeting early escape as withdrawals due to lack of efficacy. • Assessed at individual trial level
Trial duration	While most trials reported data at 24 weeks, some trials only reported outcomes at one or two years.	• Subgroup analyses for trials reporting data at 6 months versus data at one to two years.

Note: Because of the small number of trials included in the methotrexate-naive and TNF-alpha inhibitor-experienced networks, sensitivity analyses and meta-regressions were only conducted in the methotrexate-experienced analysis population. Therefore, in the methotrexate-naive and TNF-alpha inhibitor-experienced analysis populations, the influence of heterogeneity was assessed based on trial characteristics and potential influence on individual trial estimates.

Many of the variables noted in the above table have been previously identified as potential sources of heterogeneity in systematic reviews and meta-analyses of biologic agents for rheumatoid arthritis.

Analysis Populations

In order to reduce the clinical heterogeneity associated with the 35 trials included in the CADTH therapeutic review, three populations were specified for meta-analyses (see Evidence Diagrams):

- Methotrexate-experienced patients receiving concomitant methotrexate at doses ≥ 15 mg/week (n = 13).
- Methotrexate-naive patients (n = 7).
- Patients who are TNF-alpha inhibitor experienced (n = 3).

Trials in Methotrexate-experience Patients (n = 13)
The methotrexate-experienced analysis population was established in order to further reduce heterogeneity within the DMARD-experienced population. The methotrexate cut-off dose of ≥ 15 mg per week was selected based on recent clinical practice guidelines, Health Canada-approved dosing, and clinical expert input, as previously discussed.

Of the 25 trials conducted in DMARD-experienced patients:

- There were four trials excluded from the meta-analysis because they evaluated only biologic monotherapy:[9,11,29,38] van de Putte 2004 and CHANGE 2008, evaluating adalimumab; FAST4WARD 2009 evaluating certolizumab pegol; and Moreland 1999 evaluating etanercept. In these four studies, it was also a concern that patients were required to discontinue all DMARD therapies prior to study entry, which may have biased study findings.
- Four trials were excluded from meta-analyses because they evaluated low doses of concomitant methotrexate.[23,32,39,40] In both RAPID1 2008 and RAPID2 2009, which evaluated certolizumab pegol, mean methotrexate doses were approximately 12 mg to 13 mg/week. In Maini et al. 1998, evaluating infliximab, methotrexate dose was fixed at 7.5 mg/week; it has been noted that this was the first trial conducted evaluating a TNF-alpha inhibitor in combination with methotrexate. In Edwards 2004, evaluating rituximab, median methotrexate doses were between 12.5 mg and 15 mg/week and trial inclusion criteria were having active RA despite methotrexate at 10 mg/week, which is not consistent with current methotrexate dosing practices.
- Three trials were excluded from the meta-analysis because they evaluated concomitant DMARD therapy and not specifically concomitant methotrexate: STAR 2003, which was a trial evaluating harms associated with adalimumab; Weinblatt et al. 2006 evaluating abatacept; and Fleischman 2003 evaluating anakinra in a real-world clinical practice population.[6,17,26]
- One trial was excluded from the meta-analysis because it evaluated etanercept with concomitant sulfasalazine rather than methotrexate (Combe et al. 2009).[31]

This left 13 trials for analysis in the methotrexate-experienced population. Even within this set of 13 trials, clinical heterogeneity existed:

- Three trials evaluating adalimumab were included (ARMADA 2003, Keystone 2004, Kim 2007). Kim 2007 was conducted in a Korean population and baseline swollen and tender joint counts were lower than expected.
- Two trials evaluating etanercept were included (TEMPO 2004, Weinblatt 1999). Patients included in TEMPO 2004 were only required to be DMARD-experienced. Approximately 42% to 43% of the enrolled population had never received methotrexate; therefore, in a trial evaluating etanercept with concomitant methotrexate, higher than expected responses may have been observed.
- One trial evaluating golimumab was included (GO-FORWARD 2009).
- Two trials evaluating infliximab (ATTRACT 2000 and ATTEST 2008, a placebo-controlled trial that included an infliximab reference group)
- Three trials evaluating abatacept (Kremer 2003, AIM 2006, ATTEST 2008)
- Two trials evaluating anakinra (Cohen 2002, Cohen 2004)
- One trial evaluating rituximab was included (DANCER 2006). While all patients included in DANCER 2006 were DMARD-experienced, a considerable proportion had also been exposed to TNF-alpha inhibitors, which may have resulted in lower than expected response in this trial compared with other trials included in these meta-analyses. Rituximab is only approved in Canada for use in patients who have had an inadequate response or intolerance to one or more TNF-alpha inhibitors.

Figure A2: Evidence Diagrams for Analysis Populations

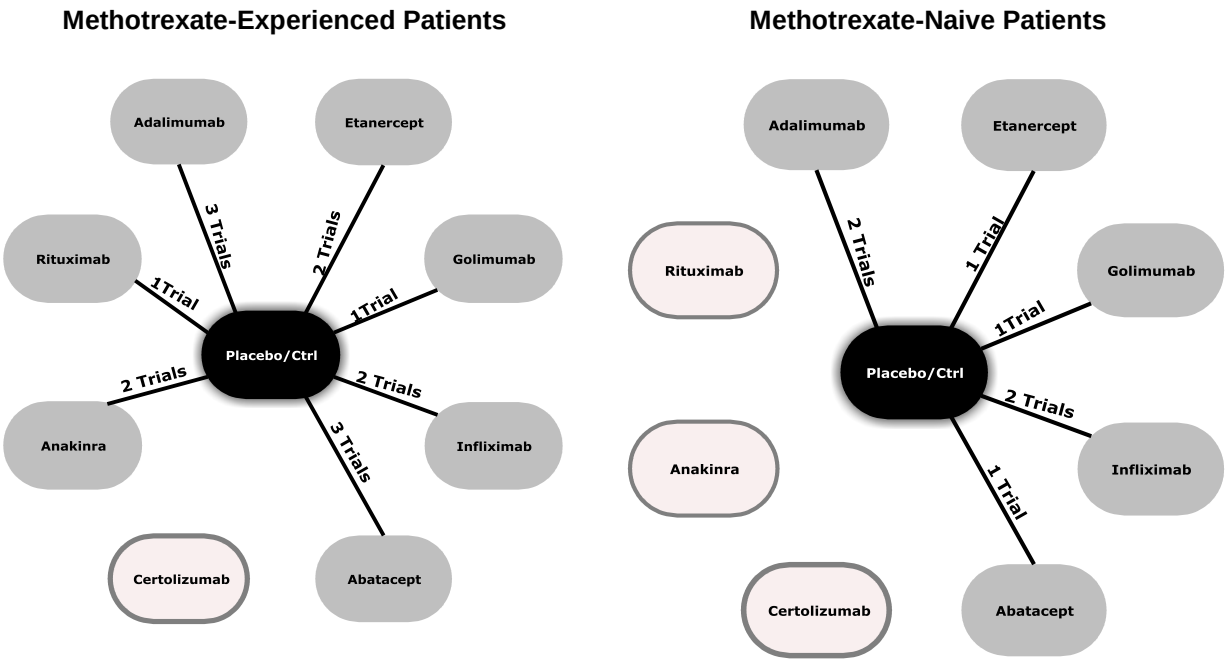
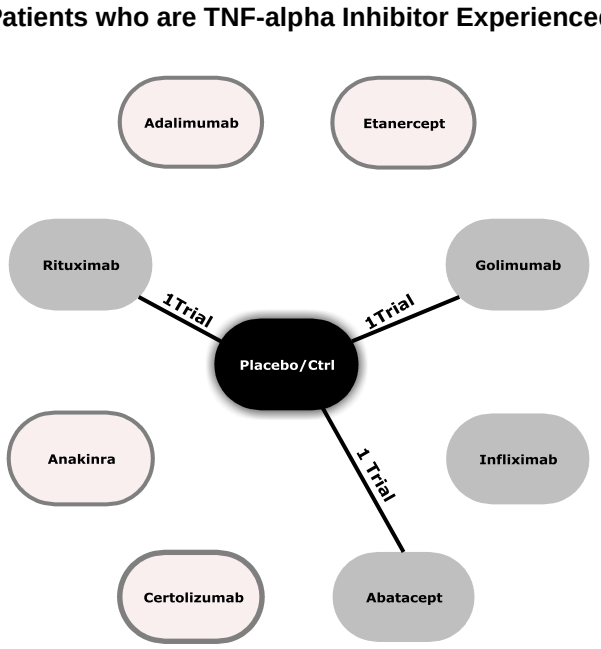


Figure A2: Evidence Diagrams for Analysis Populations (cont'd)



APPENDIX 2: DETAILED TRIAL CHARACTERISTICS AND RESULTS

Table A3: Summary of Therapeutic Review Included Study Characteristics

Study	N	Interventions	Mean MTX (mg per week)	Treatment Experience	# Prior DMARDs	Disease Stage†	Mean TJC	Mean SJC	Early Escape††	Duration (weeks)
TNF-alpha Inhibitors										
Adalimumab										
ARMADA 2003[7]	271	ADAL/MTX versus PL/MTX	16.4v16.5	MTX/DMARD-experienced	2.9v3.1	Late	28.9	17.2	Week 16	24
Keystone 2004[8]	619	ADAL/MTX versus PL/MTX	16.7v16.7	MTX-experienced	2.4	Late	27.8	19.3	Week 16	52
Kim 2007[10]	128	ADAL/MTX versus PL/MTX	16.6v16.3	MTX/DMARD-experienced	NR	Established	19.2v20.3	12.2v12.8	None	24
STAR 2003[6]	636	ADAL/DMARD versus PL/DMARD	NR	MTX/DMARD-experienced	≥4 (15v18%)	Established/Late	27.3v27.6	20.9v21.3	Week 12	24
Van de Putte 2004[9]	544	ADAL versus PL	NA	MTX/DMARD-experienced	3.6v3.8	Late	34.4	19.8	Week 8	26
CHANGE 2008[11]	265	ADAL versus PL	NA	MTX/DMARD-experienced	≥1	Established	24.6	19.7	Week 8	24
PREMIER 2006[12]	799	ADAL/MTX versus PL/MTX	NR	MTX-naïve	≥1 (31v33%)	Early	30.7v32.3	21.1v22.1	Week 16	104
Bejarano 2008[13]	148	ADAL/MTX versus PL/MTX	15.5v16.2	MTX-naive	0.2	Early	12.8v12.9	9.4v10.4	None	56
Certolizumab Pegol										
RAPID-1 2008[39]	592	CERT/MTX versus PL/MTX	13.6v13.4	MTX-experienced	1.3v1.4	Established	30v31	21v22	None	52
RAPID-2 2009[40]	371	CERT/MTX versus PL/MTX	12.6v12.2	MTX-experienced	1.2v1.3	Established	30	21v22	None	24
FAST4WARD2009[38]	210	CERT versus PL	NA	MTX-experienced	2	Established/Late	28-30	20v21	None	24
Etanercept										
TEMPO 2004[27]	682	ETAN/MTX versus PL/MTX	16.9v17.2	DMARD-experienced	2.3	Established	33.1v35.0	22.1v23.0	None	52
Weinblatt 1999[30]	89	ETAN/MTX versus PL/MTX	19v18	MTX-experienced	2.7v2.8	Late	28	18	None	24
Moreland 1999[29]	234	ETAN versus PL	NA	DMARD-experienced	3.0v3.4	Late	33v35	25	None	26
Combe 2009[31]	254	ETAN/SULF versus PL/SULF	NA	SULF-experienced	NR	NR	NR	NR	None	104
COMET2008[28]	542	ETAN/MTX versus PL/MTX	16.8v19.6*	MTX-naive	≥1 (18v24%)	Early	25.0	17.3	None	52

Table A3: Summary of Therapeutic Review Included Study Characteristics										
Study	**N**	**Interventions**	**Mean MTX (mg per week)**	**Treatment Experience**	**# Prior DMARDs**	**Disease Stage†**	**Mean TJC**	**Mean SJC**	**Early Escape††**	**Duration (weeks)**
Golimumab										
GO-FORWARD 2009[37]	444	GOL/MTX versus PL/MTX	15v15	MTX-experienced	NR	Established	25v28	15v17	Week 16	24
GO-BEFORE2009[35]	637	GOL/MTX versus PL/MTX	19.2v19.1	MTX-naive	NR	Established	27v29	15v16	None	24 ‡
GO-AFTER 2009[36]	461	GOL/DMARD versus PL/DMARD	NR	TNFi-experienced	NR	Late	29v31	15v18	Week 16	24
Infliximab										
ATTRACT 2000[20]	428	IFX/MTX versus PL/MTX	16v16	MTX-experienced	NR	Established/Late	31v34	21v24	None	54
ATTEST 2008[18]	431	IFX/MTX versus PL/MTX (ABAT/MTX trial)	16.3v16.6	MTX-experienced	NR	Established	30.3v31.7	20.1v21.3	None	24
Maini 1998[23]	101	IFX/MTX versus PL/MTX	7.5v7.5	MTX-experienced	2v3 (med)	Established/Late	17v33	16v20	None	26
ASPIRE 2004[21]	1049	IFX/MTX versus PL/MTX	NR	MTX-naive	0 (65v71%)	Early	32v34	21v22	None	46
Quinn 2005[22]	20	IFX/MTX versus PL/MTX	15v15	DMARD-naive	0	Early	NR	NR	NR	52
T-CELL (CD28) Co-Stimulatory Modulators										
Abatacept										
Kremer 2003[14]	339	ABAT/MTX versus PL/MTX	15v15.8	MTX-experienced	NR	Established	28.2v30.8	20.2 to 21.8	None	24
AIM 2006[15]	652	ABAT/MTX versus PL/MTX	16.1v15.7	MTX-experienced	NR	Established	31v32.3	21.4- to 22.1	None	54
Weinblatt 2006[17]	1441	ABAT/DMARD versus PL/DMARD	NR	MTX-experienced	NR	Established/Late	NR	NR	None	52
ATTEST 2008[18]	431	ABAT/MTX versus PL/MTX (IFX/MTX reference arm)	16.5v16.6	MTX-experienced	NR	Established	30.3v31.7	20.1 to 21.3	None	24
AGREE 2009[19]	509	ABAT/MTX versus PL/MTX	18.1v19.0	MTX-naïve	NR	Early	30.8v31.3	21.9 to 22.9	None	52
ATTAIN 2005[16]	391	ABAT/DMARD versus PL/DMARD	15.2v14.4	TNFi-experienced	NR	Late	31.2v32.8	22.0 to 22.3	None	24

Table A3: Summary of Therapeutic Review Included Study Characteristics										
Study	**N**	**Interventions**	**Mean MTX (mg per week)**	**Treatment Experience**	**# Prior DMARDs**	**Disease Stage†**	**Mean TJC**	**Mean SJC**	**Early Escape††**	**Duration (weeks)**
IL-1 Antagonist										
Anakinra										
Cohen 2002[24]	419	ANAK/MTX versus PL/MTX	16.8v16.3	MTX-experienced	1.4v2.1	Established	22.0v28.1	17.4v19.1	None	24
Cohen 2004[25]	501	ANAK/MTX versus PL/MTX	16v16	MTX-experienced	NR	Late	24.5v26.8	20.0v20.1	None	24
Fleischmann 2003[26]	1,399	ANAK/DMARD versus PL/DMARD	NR	MTX-naive/experienced	NR	Late	22.6	18.3v18.8	None	24
CD20+ B-Lymphocyte Inhibitor										
Rituximab										
DANCER 2006[33]	465	RTX/MTX versus PL/MTX	14.9v15.6	MTX-experienced	3.2v3.5	Established/Late	32v35	21v22	None	24
Edwards 2004[32]	161	RTX/MTX versus PL/MTX	12.5v15*	MTX-experienced	2.5v2.6	Established/Late	32v34	19v23	None	48
REFLEX 2006[34]	517	RTX/MTX versus PL/MTX	16.4v16.7	TNFi-experienced	3.4v3.6	Late	33.0v33.9	22.9v23.4	Week 16	24

ABAT = abatacept; ADAL = adalimumab; ANAK = anakinra; CERT = certolizumab pegol; ETAN = etanercept; GOL = golimumab; HAQ-DI = Health Assessment Questionnaire – Disability Index; IFX = infliximab; med = median; MTX = methotrexate; NR = not reported; RA = rheumatoid arthritis; RTX = rituximab; SJC = swollen joint count; SULF = sulfasalazine; TJC = tender joint count; TNFi = tumor necrosis factor-alpha inhibitor; Tx = treatment.

* Median values reported instead of mean values

† RA stage determined based on mean disease duration at study enrolment: early (≤ 2 years), established (2 to 10 years) and late (≥ 10 years).

‡ Trial is ongoing to 52 weeks but only 24 week data currently published with the exception of 52 week radiographic data available in abstracts

†† Early escape indicates the time point during the trial at which study protocols indicated that patients could receive specified rescue therapy if they were having an inadequate response to their randomized treatment. There were five of nine studies where patients meeting early escape were not counted as withdrawals due to lack of efficacy (Keystone 2004, CHANGE, PREMIER, GO-AFTER, GO-FORWARD). See Patient Disposition for more details.

Study Characteristics

Table A4: Summary of Included Studies, MTX-Experienced (included in meta-analysis, concomitant MTX > 15 mg per week)

Drug	Study (Year); Country; Study Funding; # centers; Trial Duration; Sample Size Interventions	Prior Therapy (Inclusion/Exclusion Criteria)	Notes on study design and potential biases
ADALIMUMAB	ARMADA, Weinblatt et al.[7] (2003); US, Canada; Abbott; 35 24 weeks; N = 271 ADAL 20 mg sc every 2 weeks (n = 69); ADAL 40 mg sc every 2 weeks (n = 67); ADAL 80 mg sc every 2 weeks (n = 73); PL (n = 62)	Failed treatment with at least 1 prior DMARD other than MTX, but no more than 4 DMARDs; 4 week washout period. MTX treatment for a minimum of 6 months, with stable weekly dose for at least 4 weeks. No prior use of other biologic agents, anti-CD4 therapy or TNF-alpha antagonists	Allocation concealment unclear; ITT analysis; No description of methods for generating randomization sequence; imbalance in use of concurrent corticosteroids during study; early escape design resulting in differential proportions of patients meeting early escape across treatment groups; no information on the distribution of number and reasons for withdrawal among the study arms;
	Keystone et al.[8] (2004); US, Canada; Abbott Laboratories; 89 52 weeks; N = 619 ADAL+ MTX (40 mg eow; n = 207), ADAL+ MTX (20 mg eow; n = 212), PL + MTX (n = 200)	Stable MTX therapy for 3 or more months (12.5 to 25 mg/week , or ≥10 mg/week for patients intolerant to MTX) No prior TNF-alpha antagonists or anti-CD4 antibody therapy	Allocation concealment not reported; mITT analysis; At week 16 or later, patients not achieving an ACR 20 response offered rescue treatment with another DMARD. Patients beginning treatment with other therapies after such a treatment non-response were classified as treatment failures for efficacy analysis; their radiographic scores were used for radiographic analysis. These patients were not counted as withdrawals from the study, which would underestimate study withdrawals. Patients who withdrew from the study were also classified as treatment failures. Missing Sharp score values were imputed using linear extrapolation at weeks 24 and 52.
	Kim et al.[10] (2007); Korea; Abbott Laboratories USA; 6 24 weeks; N = 128 PL (n = 63), ADAL (40 mg every other week; n = 65)	Received at least 1 prior DMARD other than MTX (but efficacy failures to no more than 4); needed to be treated with MTX > 6 months (stable dose > 4 weeks)	Allocation concealment unclear; ITT analysis; At week 18, early escape available if there was non-response (< 20% reduction in TJ, SJ); patients with missing data at week 24 and patients switching to OL rescue therapy were considered non-responders in data analysis; missing data for secondary efficacy outcomes filled using LOCF; randomization and blinding details not reported; reported withdrawals include both patients discontinuing and patients receiving rescue therapy. Korean population may reduce external generalizability; low swollen joint counts compared with other trials.
ETANERCEPT	TEMPO, Klareskog et al.[27] (2004); Multiple countries in Europe; Wyeth Research; NR 52 weeks; N = 461 MTX (20 mg/week; n = 228), ETAN (25 mg twice per week; n = 223), MTX + ETAN (n = 231)	Less than satisfactory response to ≥ 1 DMARD other than MTX; patients previously treated with MTX could enrol if they hadn't had clinically important toxic effects or lack of response, and had not been treated with MTX within 6 months Excluded if previous treatment with ETAN or other TNF-alpha inhibitor; immunosuppressive drugs within 6 months; any investigational drug within 3 months; any other DMARD or corticosteroid injection within 4 months	Allocation concealment clear; ITT analysis; Use of LOCF approach for missing data at 24 weeks for ACR-N, ACR response rates, disease activity score, HAQ-DI. Use of linear extrapolation to deal with missing values for analysis of total Sharp score at 52 weeks follow-up. Approximately 50% of patients had never received MTX.

Table A4: Summary of Included Studies, MTX-Experienced (included in meta-analysis, concomitant MTX > 15 mg per week)			
Drug	**Study (Year); Country; Study Funding; # centers; Trial Duration; Sample Size Interventions**	**Prior Therapy (Inclusion/Exclusion Criteria)**	**Notes on study design and potential biases**
	Weinblatt et al.[30] (1999), North America, other locations not specified; # sites NR, 24 weeks; N = 89 PL (n = 30) ETAN 25 mg twice weekly (n = 59) All patients received MTX	MTX treatment for at least 6 months; stable dose between 15 and 25 mg/week for 4 weeks Prior biologic therapy NR	Allocation concealment unclear; ITT analysis; Patients who withdrew from the study were considered not to have had a response at all points after withdrawal; LOCF used for outcomes such as TJ, SJ, global assessments in cases where patients withdrew; small sample size; mechanism of randomization not reported in sufficient detail; 20% PL versus 8% experimental group receiving DMARDs in addition to MTX at baseline; 70% PL versus 53% experimental group receiving corticosteroids at baseline; mean MTX durations of 35 months (PL) versus 58 months (experimental group).
GOLIMUMAB	Keystone et al., GO-FORWARD[37] (2009); NA, LA, Australia, Europe, Asia; Schering Plough; NR 24 weeks; N = 444 GOL 50 mg +MTX 15 mg/week (n = 89), GOL 100 mg + MTX 15 mg/week (n = 89), GOL 100 mg + PL (n = 133), PL + MTX 15m g/week (n = 133); every 4 weeks in all groups	Stable MTX dose (15 mg to 25 mg/week) in 4 weeks prior. Tolerant of MTX 15 mg/week for ≥ 3 months (i.e., MTX-experienced, not MTX inadequate responders). No prior use of any anti–TNF-alpha, rituximab, natalizumab, or cytotoxic agents or anakinra. No prior DMARDs besides MTX in the 4 weeks preceding the study.	Allocation concealment clear; Early escape design (16 weeks) resulting in differential proportions of patients meeting early escape across treatment groups with handling of their data using a LOCF approach; early escape patients not counted as withdrawals; early escape blinded; handling of missing radiographic data using linear extrapolation; inclusion criteria regarding tender and swollen joint count were low relative to other trials which could limit external generalizability; bias in the comparison with placebo +M TX as patients already have active disease while on methotrexate; potential for unblinding due to injection site reactions; entry into early escape phase was blinded, which can help minimize bias.
INFLIXIMAB	ATTRACT[20] (Lipsky 2000); US, Netherlands, Germany, Austria, UK; Centocor; NR 54 weeks N = 428 MTX+PL (n = 88), MTX+ IFX (3 mg/kg per 8 weeks; n = 86), MTX+ IFX (3 mg/kg per 4 weeks; n = 86), MTX+ IFX (10 mg/kg per 8 weeks; n = 87), MTX+ IFX (10 mg/kg per 4 weeks; n = 81)	Treatment with at least 12.5 mg/week Prior biologic therapy not reported	Allocation concealment clear; ITT analysis; Methods used for missing data are not described; clearly specified use of centralized randomization and independent trial monitoring; short duration for assessment of harms outcomes; median methotrexate doses lower than recommended standards; notably greater withdrawal in the placebo group mostly due to lack of efficacy (similar withdrawals due to adverse events); indicate that there were relatively few infusion reactions; a subset of these patients were also in Maini 1998, therefore patients may be double-counted between these two studies.
	ATTEST[18] (Schiff, 2008) 86 cites: Europe, Canada, Australia, Mexico, Argentina, Brazil, Peru, SA: sponsor not identified 1 year; N = 748 enrolled, N = 431 treated ABAT + MTX: ~10 mg/kg (n = 156) IFX + MTX: 3 mg/kg (n = 165) PL + MTX (n = 110) PL patients switched to ABAT at 6 months. ABAT infused on day 1, 15, 29 and then once every 28 days to day 337. IFX infused on day	MTX (≥ 15 mg/week for ≥ 3 months, stable for 28 days) No prior TNF-alpha inhibitor or ABAT allowed	Allocation concealment unclear; mITT analysis; IFX dose escalation not permitted, which is not entirely reflective of clinical practice; blinding was maintained for 1 year; control group lost after 6 months due to the adjustment of concomitant medications; use of PL was limited to days 1 to 197, but blinding maintained; weight based dosing was used for ABAT and IFX. Two infusions of drug/PL and NS were given at each time point to account for the different infusion time; missing data imputed as non-responders for dichotomous data and LOCF for continuous end points; predefine sensitivity analysis based on last DAS 28 (ESR) before initiation of other DMARDs or MTX dose adjustment; denominator of the 365 week data does not include those PL patients who started ABAT on day 198. There are no harms data on that group from day 198 to 365 so the data on ABAT harms at day 365 are incomplete.

Table A4: Summary of Included Studies, MTX-Experienced (included in meta-analysis, concomitant MTX > 15 mg per week)			
Drug	**Study (Year); Country; Study Funding; # centers; Trial Duration; Sample Size Interventions**	**Prior Therapy (Inclusion/Exclusion Criteria)**	**Notes on study design and potential biases**
	1,15,43 and 85 then once every 56 days		
ABATACEPT	Kremer et al.[14] (2003); USA, Belgium, Argentina, Germany, Canada, France, UK; Bristol Myers Squibb; NR 52 weeks; N = 339 PL + MTX (mean 15 mg/week; n = 119), ABAT + MTX (2 mg/kg; n = 105), ABAT + MTX (10 mg/kg; n = 115)	Received MTX for 6 or more months (10 mg to 30 mg/week) with a stable dose for 28 or more days; all continued on MTX, while all other DMARDs were discontinued. Prior biologic therapy unknown; IFX discontinued at least 60 days before study if used	Allocation concealment clear; mITT analysis; Patients who withdrew from the study due to worsening disease were considered non-responders; for all other patients with missing data, LOCF used; in sensitivity analysis, patients withdrawing for any reason were considered non-responders; mechanism of generation of randomization scheme not described in sufficient detail.
	AIM[15] (Kremer 2006); multinational; Industry sponsored; multisite 1 year; N = 656 ABAT 10 mg/kg + MTX (n = 433) PL + MTX (n = 219)	MTX ≥ 15 g/week for ≥ 3 months (stable for 28 days before enrolment) Prior biologic therapy not specified	Allocation concealment unclear; mITT analysis; Non-responder imputation used for missing data for ACR 20 and clinically meaningful improvement in HAQ-DI (≥ 0.3 units); implications of missing on the ACR 20 cannot be ascertained, as the timing of study withdrawal is not recorded; missing radiographs at 1 year imputed by linear extrapolation using baseline values and on-treatment assessment at the time of discontinuation; HAQ-DI was imputed using LOCF; more patients in the placebo group (14.4%) than the ABAT group (3.7%) received an additional DMARD between 6 and 12 months — may minimize the treatment effect of ABAT for the HAQ-DI and erosion scores; allowing patients to add a DMARD increases the external validity.
	ATTEST[18] (Schiff, 2008) 86 cites: Europe, Canada, Australia, Mexico, Argentina, Brazil, Peru, SA: sponsor not identified 1 year; N = 748 enrolled, N = 431 treated ABAT+MTX: ~10 mg/kg (n = 156) IFX + MTX: 3 mg/kg (n = 165) PL + MTX (n = 110) PL patients switched to ABAT at 6 months. ABAT infused on day 1, 15, 29 and then every 28 days to day 337. IFX infused on day 1,15,43 and 85 then every 56 days.	MTX (≥ 15 mg/week for ≥ 3 months, stable x 28 days No prior TNF-alpha inhibitor or ABAT allowed	Allocation concealment unclear; mITT analysis; IFX dose escalation not permitted, which is not entirely reflective of clinical practice; blinding was maintained for 1 year; control group lost after 6 months due to the adjustment of concomitant medications; use of PL was limited to days 1 to 197, but blinding maintained; weight based dosing was used for ABA & INF. Two infusions of drug/PL and NS were given at each time point to account for the different infusion time; missing data imputed as non-responders for dichotomous data and LOCF for continuous end points; predefine sensitivity analysis based on last DAS 28 (ESR) before initiation of other DMARDs or MTX dose adjustment; denominator of the 365 week data does not include those PL patients who started ABAT on day 198. There are no harms data on that group from day 198 to 365 so the data on ABAT harms at day 365 are incomplete.
ANAKINRA	Cohen[24] (2002), North America, Australia; industry; 36 24 weeks; N = 419 PL (n = 74); ANAK 0.04 mg/kg/day (n = 63); ANAK 0.1 mg/kg/day (n = 74); ANAK 0.4 mg/kg/day (n = 77); ANAK 1.0 mg/kg/day (n = 59); ANAK 2.0 mg/kg/d (n = 72) All patients received MTX	Stable MTX (15 mg to 25 mg/ week for at least 6 months Prior biologic therapy not stated	Allocation concealment unclear; ITT analysis; The protocol was changed during the trial to allow more enrolment; patients enrolled prior to the protocol change (n = 102) were analyzed at 12 weeks, while patients after the protocol change (n = 317) were analyzed at 24 weeks (making reporting of patient withdrawals difficult); LOCF used to handle missing data.

Table A4: Summary of Included Studies, MTX-Experienced (included in meta-analysis, concomitant MTX > 15 mg per week)			
Drug	**Study (Year); Country; Study Funding; # centers; Trial Duration; Sample Size Interventions**	**Prior Therapy (Inclusion/Exclusion Criteria)**	**Notes on study design and potential biases**
	Cohen[25] (2004); North America, other locations not specified; NR 24 weeks; N = 506 ANAK (n = 250); PL (n = 251) All patients received MTX.	Stable MTX (10 mg to 25 mg/week) for at least 24 weeks Prior IL1 receptor antagonists not permitted. TNF-alpha use not explicitly prohibited	Allocation concealment unclear; mITT analysis; High drop out rates (23% of patients could not be assessed for the primary outcome at week 24) limit confidence in the results; the trial was performed with all patients receiving MTX, but at lower than usual recommended dosages. This may reduce external validity; LOCF approach to handling missing data.
RITUXIMAB	DANCER[33] (Emery, 2006); Australia, Brazil, Canada, Finland, Germany, Italy, Mexico, Spain, New Zealand, Sweden, UK, US; Genotech, Hoffmann-La Roche; NR 24 weeks; N = 465 PL + MTX (10 mg to 25 mg/week; n = 149), RTX (500 mg)+MTX (10 mg to 25 mg/week; n = 124), RTX (1,000 mg)+MTX (10 mg to 25 mg/week; n = 192)	Moderate or severe RA despite concomitant MTX 10 mg to 25 mg/week for at least ≥12 weeks (≥ 4 weeks at stable dose) Failed at least one biologic or non-biologic DMARD (excluding MTX)	Allocation concealment unclear; ITT analysis; Rescue treatment could be given at week 16 if they had failed to achieve a ≥20% improvement in tender and swollen joint count; patients who received rescue or withdrew were imputed as non-responders; since rescue therapy was offered prior to the primary end point and the withdrawals were different between the groups, the use of non-responder imputation may bias the result in favour of RTX; placebo response rate was lower than expected in the calculation of sample size, which may have been a reflection of high withdrawals in PL group and non-responder imputation, biasing the treatment effect in favour of RTX; use of lower than recommended MTX dose; effect size was larger outside of the US, which may speak to the subjective nature of the outcomes and internal validity of the trial. Approximately 15% of patients had previously received a TNF-alpha inhibitor.

Table A5: Summary of Included Studies, DMARD-Experienced (excluded from Meta-Analysis)			
Drug	**Study (Year); Country; Study Funding; # centers; Trial Duration; Sample Size Interventions**	**Prior Therapy (Inclusion/Exclusion Criteria)**	**Notes on study design and potential biases**
ADALIMUMAB	STAR, Furst[6] (2003); United States, Canada; Abbott; 69 24 weeks; N = 636 ADAL 40 mg sc every 2 weeks + standard therapy (n = 318); PL + standard therapy (n = 318)	Previous use of traditional DMARD permitted and stable dose continued No prior use of biologic or anti-CD4 therapy	Allocation concealment unclear; ITT analysis; No description of methods for generating randomization sequence; potential for bias in dose increases / introduction of new DMARD if blinding not adequately maintained; limited information on the dose of concomitant standard therapies received during the study period (e.g., MTX, DMARD); short duration controlled trial for assessing harms in a chronic disease; changes in DMARD therapy permitted at week 12 (rescue therapy) but did not impact on classification of withdrawals.
	van de Putte[9] (2004); Europe, Canada, Australia; Abbott; 52 26 weeks; N = 544 ADAL 20 mg sc every 2 weeks (n = 106); ADAL 20 mg sc every week (n = 112); ADAL 40 mg sc every other week (n = 113); ADAL 40 mg sc every week (n = 103); PL (n = 110)	Failed treatment with at least 1 prior DMARD; 4 week washout period No biologic within 6 months of screening	Allocation concealment unclear; ITT analysis; Early escape design (8 weeks) resulting differential proportions of patients meeting early escape across treatment groups with handling of their data using a imputation of non-response; uncertain if early escape patients were counted as withdrawals but a large % of patients withdrawing due to lack of efficacy therefore, this bias is unlikely. proportion of patients using concomitant medications differed between treatment arms (e.g., CS); large difference in % of patients withdrawn across groups; external generalizability limited by exclusion of patients susceptible to infection and comorbidities; short duration controlled trial for assessing harms in a chronic disease.
	CHANGE; Miyasaka[11] (2008); Japan; Abbott; 68 24 weeks; N = 352 ADAL 20 mg sc every 2 weeks (n = 87); ADAL 40 mg sc every 2 weeks (n = 91); ADAL 60 mg every 2 weeks (n = 87); PL (n = 87)	Failed treatment with at least 1 prior DMARD; 4 week washout period No treatment with any TNF-alpha antagonist or alkylating agent	Allocation concealment unclear; no ITT analysis; Early escape design at week 8 resulting in differential proportions of patients meeting early escape across treatment groups with handling of their data using last observation carried forward; patients meeting early escape were not counted as withdrawals. no information of dose of concurrent medication use (e.g., NSAID, CS); possibility for unblinding, since infusion site reactions occurred much more frequently in the treatment groups (27 to 29 patients per group) compared with placebo group (2 patients); Japanese population reduces external validity.
CERTOLIZUMAB PEGOL	Keystone, RAPID1[39] (2008); several countries (details not reported); UCB; 147 52 weeks; N = 982 CERT 400 mg at week 0,2 and 4; followed by either: 200 mg (n = 393), 400 mg (n = 390), Or PL (n = 199) every 2 weeks	Prior MTX ≥ 6 months (stable dose ≥ 10 mg/week for ≥ 2 months before enrolment) No biologic for RA within 6 months before enrolment (3 months for etanercept, anakinra); excluded if a prior biologic treatment led to a hypersensitivity or anaphylactic reaction, or there was a prior non-response to anti–TNF-alpha therapy	Allocation concealment unclear; ITT analysis; Did not explicitly state that the comparator was identical in appearance to the intervention; used placebo with no concomitant DMARD; high and uneven withdrawal rates; short duration. Patients could withdraw at 16 weeks.

Table A5: Summary of Included Studies, DMARD-Experienced (excluded from Meta-Analysis)			
Drug	**Study (Year); Country; Study Funding; # centers; Trial Duration; Sample Size Interventions**	**Prior Therapy (Inclusion/Exclusion Criteria)**	**Notes on study design and potential biases**
	Smolen, RAPID2[40] (2009); 13 countries; UCB; 76 24 weeks; N = 619 CERT 400 mg at week 0,2 and 4, followed by one of: 200 mg (n=246), 400 mg (n=246), or PL (n=127); every 2 weeks; 24 weeks	Prior MTX ≥ 6 months (stable dose ≥ 10 mg/week for ≥ 2 months before enrolment) No biologic for RA within 6 months before enrolment (3 months for etanercept, anakinra); excluded if a prior biologic tx led to a hypersensitivity or anaphylactic reaction, or there was a prior non-response to anti–TNF-alpha therapy	Allocation concealment unclear; ITT analysis; External validity of the trial is reduced since comparator is not representative of current practice; high withdrawal rates and use of imputation methods such as non-responder imputation and last observation carried forward (LOCF) may bias the result of the trial in favour of the certolizumab pegol group and reduce the internal validity of the trial; use of linear extrapolation to impute missing data for mTSS at week 24 may not accurately reflect the pattern of changes in joint erosions or joint space narrowing; unblinding was possible and a threat to internal validity as the viscosities of the control and active treatment were dissimilar; the study population was not reflective of the Canadian population and may reduce the external validity of the results.
	Fleishchmann, FAST4WARD[38] (2009); USA, Austria, Czech Republic; UCB; 36 24 weeks; N = 220 CERT 400 mg (n = 111) versus PL (n = 109) (every 4 weeks)	Patients who had failed ≥1 DMARD due to lack of efficacy or intolerance No biologic for RA within 6 months before enrolment; or prior TNF-alpha inhibitor therapy	Allocation concealment clear; mITT analysis; External validity of the trial is reduced as a result of a choice of comparator that is not representative of current practice; high withdrawal rates and use of imputation methods such as non-responder imputation and last observation carried forward (LOCF) that may bias the result of the trial in favour of the certolizumab pegol group and reduce the internal validity of the trial; use of linear extrapolation to impute missing data for mTSS at week 24 and 52 may not accurately reflect the pattern of changes in joint erosions or joint space narrowing; unblinding was possible and a threat to internal validity as the viscosities of the control and active treatment were dissimilar.
ETANERCEPT	Moreland[29] (1999); North America; industry sponsored; 13; 6 months; N = 246 ETAN 10 mg twice weekly (n = 80); ETAN 25 mg twice weekly (n = 76); placebo (n = 78)	Inadequate response to DMARDs for inclusion (including MTX). No DMARDs given 1 month prior to study. Prior biologic therapy unlikely since study was performed in 1999	Allocation concealment unclear; mITT analysis; An older trial, therefore external validity may be limited (e.g., number of previous DMARDs is higher than some newer trials, as is duration of disease); patients who withdrew were counted as non-responders; high dropout rate; higher number of patients using CS at baseline in the ETAN 25 mg twice weekly group; more PL patients receiving NSAIDs at baseline; most patients were taking DMARDs prior to the study, but had to be off them for 1 month before randomization, which may have resulted in low baseline ACR measurements (artificially elevating the response to therapy relative to trials that did not use such a washout period); LOCF used to deal with missing data.
	Combe[31](2009); NR; funded by Wyeth; NR 104 weeks ETAN 25 mg sc twice weekly + PL; SULF 2 g to 3 g + PL; ETAN + SULF	Inadequate response to sulfasalazine (receiving stable doses, 2 g to 3 g daily, for 4 months before screening)	Allocation concealment unclear; mITT analysis; No description of methods for randomization or blinding; high withdrawal rate in SULF arm

Table A5: Summary of Included Studies, DMARD-Experienced (excluded from Meta-Analysis)			
Drug	**Study (Year); Country; Study Funding; # centers; Trial Duration; Sample Size Interventions**	**Prior Therapy (Inclusion/Exclusion Criteria)**	**Notes on study design and potential biases**
INFLIXIMAB	Maini et al.[23] (1998); UK, Netherlands, Germany, Austria, UK ; Centocor; NR 26 weeks; N=101 PL+MTX (n = 14), 1 mg/kg IFX+ MTX (n = 14), 1 mg/kg IFX+ no MTX (n = 15), 3 mg/kg IFX+ MTX n = 15), 3 mg/kg IFX + no MTX (n = 14), 10 mg/kg IFX+ MTX (n = 14), 10 mg/kg IFX+ no MTX (n = 15)	MTX 7.5 mg to 15 mg/week for 6 or more months; All DMARDs stopped 4 weeks before study	Allocation concealment clear; ITT analysis unknown; Low dose of MTX used in this study; some notable differences in baseline traits (disease duration, RF+, TJ count, others), though none were statistically significantly different due to small sample size; patients unable to complete 26 week study for any reason (including discontinuation at their own choice or their physician's choice, due to an AE, or due to an increase in dose of MTX or oral CS or a new DMARD treatment was needed) were considered non-responders; 8/14 (57%) of placebo patients withdrew by week 14, much more than other groups; patients were a subset of the ATTRACT trial and therefore may be double-counted.
ABATACEPT	Weinblatt et al.[17] (2006); multinational; Bristol Myers Squibb; NR 52 weeks; N = 1,456 ABAT (10 mg/kg; n = 959), PL (n = 482); continued background treatment (biologic/non-biologic DMARDs)	Receiving 1 or more biologic and/or non-biologic DMARDs for at least 3 months at a stable dose for at least 28 days	Allocation concealment unclear; mITT analysis; Exclusion of patients with other notable comorbidities may limit external validity; patients were permitted to continue background DMARD therapy, NSAIDs, and corticosteroids, which may enhance generalizability; manufacturer involved in the study design, data collection, and data analysis; as efficacy was secondary of interest in this study, no description of any methods used to deal with missing data for efficacy measures
ANAKINRA	Fleischmann et al.[26] (2003); US, Canada, Europe, Australia; Amgen; 169 24 weeks; N = 1,414 ANAK (100 mg; n = 1116), PL (n = 283)	Use DMARDS were permitted if dose stable for at least 2 months before enrolment. Use of TNF-alpha inhibitors not permitted	Allocation concealment unclear; mITT analysis; No evaluation of efficacy outcomes, only report on adverse events and withdrawals; mechanisms of randomization and blinding not explained in detail
RITUXIMAB	Edwards et al.[32] (2004); Australia, Canada, Israel, EU; Manufacturer Sponsored; 26 48 weeks; N = 161 RTX + MTX (n = 40); RTX + PL (n = 40); RTX + CYC (n = 41); PL + MTX (n = 40)	Active disease despite concomitant MTX ≥10 mg/week. Receiving MTX for ≥16 weeks (stable dose ≥4 weeks). Criteria with respect to prior biologic therapy unknown/not reported.	Allocation concealment unclear; ITT analysis; LOCF was used to impute missing data; small sample size; use of steroids in all patients is not reflective of clinical practice and will impact the effect size and PL response rate; low MTX doses and entry inclusion criteria; compared to the other trials, allowed a higher dose of concomitant steroid; more patients in the PL+ MTX group withdrew, which may bias the effect estimate in favour of the experimental group.

Table A6: Summary of Included Studies, MTX-Naive			
Drug	**Study (Year); Country; Study Funding; # centers; Trial Duration; Sample Size Interventions**	**Prior Therapy (Inclusion/Exclusion Criteria)**	**Notes on study design and potential biases**
ADALIMUMAB	PREMIER; Breedvelt et al.[12] (2006); Australia, Europe, NR; 133 104 weeks; N=799 ADAL 40 mg sc every 2 weeks + 20 mg/week MTX (n = 268); ADAL 40 mg sc every 2 weeks (n = 274) + PL; 20 mg/week MTX (n = 257) + PL	One third of patients received previous DMARD; 4 week washout period No prior treatment with MTX, cyclophosphamide, cyclosporine, azathioprine, or > 2 other DMARDS	Allocation concealment unclear; ITT analysis; No description of methods generating randomization sequence; imbalance of withdrawal rates across study groups, including withdrawal due to lack of efficacy; no information on handling of missing data; limited information on concurrent medications permitted during study period; low concomitant doses of methotrexate Rescue therapy at week 16 = dose escalation of adalimumab. Withdrawals would be underestimated because of this option. No data imputed for patients whose dose were escalated.
	Bejarano et al.[13] (2008); Europe; Abbott; NR 56 weeks; N = 148 ADAL 0.8 ml sc every 2 weeks (n = 75); or PL (n = 73) every 2 weeks	Mean 0.2 previous DMARDs; patients receiving DMARD underwent 4 week washout period prior to study No prior use of MTX or biologic agents	Allocation concealment clear; ITT analysis; Early escape and potential loss of blinding and differences in proportions of patients meeting early escape across treatment groups; analyzed as non-responders (sensitivity analysis using other methods for data imputation was conducted); lower concomitant doses of MTX than used in clinical practice; little information regarding prior concomitant medications; inclusion of only patients with paid employment (reduced generalizability); exclusion of patients susceptible to infection and comorbidities reduces generalizability; short duration controlled trial for assessing harms in a chronic disease
ETANERCEPT	COMET, Emery et al.[28] (2004); UK, Netherlands, Australia, Belgium, USA; Wyeth Research; NR 52 weeks; N = 542 MTX (titrated from 7.5 mg/week up to 20 mg max; n = 268), MTX (same) + ETAN (50 mg/week; n = 274)	No prior MTX; no other DMARDs within 4 weeks of baseline assessment No prior TNF-alpha therapy	Allocation concealment clear; mITT analysis; Missing values imputed using LOCF for clinical end points; for patients without radiographic data at 52 weeks, values imputed by linear extrapolation from time of final on treatment assessment, unless the final radiograph was obtained during the first 3 months of the study.
GOLIMUMAB	Emery et al., GO-BEFORE[35] (2009); Asia, Europe, NA, LA, Australia; Cenetcor, Schering Plough; 90 52 weeks; N = 637 GOL 50 mg +MTX (n = 159); GOL 100 mg + MTX (n = 159); GOL 100 mg +PL (n = 159); PL+MTX (n = 160)	Had not received more than 3 oral MTX treatments (i.e., MTX-naive) Exclusions: Prior TNF-alpha inhibitor use and/or use of DMARDs/systemic immunosuppressive agents; intra-articular, IM, or IV corticosteroids; or anakinra ≤ 4 weeks before	Allocation concealment unclear; ITT analysis; Handling of missing radiographic data using linear extrapolation; longer duration disease compared with other early RA trials (3 years versus 1 year), which would limit external generalizability.
INFLIXIMAB	ASPIRE[21] (St. Clair, 2004); US, Netherlands, Austria, UK, Canada, Germany; Centocor; 54 weeks; N = 1,049 MTX + PL (n = 298), MTX + IFX (3 mg/kg; n = 373), MTX + IFX (6 mg/kg; n = 378)	No prior MTX treatment permitted; no other DMARDs within 4 weeks of study, or leflunomide within past 6 months No prior treatment with infliximab, etanercept, adalimumab, or other TNF-alpha antagonist.	Allocation concealment clear; ITT analysis unknown; Mechanism for generating randomization scheme not reported in enough detail; LOCF used to handle missing data between weeks 30 to 54; linear extrapolation used for radiographic data; additional sensitivity analyses for dealing with missing data pursued; similar frequencies of withdrawal, though for varied reasons (lack of efficacy versus adverse events); dose of MTX below recommended guidelines; potential lack of study generalizability due to inclusion/exclusion criteria used (i.e., results may not apply to those with less severe RA)

Table A6: Summary of Included Studies, MTX-Naive			
Drug	**Study (Year); Country; Study Funding; # centers; Trial Duration; Sample Size Interventions**	**Prior Therapy (Inclusion/Exclusion Criteria)**	**Notes on study design and potential biases**
	Quinn et al.[22] (2005); UK; Unclear, partial support by Arthritis Research Campaign; NR 24 months; N = 20 IFX 3 mg/kg [baseline, 2 week, 6 week, then 8 week intervals to 46 weeks] (n = 10); placebo (n = 10)	No previous treatment with DMARD No prior use of anti–TNF-alpha agents, cyclophosphamide, nitrogen mustard, chlorambucil, or other alkylating agents	Small sample sizes; patients in placebo group received more MTX, corticosteroids and rescue DMARDs compared with those in the active comparison group; no indication as to how missing data were handled; external validity limited by exclusion of patients susceptible to infection/comorbidities
ABATACEPT	AGREE[19] (Westhovens, 2009) Multinational RCT 1 year; N=1,052 enrolled, N = 509 randomized and treated ABAT+MTX (n = 256) ~10 mg/kg PL+MTX (n = 253)	Not described other that MTX use (see "others"). Prior biologic therapy not described	Addition of one non-biologic DMARD was allowed at 6 months which may compromise the internal validity of the study past this point, although the numbers of patients who added an agent were small and probably not likely to alter the outcome (6 patients in ABA + MTX and 17 patients in PL+MTX added a non-biologic DMARD); use of NSAIDs not mentioned and the need for the dose of prednisone to be stable for a certain period before randomization was not defined and may threaten the internal validity of the trial; analysis set was on patients randomized and treated; non-responder imputation of DAS 28 (ESR) remission, LOCF for most continuous variables, for radiographs 'all available data were included' (may be observed case, but this is not specified).

Table A7: Summary of Included Studies, TNF-alpha Inhibitor Experienced			
Drug	**Study (Year); Country; Study Funding; # centers; Trial Duration; Sample Size Interventions**	**Prior Therapy (Inclusion/Exclusion Criteria)**	**Notes on study design and potential biases**
GOLIMUMAB	Smolen, GO-AFTER[36] (2009); Canada, Finland, Germany, Netherlands, New Zealand, Spain, UK, USA; Centocor, Schering Plough; 82 24 weeks; N = 461 GO 50 mg (n = 153); GO 100 mg (n = 153); PL (n = 155)	Concomitant DMARD treatment with MTX, sulfasalazine, and hydroxychloriquine was permitted but not required. Treated with a TNF-alpha inhibitor with the last dose 8 or 12 weeks before study. Patients could have discontinued the TNF-alpha inhibitor for any reason.	Early escape design (16 weeks) resulting differential proportions of patients meeting early escape across treatment groups with handling of their data using a last observation carried forward approach; early escape patients not counted as withdrawals; early escape blinded; inclusion of patients who had experience with one dose of TNF-alpha inhibitor instead of patients refractory to TNF-alpha inhibitor therapy as occurred in other trials of biologic agents.
ABATACEPT	ATTAIN, Genovese et al.[16] (2005); NR; 89 6 months; N = 393 ABAT 10 mg/kg [days 1, 15, 29, then every 28 days] + stable DMARD (n = 258); PL + stable DMARD (n = 133)	No specific requirements for failure of prior non-biologic DMARDs. Inadequate response to TNF-alpha inhibitor after ≥ 3 months of tx.	Missing data handled with non-responder imputation for the two primary end points and LOCF used for secondary outcome variables; generalizability possibly compromised, as a number of concomitant DMARDS not reported; in current users, discontinuation of TNF-alpha inhibitor and initiation of a different DMARD (non–TNF-alpha inhibitor) may have allowed for a period of worsening of disease; current users of ETAN or IFX were required to have 28 or 60 days free of the TNF-alpha inhibitor therefore the PL response may be underestimated, which may make the treatment effect, appear larger than it is; method of blinding is unclear; two randomized patients not included in the analysis.
RITUXIMAB	REFLEX, Cohen et al.[34] (2006); US, Europe, Canada & Israel; manufacturer sponsored; 114 24 weeks; N = 520 RTX + MTX (n = 311), PL + MTX (n = 209)	Ongoing MTX treatment for at least 3 months before randomization at a dose of 10 mg to 25 mg/week stable for 4 weeks before study; failure of a prior treatment defined as lack or loss of response with between 1 to 5 DMARDS other than MTX and/or biologic response modifiers. Required to discontinue any biologic therapies prior to study (IFX, ETAN or ADAL).	MTX dose below recommended levels; short trial duration; non-responder imputation used for all categorical end points, and LOCF used for continuous variables; all patients withdrawing from the trial considered non-responders for categorical end points; considerable difference in withdrawals and number completing 24 weeks, most of which in PL group were due to insufficient response and were likely imputed as non-responders.

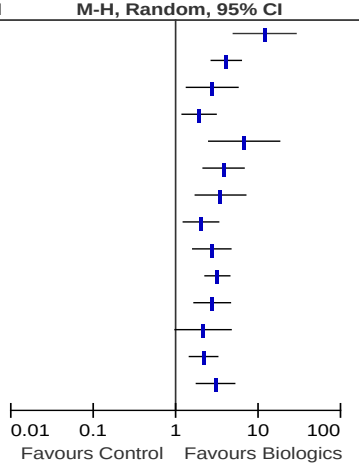
Summary of Outcomes: Direct Estimates from Individual Trials

Figure A3: ACR 20, Data from Individual Randomized Controlled Trials and Direct Estimates from Meta-Analyses

MTX-Experienced Patients (included in meta-analyses)

Trials where MTX is used concomitantly at doses > 15 mg/week

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Odds Ratio M-H, Random, 95% CI
ADAL ARMADA 2003	45	67	9	62	12.05 [5.04, 28.79]
ADAL KEYSTONE 2004	131	207	59	200	4.12 [2.72, 6.24]
ADAL KIM 2007	40	65	23	63	2.78 [1.36, 5.69]
ETAN TEMPO 2004	197	231	171	228	1.93 [1.21, 3.09]
ETAN WEINBLATT 1999	42	59	8	30	6.79 [2.53, 18.21]
GOL GO-FORWARD 2009	53	89	37	133	3.82 [2.16, 6.74]
IFX ATTRACT 2000	36	86	15	88	3.50 [1.74, 7.07]
IFX ATTEST 2008	98	165	46	110	2.04 [1.25, 3.32]
ABAT KREMER 2003	69	115	42	119	2.75 [1.62, 4.67]
ABAT AIM 2006	288	424	85	214	3.21 [2.28, 4.52]
ABAT ATTEST 2008	104	156	46	110	2.78 [1.68, 4.61]
ANAK COHEN 2002	41	105	11	48	2.15 [0.99, 4.70]
ANAK COHEN 2004	95	250	55	251	2.18 [1.47, 3.24]
RTX DANCER 2006	66	122	34	122	3.05 [1.79, 5.19]



DIRECT META-ANALYSES

Drug, n Trials, OR (95% CI), (I^2 reported if ≥ 50%)

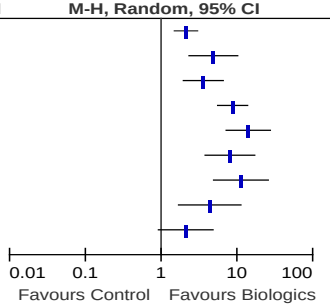
Subtotals

ADAL (n = 3): 4.88 (2.43 to 9.78) (I^2 = 71%)
ETAN (n = 2): 3.35 (0.99 to 11.39) (I^2 = 80%)
GOL (n = 1): 3.82 (2.16 to 6.74)
IFX (n = 2): 2.51 (1.50 to 4.23)
ABAT (n = 3): 3.00 (2.34 to 3.85)
ANAK (n = 2): 2.18 (1.53 to 3.09)
RTX (n = 1): 3.05 (1.79 to 5.19)

MTX-Experienced Patients (excluded from meta-analyses)

Trials where MTX is not used concomitantly at doses > 15 mg/week

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ADAL STAR 2003	140	261	95	270		2.13 [1.50, 3.02]
ADAL CHANGE 2008	40	91	12	87		4.90 [2.35, 10.24]
ADAL VAN DE PUTTE 2004	52	113	21	110		3.61 [1.98, 6.60]
CERT RAPID1 2008	228	393	27	199		8.80 [5.60, 13.84]
CERT RAPID2 2009	141	246	11	127		14.16 [7.26, 27.62]
CERT FAST4WARD 2009	50	111	10	109		8.11 [3.83, 17.18]
ETAN MORELAND 1999	46	78	9	80		11.34 [4.96, 25.94]
RTX EDWARDS 2004	29	40	15	40		4.39 [1.71, 11.30]
ABAT WEINBLATT 2006	41	85	11	36		2.12 [0.93, 4.84]

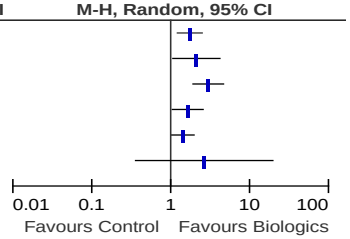


Subtotals

NOTE: Trials not pooled because of clinical heterogeneity.

MTX-Naive Patients

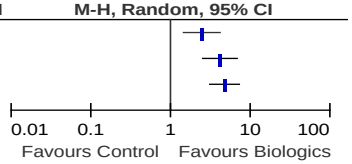
Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ADAL PREMIER 2006	185	268	144	257		1.75 [1.22, 2.50]
ADAL BEJERANO 2008	54	75	40	73		2.12 [1.07, 4.20]
ETAN COMET 2008	220	256	163	243		3.00 [1.93, 4.67]
GOL GO-BEFORE 2009	98	159	79	160		1.65 [1.06, 2.57]
IFX ASPIRE 2004	219	351	147	274		1.43 [1.04, 1.98]
IFX QUINN 2005	8	10	6	10		2.67 [0.36, 19.71]



Subtotals
ADAL (n = 2):1.82 (1.33 to 2.50)
ETAN (n = 1): 3.00 (1.93 to 4.67)
GOL (n = 1): 1.65 (1.06 to 2.57)
IFX (n = 2): 1.46 (1.06 to 2.00)

Patients Who Are TNF-alpha Inhibitor Experienced

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
GOL GO-AFTER 2009	54	153	28	155		2.47 [1.46, 4.19]
ABAT ATTAIN 2005	129	256	26	133		4.18 [2.55, 6.85]
RTX REFLEX 2006	152	298	36	201		4.77 [3.12, 7.31]



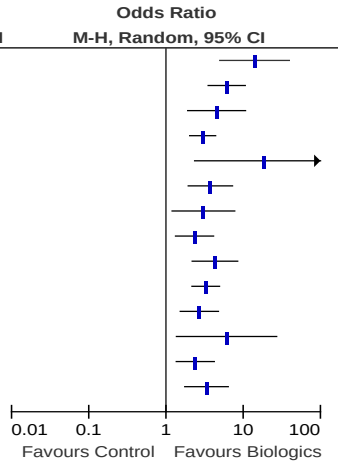
Subtotals
GOL (n = 1): 2.47 (1.46 to 4.19)
ABAT (n = 1): 4.18 (2.55 to 6.85)
RTX (n = 1): 4.77 (3.12, to 7.31)

Figure A4: ACR 50, Data from Individual Randomized Controlled Trials and Direct Estimates from Meta-Analyses

MTX-Experienced Patients (included in meta-analyses)

Trials where MTX is used concomitantly at doses > 15 mg/week

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ADAL ARMADA 2003	37	67	5	62		14.06 [5.00, 39.51]
ADAL KEYSTONE 2004	81	207	19	200		6.12 [3.54, 10.60]
ADAL KIM 2007	28	65	9	63		4.54 [1.92, 10.73]
ETAN TEMPO 2004	160	231	98	228		2.99 [2.04, 4.39]
ETAN WEINBLATT 1999	23	59	1	30		18.53 [2.36, 145.51]
GOL GO-FORWARD 2009	33	89	18	133		3.76 [1.95, 7.26]
IFX ATTRACT 2000	18	86	7	88		3.06 [1.21, 7.77]
IFX ATTEST 2008	61	165	22	110		2.35 [1.33, 4.12]
ABAT KREMER 2003	42	115	14	119		4.32 [2.20, 8.47]
ABAT AIM 2006	169	424	36	214		3.28 [2.18, 4.93]
ABAT ATTEST 2008	63	156	22	110		2.71 [1.54, 4.77]
ANAK COHEN 2002	22	105	2	48		6.10 [1.37, 27.10]
ANAK COHEN 2004	43	250	20	251		2.40 [1.37, 4.21]
RTX DANCER 2006	41	122	16	122		3.35 [1.76, 6.40]



DIRECT META-ANALYSES

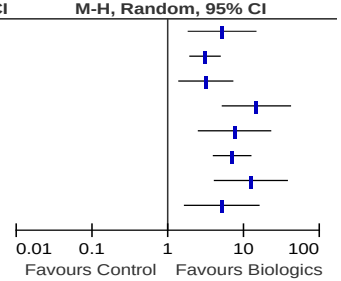
Drug, n Trials, OR (95% CI) (I^2 reported if ≥ 50%)

Subtotals
ADAL (n = 3): 6.72 (3.93 to 11.48)
ETAN (n = 2): 5.62 (0.99 to 31.83) (I^2 = 67%)
GOL (n = 1): 3.76 (1.95 to 7.26)
IFX (n = 2): 2.52 (1.56 to 4.08)
ABAT (n = 3): 3.28 (2.44 to 4.41)
ANAK (n = 2): 2.95 (1.37 to 6.36)
RTX (n = 1): 3.35 (1.76 to 6.40)

MTX-Experienced Patients (excluded from meta-analyses)

Trials where MTX is not used concomitantly at doses > 15 mg/week

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ADAL CHANGE 2008	22	91	5	87		5.23 [1.88, 14.54]
ADAL STAR 2003	77	261	32	270		3.11 [1.97, 4.91]
ADAL VAN DE PUTTE 2004	25	113	9	110		3.19 [1.41, 7.19]
CERT RAPID2 2009	80	246	4	127		14.82 [5.29, 41.55]
CERT FAST4WARD 2009	25	111	4	109		7.63 [2.56, 22.77]
CERT RAPID1 2008	144	393	15	199		7.09 [4.03, 12.48]
ETAN MORELAND 1999	31	78	4	80		12.53 [4.16, 37.76]
RTX EDWARDS 2004	17	40	5	40		5.17 [1.68, 15.98]

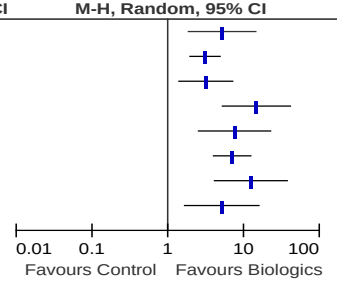


Subtotals

NOTE: Trials not pooled because of clinical heterogeneity.

MTX-Naive Patients

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ADAL CHANGE 2008	22	91	5	87		5.23 [1.88, 14.54]
ADAL STAR 2003	77	261	32	270		3.11 [1.97, 4.91]
ADAL VAN DE PUTTE 2004	25	113	9	110		3.19 [1.41, 7.19]
CERT RAPID2 2009	80	246	4	127		14.82 [5.29, 41.55]
CERT FAST4WARD 2009	25	111	4	109		7.63 [2.56, 22.77]
CERT RAPID1 2008	144	393	15	199		7.09 [4.03, 12.48]
ETAN MORELAND 1999	31	78	4	80		12.53 [4.16, 37.76]
RTX EDWARDS 2004	17	40	5	40		5.17 [1.68, 15.98]

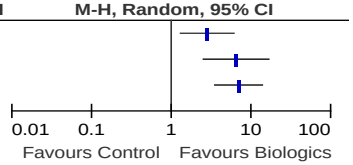


Subtotals

ADAL (n = 2): 1.81 (1.33 to 2.45)
ETAN (n = 1): 2.51 (1.74 to 3.63)
GOL (n = 1): 1.62 (1.02 to 2.58)
IFX (n = 2): 2.16 (0.92 to 5.06)
ABAT (n = 1): 1.84 (1.29 to 2.62)

Patients Who Are TNF-alpha Inhibitor Experienced

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
GOL GO-AFTER 2009	25	153	10	155		2.83 [1.31, 6.12]
ABAT ATTAIN 2005	52	256	5	133		6.53 [2.54, 16.77]
RTX REFLEX 2006	80	298	10	201		7.01 [3.53, 13.91]



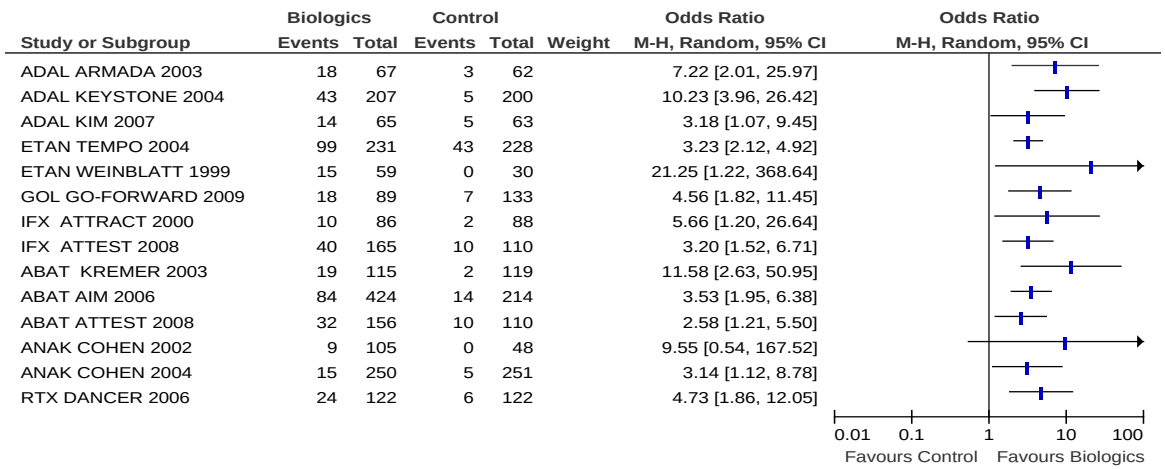
Subtotals

GOL (n = 1): 2.83 (1.31 to 6.12)
ABAT (n = 1): 6.53 (2.54 to 16.77)
RTX (n = 1): 7.01 (3.53 to 13.91)

Figure A5: ACR 70, Data from Individual Randomized Controlled Trials and Direct Estimates from Meta-Analyses

MTX-Experienced Patients (Included in Meta-Analyses)

Trials where MTX is used concomitantly at doses > 15 mg/week



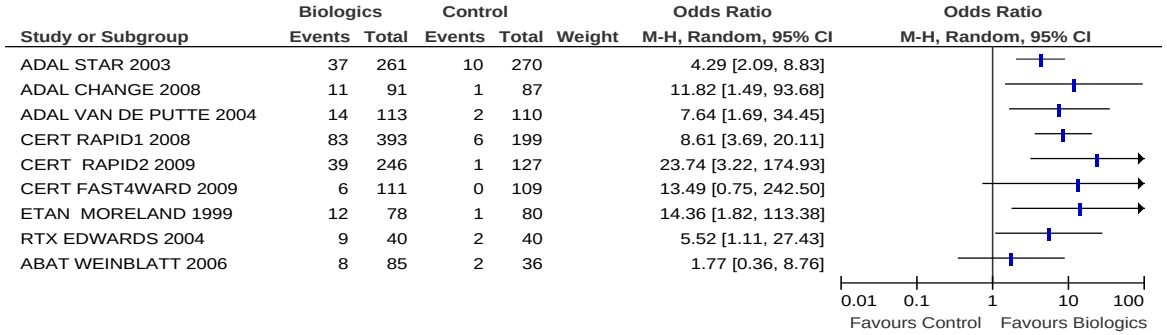
DIRECT META-ANALYSES

Drug, n Trials, OR (95% CI) (I^2 reported if ≥ 50%)

Subtotals
ADAL (n = 3): 6.24 (3.09 to 12.98)
ETAN (n = 2): 4.91 (1.01 to 23.76)
GOL (n = 1): 4.56 (1.82 to 11.45)
IFX (n = 2): 3.56 (1.82 to 6.94)
ABAT (n = 3): 3.72 (2.02 to 6.84)
ANAK (n = 2): 3.57 (1.35 to 9.38)
RTX (n = 1): 4.73 (1.86 to 12.05)

MTX-Experienced Patients (Excluded from Meta-Analyses)

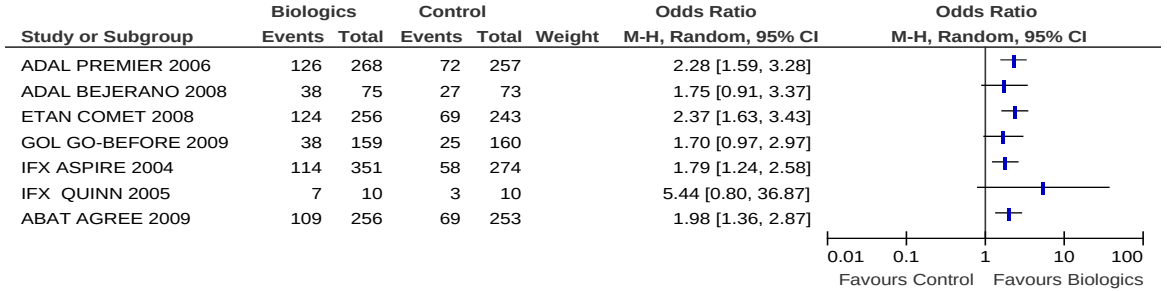
Trials where MTX is not used concomitantly at doses > 15 mg/week



Subtotals

NOTE: Trials not pooled because of clinical heterogeneity.

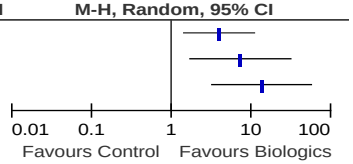
MTX-Naive Patients



Subtotals
ADAL (n = 2): 2.14 (1.56 to 2.94)
ETAN (n = 1): 2.37 (1.63 to 3.43)
GOL (n = 1): 1.70 (0.97 to 2.97)
IFX (n = 2): 2.07 (1.00 to 4.29)
ABAT: (N = 1): 1.98 (1.36 to 2.87)

Patients Who Are TNF-alpha Inhibitor Experienced

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
GOL GO-AFTER 2009	18	153	5	155		4.00 [1.45, 11.07]
ABAT ATTAIN 2005	26	256	2	133		7.40 [1.73, 31.70]
RTX REFLEX 2006	36	298	2	201		13.67 [3.25, 57.46]



Subtotals

GOL (n = 1): 4.00 (1.45 to 11.07)

ABAT (n = 1): 7.40 (1.73 to 31.70)

RTX (n = 1): 13.67 (3.25 to 57.46)

Table A8: Summary of Trial Outcomes, HAQ-DI absolute mean (SD) changes					
Drug	**Study**	**Control Δ BL, mean (SD)**	**Intervention Δ BL, mean (SD)**	**Mean Difference (95% CI)**	**HAQ-DI Results Reported via different methods**
MTX-Experienced (Concomitant MTX > 15 mg/week)					
ADAL	ARAMADA 2003	–0.27 (0.57)	–0.62 (0.63)	–0.35 (–0.56 to –0.14)	NA
	Keystone 2004	–0.24 (0.52)	–0.56 (0.52)	–0.32 (–0.45 to –0.23)	NA
	Kim 2007	–0.2 (0.5)	–0.50 (0.55)	–0.30 (–0.48 to –0.12)	NA
ETAN	TEMPO 2004 (52 weeks)	–0.6	–0.1	–0.4 (P < 0.0001)	NA
	Weinblatt 1999	NR	NR	NR	Change in median HAQ-DI was 1.5 in both groups. At 24 weeks, HAQ-DI was 0.8 in the ETAN group and 1.1 in the PL group (P < 0.001).
GOL	GO-FORWARD	–0.13 (0.58)	–0.47 (0.55)	–0.34 (SS)	Median change from baseline SS favouring GOL (P <0.001)
IFX	ATTRACT 2000	NR	NR	NR	SS improvements in HAQ-DI favouring IFX + MTX over MTX
	ATTEST 2008	NR	NR	NR	At 6 months, significantly more ABAT patients compared with PL patients achieved a ≥ 0.3-point improvement in HAQ-DI (61.5% versus 40.9%, P = 0.001). Similar results were observed for IFX compared with PL (58.8% versus 40.9%, P = 0.005). Mean % changes in HAQ-DI were similar between ABAT and IFX at 1 year (57.7% and 52.7%, respectively)
ABAT	Kremer 2003	NR	NR	NR	Mean % Δ BL SS better for ABAT (41.5% versus 14.1%, P <0.05).
	AIM 2006	NR	NR	NR	At 1 year, significantly more ABAT patients compared with control patients had a HAQ-DI improvement (63.7% versus 39.3%, P <0.001). The magnitude of the improvement was not defined.
	ATTEST 2008	NR	NR	NR	At 6 months, SS more ABAT patients than PL patients achieved a ≥ 0.3 point improvement in HAQ-DI (61.5% versus 40.9%, P = 0.001). Similar results were observed for IFX versus PL (58.8% versus 40.9%, P = 0.005). Mean % changes in HAQ-DI were similar between ABAT and IFX at 1 year (57.7% and 52.7% respectively)
ANAK	Cohen 2002	0.77 (NR)	–0.19 (NR)	–0.96 (P = 0.2)	NA
	Cohen 2004	–0.18 (0.48)	–0.29 (0.47)	–0.11 (–0.19 to –0.03)	NA
RTX	DANCER 2006	–0.16 (0.50)	–0.49 (0.60)	–0.33 (–0.47 to –0.19)	NA
MTX-Experienced (no concomitant MTX > 15 mg/week)					
ADAL	STAR 2003	NR	NR	NR	HAQ-DI measured as component of ACR, but results NR.
	Van De Putte 2004	–0.07 (0.49)	–0.38 (0.60)	–0.31(–0.45 to –0.17)	NA
	CHANGE 2008	+0.1 (0.6)	–0.20 (0.60)	–0.30 (–0.48 to –0.12)	NA

Table A8: Summary of Trial Outcomes, HAQ-DI absolute mean (SD) changes					
Drug	**Study**	**Control Δ BL, mean (SD)**	**Intervention Δ BL, mean (SD)**	**Mean Difference (95% CI)**	**HAQ-DI Results Reported via different methods**
CERT	RAPID1	–0.17 (0.56)	–0.58 (0.59)	–0.41 (–0.51 to –0.31)	NA
	RAPID2	–0.12 (0.45)	–0.44 (0.47)	–0.32 (–0.42 to –0.22)	NA
	FAST4WARD	0.13 (NR)	–0.36 (NR)	–0.49 (P <0.001)	NA
ETAN	Moreland 1999	NR	NR	NR	Mean % Δ BL was SS greater for ETAN (39% versus 2%, P<0.05)
	Combe 2009	NR	NR	NR	Mean HAQ-DI values SS greater in ETAN versus control at 2 years (P <0.001). Similarly, a greater % of ETAN + SULF patients achieved a HAQ-DI improvement of ≥ 0.22 compared with SULF alone (P <0.01).
MTX-Experienced (no concomitant MTX > 15 mg/week)					
IFX	Maini 1998	NR	NR	NR	HAQ-DI measured but results NR
ABAT	Weinblatt 2006	–0.26	–0.47	–0.21 (SS)	NA
ANAK	Fleischmann 2003	NR	NR	NR	Not reported and not measured.
RTX	Edwards 2004	NR	NR	NR	HAQ-DI measured as component of ACR, but results NR
MTX-Naive					
ADAL	PREMIER 2006	–0.9 (0.6)	–1 (0.7)	–0.10 (–0.21, 0.01)	NA
	Bejarano 2008	–0.4 (0.7)	–0.7 (0.6)	–0.3 (–0.5, –0.1)	NA
ETAN	COMET 2008	NR	NR	NR	At 52 weeks, significantly more ETAN patients compared with PL patients achieved an absolute HAQ-DI of 0.5 (55% versus 39%, Δ = 16% (95% CI 7.44% to 24.76%, P = 0.0004). The % of patients with improvement was greater in the ETAN group (61%, range from 1.7 to 0.7) compared with PL alone (44%, range from 1.6 to 0.9)
GOL	GO-BEFORE 2009	NR	NR	NR	Median % improvement NS (43.65 versus 36.95, P = 0.141, respectively)
IFX	ASPIRE 2004 (30 to 54 weeks)	–0.68 (0.63)	–0.8 (0.65)	–0.12 (P<0.001)	NA
	Quinn 2005	NR	NR	NR	Median % improvement: SS favouring IFX at 14, 54 and 104 weeks, (P <0.05).
TNF-alpha Inhibitor Experienced					
GOL	GO-AFTER 2009	–0.06 (0.51)	–0.20 (0.51)	–0.14 (SS)	SS favouring GOL for median % change from baseline (P = 0.0003)
ABAT	ATTAIN 2005	NR	NR	NR	% with HAQ-DI improvement ≥0.3 favouring ABAT (47.3% versus 23.3%, P <0.001) at 24 weeks.
RTX	REFLEX 2006	–0.10 (0.50)	–0.40 (0.60)	–0.30 (–0.40, –0.20)	NA

BL = baseline; NA = not applicable; NR = not reported; NS = not statistically significant; SS = statistically significant.

Table A9: Radiographic Progression, Reported Data from Randomized Controlled Trials					
Drug	**Study, Duration Analysis Population**	**outcome Measure**	**Treatment Groups**	**RP Change from Baseline, mean (SD)**	**Summary of Reported Findings**
TNF-alpha Inhibitors					
ADAL	Keystone 2004 52 weeks **MTX-exper**	mTSS	ADAL+MTX	+0.1 (4.8)	Differences in RP between ADAL and PL were SS at both 24 and 52 weeks, favouring ADAL; SS fewer joint erosions occurred ADAL versus PL patients [0.0 (2.8) versus 1.6 (4.4); P <0.01].
			PL+MTX	+2.7 (6.8)	
	PREMIER **MTX-naive**	vdH mTSS	ADAL+MTX	6 months: +0.8 (NR); 1 year: +1.3 (NR); 2 years: +1.9 (NR)	SS less RP, less change in erosion scores and less change in joint space narrowing scores at 6 months, 1 year, and 2 years in patients treated with ADAL compared to PL. The % of patients in each group with no RP (defined as Sharp score $\leq$0.5 from baseline) was SS greater in patients treated with ADAL compared with PL (64% versus 37% year 1; 61% versus 34% year 2).
			PL+MTX	6 months: +3.5 (NR); 1 year: +5.7 (NR); 2 years: +10.4 (NR)	
CERT	RAPID2 24 weeks —	vdH mTSS	CERT+MTX	+0.2 (95% CI –0.1 to 0.6)	SS less RP in the CERT group compared to the PL group (0.2 versus 1.2, P=0.003). Changes in erosion score and joint space narrowing score in the PL+MTX group were +0.7 (95% CI 0.3 to 1.2) and +0.5 (95% CI 0.1 to 0.9), while corresponding changes in the CERT+MTX group were +0.1 (95% CI –0.1 to 0.4) and +0.1 (95% CI –0.1 to 0.3).
			PL+MTX	+1.2 (95% CI 0.5 to 2.0)	
	RAPID1 52 weeks —	vdH mTSS	CERT+MTX	+0.4 (no SD)	Based on the change from BL in mTSS, CERT delayed worsening RP compared with PL (0.4 versus 2.8, P<0.001). Results were also described as SS in favour of CERT at 24 weeks. Analyses of erosion and joint space narrowing scores were also SS, favouring CERT.
			PL+MTX	+2.8 (no SD)	
ETAN	TEMPO 52 weeks **MTX-exper**	mTSS	ETAN+MTX	–0.54 (95% CI –1.0 to –0.07)	The difference between ETAN versus PL was SS (MD: –3.34, 95% CI –4.86 to –1.81, P <0.05). Patients treated with ETAN showed less change in erosion score than PL. Changes in joint space narrowing were NS between groups. There were more patients without progression (defined as a total Sharp score $\leq$0.05) in the ETAN group (80%; 95% CI 74% to 85%) than the PL group (57%; 95% CI 50% to 64%).
			PL+MTX	+2.80 (95% CI 1.08 to 4.51)	
	COMET 52 weeks **MTX-naive**	vdH mTSS	ETAN+MTX	0.27 (95% CI –0.13 to 0.68)	No difference comparing changes in mTSS between groups was reported. Radiographic non-progression (defined as mTSS of 0.5 or smaller) attained by 135/230 = 59% (95% CI 53% to 65%) of subjects in the PL group and 196/246 = 80% (95% CI 75% to 85%) in the ETAN group (P < 0.0001).
			PL+MTX	+2.44 (95% CI 1.45 to 3.43)	
IFX	ASPIRE 54 weeks **MTX-naive**	vdH mTSS	IFX+MTX	+0.4 (5.8)	RP was SS less in the IFX group than the PL group. Analyses of erosion and joint space narrowing scores favoured IFX. The % patients demonstrating radiographic progression which was above the SDD of vdH-S > 9.03 was less in the infliximab group (3.9% versus 11%).
			PL+MTX	+3.7 (9.6)	
	ATTRACT 54 weeks **MTX-exper**	vdH mTSS	IFX+MTX	+1.3 (6.0)	RP was SS less with IFX compared with PL (P <0.01); both the erosion and joint space narrowing scores were SS lower. Major progression (as defined by Lassere et al) was achieved by significantly fewer individuals receiving IFX (8%) than PL (31%).
			PL+MTX	+7 (10.3)	

Table A9: Radiographic Progression, Reported Data from Randomized Controlled Trials					
Drug	**Study, Duration Analysis Population**	**outcome Measure**	**Treatment Groups**	**RP Change from Baseline, mean (SD)**	**Summary of Reported Findings**
	Quinn 2005 104 weeks **MTX-naive**	vdH mTSS	IFX+MTX	+10 (no SD)	A trend toward less damage in those treated with IFX over time, differences between groups were not found to be statistically significant. The authors also noted that the study was not powered to show such differences and that the frequency of radiographic change was low.
			PL+MTX	+12 (no SD)	
GOL	GO-BEFORE 2009, 52 weeks **MTX-naive**	vdHS	GOL+MTX	+0.74 (5.23)	RP was SS less in the GOL group than the PL group as measured by the change from baseline (P = 0.015)
			PL+MTX	+1.37 (4.56)	
	GO-FORWARD 2009, 52 weeks **MTX-exper**	vdHS	GOL+MTX	+0.93 (4.86)	There was NS difference in RP between GOL and PL as measured by the change from baseline (P = 0.855)
			PL+MTX	+1.10 (4.68)	
T-CELL (CD28) Co-Stimulatory Modulators					
ABAT	AIM 2006 52 weeks **MTX-exper**	Genant modified Sharp score	ABAT+MTX	+2.32	Comparisons at 1 year showed a SS benefit in favour of ABAT compared with PL. Median changes in erosion scores were 0 (IQR 0-1) and +0.27 (IQR 0 to 1.3) for those treated with ABAT and PL, respectively (P<0.05; corresponding means were 0.63 and 1.14). Median changes in joint space narrowing scores were reported to be 0 (IQR 0 to 0.5) and 0 (IQR 0 to 1) in the ABAT and PL groups (P < 0.05; corresponding means were 0.58 and 1.18). Sensitivity analyses did not change findings.
			PL+MTX	+1.21	
	AGREE 2009 52 weeks **MTX-naive**	Genant modified Sharp score	ABAT+MTX	+0.63	At 1 year, both total scores and erosion scores were SS lower (P = 0.04 and P = 0.03) in patients receiving ABAT versus PL. Mean changes in joint space narrowing scores were NSS different (P = 0.35). Results were similar in an analysis of completers only. At 1 year, the % patients with no progression (total score $\leq$ 0) were 61.2% and 52.9% in the ABAT and PL groups respectively.
			PL+MTX	+1.06	
IL-1 Antagonists					
No data available					
CD20+ B-Lymphocyte Inhibitors					
RTX	REFLEX 2006 24, 52 weeks **TNFi-exper**	Genant modified Sharp score	RTX+MTX 24 weeks: +0.6 (1.9)	56 weeks: +1.0 (NR)	At 24 weeks, NS difference between groups in the mean changes in Genant modified Sharp score (P = 0.169), erosion scores [RTX: 0.4 (1.3) versus PL: 0.8 (2.0)] or % patients with no new erosions (66% versus 60%, P = 0.148). Changes in joint space narrowing scores were SS favouring RTX [RTX: 0.2 (0.8) versus PL: 0.5 (1.5)]. At 52 weeks, RP was SS lower for RTX versus PL (1.00 versus 2.31, P = 0.005) as were erosion scores (0.59 versus 1.32, P = 0.011) and joint space narrowing scores (0.41 versus 0.99, P<0.001).
			PL+MTX	24 weeks: +1.2 (3.3) 56 weeks: +2.31 (NR)	

ABAT = abatacept; ADAL = adalimumab; ANAK = anakinra; CERT = certolizumab pegol; eow = every other week; ETAN = etanercept; GOL = golimumab; IFX = infliximab; mTSS = modified Total Sharp Score; MTX = methotrexate; ND = not defined; NR = not reported; RITUX = rituximab; RP = radiographic progression; RR = relative risk; TNF = tumor necrosis factor-alpha; vdH mTSS = van der Heijde modified Total Sharp Score.

Figure A6: Proportion of Patients with SAEs, Data from Individual RCTs and Direct Estimates from Meta-Analyses

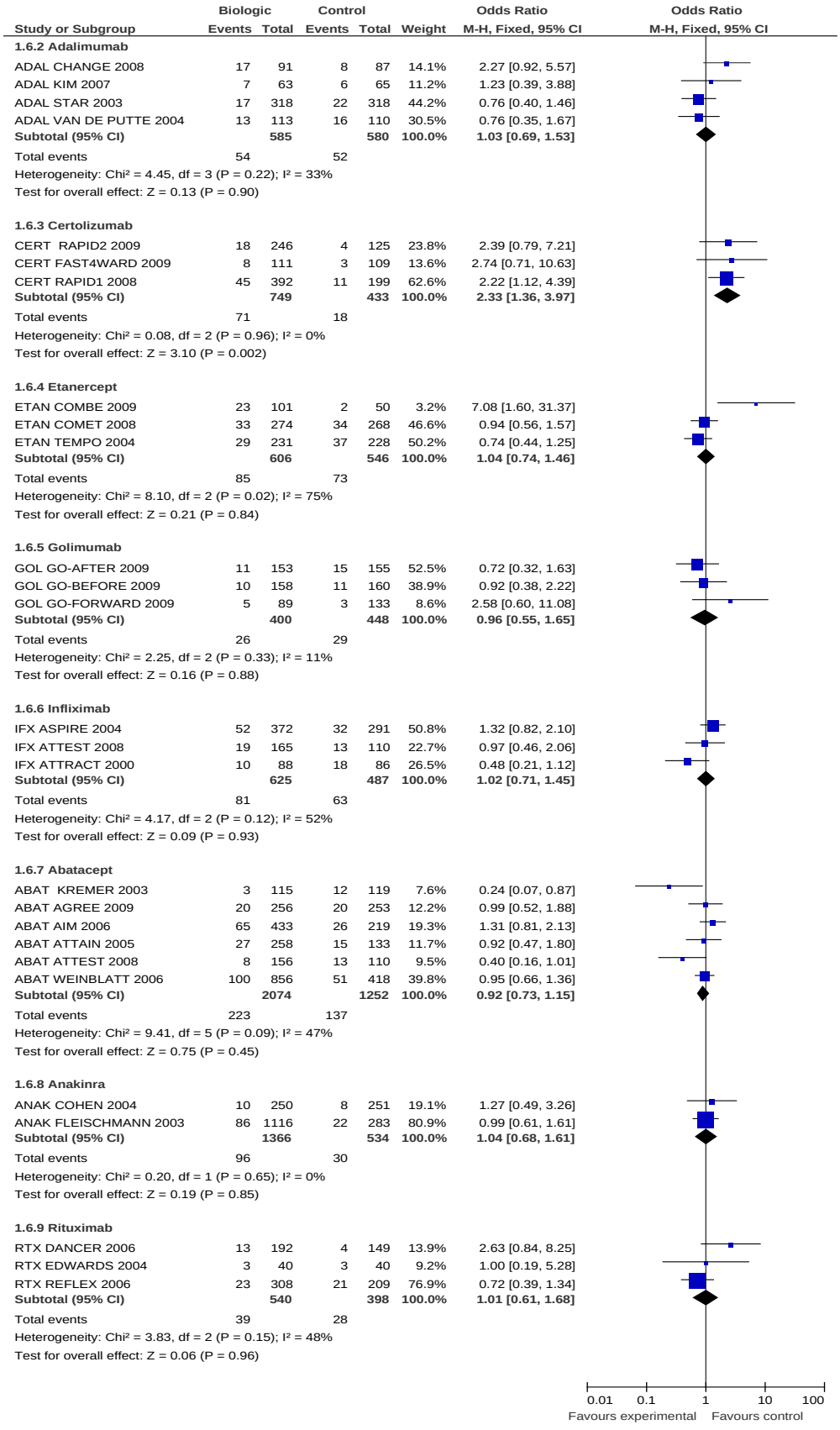
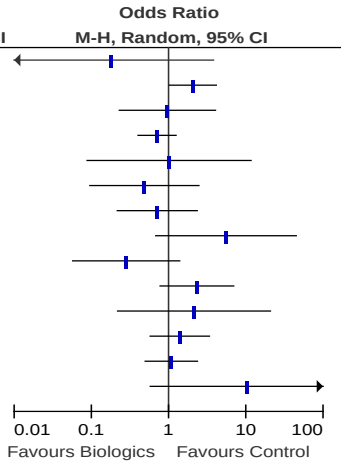


Figure A7: WDAE, Data from Individual Randomized Controlled Trials and Direct Estimates from Meta-Analyses

MTX-Experienced Patients (included in meta-analyses)

Trials where MTX is used concomitantly at doses > 15 mg/week

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ADAL ARMADA 2003	0	67	2	62		0.18 [0.01, 3.81]
ADAL KEYSTONE 2004	26	207	13	200		2.07 [1.03, 4.15]
ADAL KIM 2007	4	65	4	63		0.97 [0.23, 4.05]
ETAN TEMPO 2004	24	231	32	228		0.71 [0.40, 1.25]
ETAN WEINBLATT 1999	2	59	1	30		1.02 [0.09, 11.69]
GOL GO-FORWARD 2009	2	89	6	133		0.49 [0.10, 2.47]
IFX ATTRACT 2000	5	86	7	88		0.71 [0.22, 2.34]
IFX ATTEST 2008	8	165	1	110		5.55 [0.68, 45.05]
ABAT KREMER 2003	2	115	7	119		0.28 [0.06, 1.39]
ABAT AIM 2006	18	433	4	219		2.33 [0.78, 6.97]
ABAT ATTEST 2008	3	156	1	110		2.14 [0.22, 20.82]
ANAK COHEN 2002	19	131	8	74		1.40 [0.58, 3.38]
ANAK COHEN 2004	14	250	13	251		1.09 [0.50, 2.36]
RTX DANCER 2006	6	192	0	149		10.42 [0.58, 186.47]



DIRECT META-ANALYSES

Drug, n Trials, OR (95% CI) (I^2 reported if ≥ 50%)

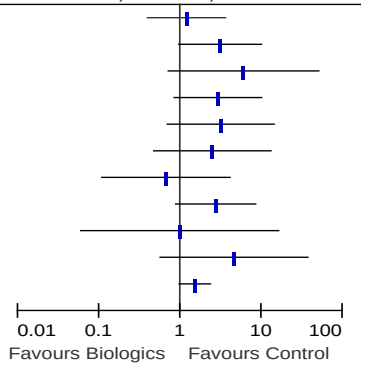
Subtotals

ADAL (n = 3) : 1.33 (0.51 to 3.45)
ETAN (n = 2) : 0.72 (0.42 to 1.25)
GOL (n = 1) : 0.49 (0.10 to 2.47)
IFX (n = 2): 1.66 (0.22 to 12.66) (I2 = 66%)
ABAT (n = 3): 1.13 (0.27 to 4.68)
ANAK (n = 2): 1.21 (0.68 to 2.17)
RTX (n = 1): 10.42 (0.58 to 186.47)

MTX-Experienced Patients (excluded from meta-analyses)

Trials where MTX is not used concomitantly at doses > 15 mg/week

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Odds Ratio M-H, Random, 95% CI
ADAL STAR 2003	7	261	6	270	1.21 [0.40, 3.66]
ADAL CHANGE 2008	12	91	4	87	3.15 [0.98, 10.18]
ADAL VAN DE PUTTE 2004	6	113	1	110	6.11 [0.72, 51.63]
CERT RAPID1 2008	17	393	3	199	2.95 [0.86, 10.20]
CERT RAPID2 2009	12	246	2	127	3.21 [0.71, 14.55]
CERT FAST4WARD 2009	5	111	2	109	2.52 [0.48, 13.29]
ETAN MORELAND 1999	2	78	3	80	0.68 [0.11, 4.16]
ETAN COMBE 2008	20	103	4	50	2.77 [0.89, 8.60]
RTX EDWARDS 2004	1	40	1	40	1.00 [0.06, 16.56]
ABAT WEINBLATT 2006	10	85	1	36	4.67 [0.57, 37.90]
ANAK FLEISCHMANN 2003	150	1116	26	283	1.53 [0.99, 2.38]

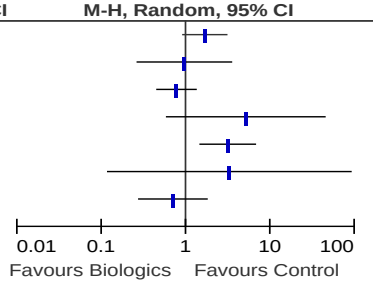


Subtotals

NOTE: Trials not pooled because of clinical heterogeneity

MTX-Naive Patients

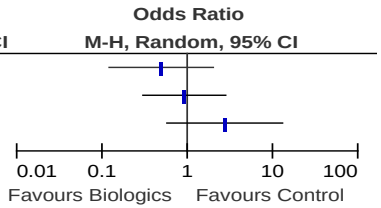
Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Odds Ratio M-H, Random, 95% CI
ADAL PREMIER 2006	32	268	19	257	1.70 [0.94, 3.08]
ADAL BEJERANO 2008	5	75	5	73	0.97 [0.27, 3.51]
ETAN COMET 2008	28	274	34	268	0.78 [0.46, 1.33]
GOL GO-BEFORE 2009	5	158	1	160	5.20 [0.60, 44.99]
IFX ASPIRE 2004	34	359	9	282	3.17 [1.50, 6.73]
IFX QUINN 2005	1	10	0	10	3.32 [0.12, 91.60]
ABAT AGREE 2009	8	256	11	253	0.71 [0.28, 1.79]



Subtotals
ADAL (n = 2): 1.54 (0.90, 2.64)
ETAN (n = 1): 0.78 (0.46, 1.33)
GOL (n = 1): 5.20 (0.60, 44.99)
IFX (n = 2): 3.18 (1.53, 6.62)
ABAT: (N = 1): 0.71 (0.28, 1.79)

Patients Who Are TNF-alpha Inhibitor Experienced

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Odds Ratio M-H, Random, 95% CI
GOL GO-AFTER 2009	3	153	6	155	0.50 [0.12, 2.02]
ABAT ATTAIN 2005	9	258	5	133	0.93 [0.30, 2.82]
RTX REFLEX 2006	8	308	2	209	2.76 [0.58, 13.13]



Subtotals
GOL (n = 1): 0.50 (0.12 to 2.02)
ABAT (n = 1): 0.93 (0.30 to 2.82)
RTX (n = 1): 2.76 (0.58 to 13.13)

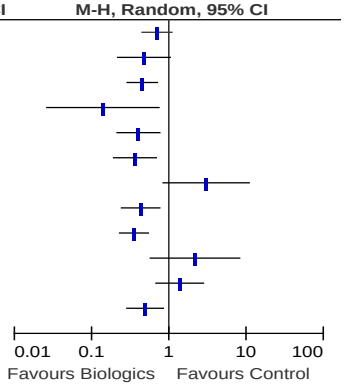
Note: WDAEs reported at 24 weeks for all trials except the following, for which WDAEs were only reported at one or two years: Keystone 2004, PREMIER 2006, Bejarano 2008, RAPID-1 2008, TEMPO 2004, COMET 2008, Combe 2008, ATTRACT 2000, ASPIRE 2004, Quinn 2005, Kremer 2006 and AGREE 2009.

Figure A8: All-Cause Withdrawals, Data from Individual Randomized Controlled Trials and Direct Estimates from Meta-Analyses

MTX-Experienced Patients (Included in Meta-Analyses)

Trials where MTX is used concomitantly at doses > 15 mg/week

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
ADAL KEYSTONE 2004	48	207	60	200		0.70 [0.45, 1.10]
ADAL KIM 2007	14	65	23	63		0.48 [0.22, 1.04]
ETAN TEMPO 2004	38	231	69	228		0.45 [0.29, 0.71]
ETAN WEINBLATT 1999	2	59	6	30		0.14 [0.03, 0.75]
GOL GO-FORWARD 2009	17	89	49	133		0.40 [0.21, 0.76]
IFX ATTRACT 2000	23	86	44	88		0.37 [0.19, 0.69]
IFX ATTEST 2008	13	165	3	110		3.05 [0.85, 10.97]
ABAT KREMER 2003	26	115	48	119		0.43 [0.24, 0.76]
ABAT AIM 2006	48	433	57	219		0.35 [0.23, 0.54]
ABAT ATTEST 2008	9	156	3	110		2.18 [0.58, 8.26]
ANAK COHEN 2002	32	131	14	74		1.39 [0.68, 2.80]
RTX DANCER 2006	27	129	52	149		0.49 [0.29, 0.85]



DIRECT META-ANALYSES (I^2 reported if ≥ 50%)

Drug, n Trials, OR (95% CI)

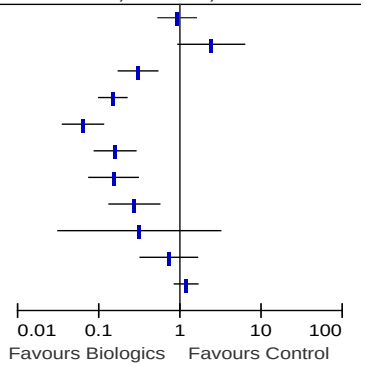
Subtotals

ADAL (n = 3) : 0.64 (0.44, 0.94)
ETAN (n = 2) 0.34 (0.12, 0.92)
GOL (n = 1) : 0.40 (0.21, 0.76)
IFX (n = 2): 0.98 (0.12, 7.94) (I^2: 88%)
ABAT (n = 3): 0.53 (0.26, 1.07) (I^2 = 69%)
ANAK (n = 2): 1.39 (0.68, 2.80)
RTX (n = 1): 0.49 (0.29, 0.85)

MTX-Experienced Patients (Excluded from Meta-Analyses)

Trials where MTX is not used concomitantly at doses > 15 mg/week

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Odds Ratio M-H, Random, 95% CI
ADAL STAR 2003	28	318	30	318	0.93 [0.54, 1.59]
ADAL CHANGE 2008	16	91	7	87	2.44 [0.95, 6.26]
ADAL VAN DE PUTTE 2004	32	113	62	110	0.31 [0.18, 0.53]
CERT RAPID1 2008	138	393	156	199	0.15 [0.10, 0.22]
CERT RAPID2 2009	72	246	110	127	0.06 [0.04, 0.11]
CERT FAST4WARD 2009	35	111	81	109	0.16 [0.09, 0.29]
ETAN MORELAND 1999	19	79	54	80	0.15 [0.08, 0.31]
ETAN COMBE 2008	38	103	34	50	0.28 [0.13, 0.56]
RTX EDWARDS 2004	1	40	3	40	0.32 [0.03, 3.18]
ABAT WEINBLATT 2006	27	85	14	36	0.73 [0.33, 1.65]
ANAK FLEISCHMANN 2003	241	1116	53	283	1.20 [0.86, 1.66]

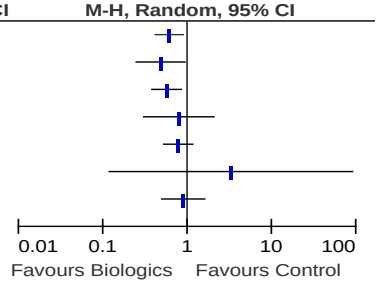


Subtotals

NOTE: Trials not pooled because of clinical heterogeneity

MTX-Naive Patients

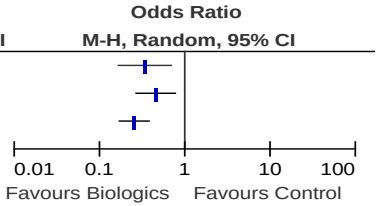
Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Odds Ratio M-H, Random, 95% CI
ADAL PREMIER 2006	65	268	88	257	0.61 [0.42, 0.90]
ADAL BEJERANO 2008	25	75	37	73	0.49 [0.25, 0.95]
ETAN COMET 2008	53	274	79	268	0.57 [0.39, 0.85]
GOL GO-BEFORE 2009	8	158	10	160	0.80 [0.31, 2.08]
IFX ASPIRE 2004	63	359	60	282	0.79 [0.53, 1.17]
IFX QUINN 2005	1	10	0	10	3.32 [0.12, 91.60]
ABAT AGREE 2009	24	256	26	253	0.90 [0.50, 1.62]



Subtotals
ADAL (n = 2): 0.58 (0.42 to 0.81)
ETAN (n = 1): 0.57 (0.39 to 0.85)
GOL (n = 1): 0.80 (0.31 to 2.08)
IFX (n = 2): 0.80 (0.54 to 1.19)
ABAT: (N = 1): 0.90 (0.50 to 1.62)

Patients Who Are TNF-alpha Inhibitor Experienced

Study or Subgroup	Biologics Events	Biologics Total	Control Events	Control Total	Odds Ratio M-H, Random, 95% CI
GOL GO-AFTER 2009	12	153	31	155	0.34 [0.17, 0.69]
ABAT ATTAIN 2005	35	258	34	133	0.46 [0.27, 0.77]
RTX REFLEX 2006	55	308	96	209	0.26 [0.17, 0.38]



Subtotals
GOL (n = 1): 0.34 (0.17 to 0.69)
ABAT (n = 1): 0.46 (0.27 to 0.77)
RTX (n = 1): 0.26 (0.17 to 0.38)

Note: Withdrawals reported at 24 weeks for all trials except the following, for which withdrawals were only reported at one or two years: Keystone 2004, PREMIER 2006, Bejarano 2008, RAPID-1 2008, TEMPO 2004, COMET 2008, Combe 2008, ATTRACT 2000, ASPIRE 2004, Quinn 2005, Kremer 2006 and AGREE 2009.

Summary of Outcomes: Indirect Estimates from MTC Meta-Analyses

Table A10: Summary of Outcomes, Results from MTC Random Effects Meta-Analyses, MTX-Experienced Patients (concomitant MTX > 15 mg/week)

Intervention	ACR 20, OR (95% CrI)	ACR 50, OR (95% CrI)	ACR 70, OR (95% CrI)	WDAEs, OR (95% CrI)
Comparisons with control as reference group				
adalimumab	4.81 (2.59 to 9.84)	7.03 (3.64 to 14.39)	5.67 (2.16 to 15.12)	1.16 (0.2 to 3.82)
abatacept	2.95 (1.58 to 5.45)	3.34 (1.84 to 6.25)	4.02 (1.81 to 11.42)	1.29 (0.36 to 5.37)
infliximab	2.55 (1.19 to 5.84)	2.6 (1.18 to 6.09)	3.8 (1.23 to 13.73)	1.64 (0.34 to 10.28)
anakinra	2.19 (0.99 to 4.88)	3.04 (1.4 to 8.15)	4.94 (1.4 to 30.8)	1.23 (0.28 to 5.46)
etanercept	2.89 (1.4 to 7.59)	3.83 (2.03 to 11.95)	3.97 (1.61 to 22.97)	0.75 (0.16 to 4.15)
rituximab	3.09 (1.03 to 9.23)	3.41 (1.14 to 10.42)	5 (1.01 to 26.23)	NE*
golimumab	3.85 (1.28 to 11.71)	3.79 (1.26 to 11.66)	4.75 (0.95 to 25.01)	0.42 (0.02 to 4.78)
Comparisons with adalimumab as reference group				
abatacept	0.61 (0.24 to 1.45)	0.48 (0.18 to 1.17)	0.71 (0.21 to 3.01)	1.12 (0.21 to 11.51)
infliximab	0.53 (0.19 to 1.48)	0.37 (0.13 to 1.07)	0.67 (0.15 to 3.37)	1.43 (0.21 to 20.31)
anakinra	0.46 (0.16 to 1.24)	0.43 (0.15 to 1.4)	0.87 (0.19 to 7.15)	1.06 (0.18 to 11.24)
etanercept	0.6 (0.22 to 1.89)	0.55 (0.22 to 2.06)	0.71 (0.2 to 5.41)	0.65 (0.1 to 8.28)
rituximab	0.64 (0.17 to 2.2)	0.49 (0.13 to 1.73)	0.88 (0.14 to 5.97)	NE
golimumab	0.8 (0.21 to 2.79)	0.54 (0.14 to 1.95)	0.84 (0.13 to 5.66)	0.37 (0.02 to 7.92)
Comparisons with abatacept as reference group				
infliximab	0.86 (0.33 to 2.46)	0.78 (0.29 to 2.2)	0.94 (0.2 to 4.13)	1.27 (0.16 to 12.04)
anakinra	0.74 (0.27 to 2.07)	0.91 (0.34 to 2.91)	1.22 (0.26 to 8.74)	0.97 (0.12 to 6.67)
etanercept	0.97 (0.39 to 3.18)	1.15 (0.5 to 4.28)	1 (0.27 to 6.6)	0.59 (0.07 to 4.93)
rituximab	1.05 (0.3 to 3.7)	1.02 (0.28 to 3.61)	1.23 (0.17 to 7.44)	NE
golimumab	1.3 (0.37 to 4.66)	1.13 (0.32 to 4.01)	1.18 (0.16 to 6.95)	0.32 (0.01 to 5.06)
Comparisons with infliximab as reference group				
anakinra	0.86 (0.27 to 2.56)	1.17 (0.38 to 4.15)	1.31 (0.24 to 11.27)	0.76 (0.07 to 6.4)
etanercept	1.14 (0.39 to 3.92)	1.49 (0.55 to 6)	1.06 (0.24 to 8.72)	0.47 (0.04 to 4.54)
rituximab	1.21 (0.3 to 4.56)	1.31 (0.32 to 5.11)	1.33 (0.16 to 9.56)	NE
golimumab	1.5 (0.37 to 5.69)	1.46 (0.36 to 5.65)	1.25 (0.16 to 9)	0.25 (0.01 to 4.41)

Table A10: Summary of Outcomes, Results from MTC Random Effects Meta-Analyses, MTX-Experienced Patients (concomitant MTX > 15 mg/week)				
Intervention	**ACR 20, OR (95% CrI)**	**ACR 50, OR (95% CrI)**	**ACR 70, OR (95% CrI)**	**WDAEs, OR (95% CrI)**
Comparisons with anakinra as reference group				
etanercept	1.32 (0.47 to 4.72)	1.28 (0.43 to 4.9)	0.83 (0.12 to 6.24)	0.61 (0.07 to 5.99)
rituximab	1.41 (0.36 to 5.46)	1.12 (0.25 to 4.16)	1.02 (0.08 to 7.17)	NE
golimumab	1.76 (0.45 to 6.83)	1.24 (0.27 to 4.71)	0.96 (0.08 to 6.84)	0.33 (0.01 to 5.8)
Comparisons with etanercept as reference group				
rituximab	1.07 (0.23 to 3.77)	0.89 (0.17 to 2.87)	1.23 (0.1 to 7.18)	NE
golimumab	1.33 (0.29 to 4.75)	0.98 (0.19 to 3.22)	1.17 (0.1 to 6.8)	0.54 (0.02 to 9.77)
Comparisons with rituximab as reference group				
golimumab	1.24 (0.26 to 5.9)	1.11 (0.23 to 5.32)	0.95 (0.1 to 9.49)	NE

CrI = credible interval; NE = not estimable; OR = odds ratio; WDAE = withdrawal due to adverse events
Note: For interpretation of MTC tables, each reference group allows for comparisons with all biologic agents, e.g., to compare the relative efficacy of adalimumab with golimumab, see section on Comparisons with adalimumab as reference group. With each successive reference group, fewer comparisons are presented as the inverse would have been presented previously in the table, e.g., in the section on Comparisons with golimumab as reference group, there is no comparison with adalimumab. Fixed effects MTC meta-analyses were also conducted for comparative purposes; similar non-significant results were observed, but with narrower CrI.
* MTC estimates of WDAEs relative to rituximab were not estimable due to the availability of only one trial providing estimates with zero events in one group in that trial; therefore, the model did not converge. MTC analyses were run including and excluding RTX and similar estimates were observed.

Table A11: Summary of Outcomes, Results from MTC Random Effects Meta-Analyses, MTX-Naive Patients				
Intervention	**ACR 20, OR (95% CrI)**	**ACR 50, OR (95% CrI)**	**ACR 70, OR (95% CrI)**	**WDAE, OR (95% CrI)**
Comparisons with control as reference group				
adalimumab	1.87 (0.59 to 6.33)	1.77 (0.47 to 6.48)	2.09 (0.55 to 7.52)	1.45 (0.27 to 6.62)
abatacept	NA	1.85 (0.3 to 11.55)	1.99 (0.32 to 12.16)	0.7 (0.07 to 6.68)
infliximab	1.54 (0.5 to 6.97)	2.11 (0.7 to 12.77)	2.12 (0.68 to 12.35)	3.77 (0.67 to 40.06)
etanercept	3.02 (0.58 to 15.61)	2.51 (0.4 to 15.64)	2.38 (0.38 to 14.47)	0.78 (0.09 to 6.81)
golimumab	1.65 (0.32 to 8.6)	1.61 (0.26 to 10.1)	1.69 (0.27 to 10.71)	7.12 (0.42 to 324.8)
Comparisons with adalimumab as reference group				
abatacept	NA	1.04 (0.11 to 10.09)	0.95 (0.1 to 9.16)	0.48 (0.03 to 8.43)
infliximab	0.83 (0.16 to 5.59)	1.19 (0.24 to 12.15)	1.01 (0.2 to 10.21)	2.62 (0.29 to 52.15)
etanercept	1.61 (0.2 to 11.73)	1.42 (0.15 to 13.58)	1.14 (0.13 to 10.99)	0.53 (0.04 to 8.72)
golimumab	0.88 (0.11 to 6.62)	0.91 (0.1 to 8.93)	0.81 (0.09 to 8.11)	5.06 (0.21 to 313.6)
Comparisons with abatacept as reference group				
infliximab	NA	1.13 (0.16 to 16.72)	1.06 (0.15 to 15.5)	5.46 (0.35 to 155.4)
etanercept	NA	1.36 (0.1 to 17.91)	1.2 (0.09 to 16.05)	1.11 (0.05 to 25.63)
golimumab	NA	0.87 (0.07 to 11.5)	0.85 (0.06 to 11.53)	10.46 (0.28 to 825.4)
Comparisons with infliximab as reference group				
etanercept	1.96 (0.19 to 13.39)	1.2 (0.08 to 8.69)	1.13 (0.08 to 8.44)	0.21 (0.01 to 2.97)
golimumab	1.07 (0.11 to 7.4)	0.76 (0.05 to 5.64)	0.8 (0.06 to 6.08)	1.84 (0.05 to 114)
Comparisons with etanercept as reference group				
golimumab	0.55 (0.05 to 5.67)	0.64 (0.05 to 8.54)	0.71 (0.05 to 9.38)	9.31 (0.27 to 681.9)

CrI = credible interval; OR = odds ratio; WDAE = withdrawal due to adverse events
Note: Trials evaluating certolizumab pegol, rituximab, and anakinra were not available in MTX-naive patients for this analysis.
Fixed effects MTC meta-analyses were also conducted for comparative purposes; similar non-significant results were observed but with narrower credible intervals.

Table A12: Summary of Outcomes Results from MTC Random Effects Meta-Analyses, Patients Who Are TNF-alpha Inhibitor Experienced

Intervention	ACR 20, OR (95% CrI)	ACR 50, OR (95% CrI)	ACR 70, OR (95% CrI)	WDAE, OR (95% CrI)
Comparisons with control as reference group				
abatacept	4.24 (0.33 to 54.21)	7.02 (0.51 to 101.7)	8.89 (0.55 to 187.9)	0.96 (0.07 to 14.55)
rituximab	4.81 (0.37 to 61.01)	7.31 (0.56 to 96.33)	16.59 (1.02 to 351.5)	3.23 (0.19 to 70.56)
golimumab	2.58 (0.2 to 33.3)	4.28 (0.31 to 59.76)	4.26 (0.3 to 63.89)	0.46 (0.03 to 7.55)
Comparisons with abatacept as reference group				
rituximab	1.14 (0.03 to 41.86)	1.04 (0.03 to 41.13)	1.87 (0.03 to 116.9)	3.39 (0.07 to 199.8)
golimumab	0.61 (0.02 to 22.83)	0.61 (0.01 to 25.09)	0.47 (0.01 to 23.06)	0.48 (0.01 to 23.49)
Comparisons with rituximab as reference group				
golimumab	0.54 (0.01 to 20.1)	0.59 (0.01 to 23.48)	0.25 (0 to 12.53)	0.14 (0 to 7.72)

CrI = credible interval; OR = odds ratio; WDAE = withdrawal due to adverse events
Note: Trials evaluating adalimumab, etanercept, infliximab, certolizumab pegol and anakinra were not available in patients who are TNF-alpha inhibitor experienced for this analysis. Fixed effects MTC meta-analyses were also conducted for comparative purposes; similar non-significant results were observed but with narrower credible intervals.

Detailed MTC Results

Methotrexate-Experienced Patients

The following tables are all based on random effect meta-analyses and include only trials conducted in methotrexate-experienced patients that evaluated biologic agents in combination with methotrexate with an adequate methotrexate dose (≥ 15 mg/week).

Trials included in this analysis were: ARMADA 2003, Keystone 2004, Kim 2007, TEMPO 2004, Weinblatt 1999, GO-FORWARD 2009, ATTRACT, ATTEST 2008, Kremer 2003, AIM 2006, Cohen 2002, Cohen 2004, DANCER 2006.

The following trials conducted in methotrexate-experienced patients were excluded from the MTC meta-analyses for the following reasons:

- STAR 2003 evaluating adalimumab (concomitant DMARDs, not methotrexate)
- Weinblatt 2006 evaluating abatacept (concomitant DMARDs, not methotrexate)
- Fleischman 2003 evaluating anakinra (concomitant DMARDs, not methotrexate)
- Combe 2009 evaluating etanercept (concomitant sulfasalzine, not methotrexate)
- Van de Putte 2004 (monotherapy)
- CHANGE 2008 evaluating adalimumab (monotherapy)
- FAST4WARD 2009 evaluating certolizumab pegol (monotherapy)
- Moreland 1999 evaluating etanercept (monotherapy)
- RAPID1 evaluating certolizumab pegol (low methotrexate dose, mean/median < 15 mg/week)
- RAPID2 evaluating certolizumab pegol (low methotrexate dose, mean/median < 15 mg/week)
- Maini 1998 evaluating infliximab (low methotrexate dose, mean/median < 15 mg/week)
- Edwards 2004 evaluating rituximab (low methotrexate dose, mean/median < 15 mg/week)

There were no trials evaluating certolizumab pegol that met these inclusion criteria, therefore, certolizumab pegol could not be included in this network analysis.

Table A13: ACR 20, MTC Results versus Control, MTX-Experienced Patients

Intervention	Number of Trials	Number of Patients	MTC Estimate, OR (95% CrI)	Direct Estimate, OR (95% CI)
TNF-alpha Inhibitors				
Adalimumab	3	664	4.81 (2.59 to 9.84)	4.88 (2.43 to 9.78)
Etanercept	2	548	2.89 (1.4 to 7.59)	3.35 (0.99 to 11.39)
Golimumab	1	222	3.85 (1.28 to 11.71)	3.82 (2.16 to 6.74)
Infliximab	2	449	2.55 (1.19 to 5.84)	2.51 (1.50 to 4.23)
T-cell (CD28) Co-Stimulatory Modulators				
Abatacept	2	1,138	2.95 (1.58 to 5.45)	3.00 (2.34 to 3.85)
IL-1 Antagonists				
Anakinra	2	654	2.19 (0.99 to 4.88)	2.18 (1.53 to 3.09)
CD20+ B-Lymphocyte Inhibitors				
Rituximab	1	244	3.09 (1.03 to 9.23)	3.05 (1.79 to 5.20)

Table A14: ACR 50, MTC Results versus Control, MTX-Experienced Patients				
Intervention	**Number of Trials**	**Number of Patients**	**MTC Estimate, OR (95% CrI)**	**Direct Estimate, OR (95% CI)**
TNF-alpha Inhibitors				
Adalimumab	3	664	7.03 (3.64 to 14.39)	6.72 (3.93 to 11.48)
Etanercept	2	548	3.83 (2.03 to 11.95)	5.62 (0.99 to 31.83)
Golimumab	1	222	3.79 (1.26 to 11.66)	3.76 (1.95 to 7.26)
Infliximab	2	449	2.6 (1.18 to 6.09)	2.52 (1.56 to 4.08)
T-cell (CD28) Co-Stimulatory Modulators				
Abatacept	2	1138	3.34 (1.84 to 6.25)	3.28 (2.44 to 4.41)
IL-1 Antagonists				
Anakinra	2	654	3.04 (1.4 to 8.15)	2.95 (1.37 to 6.36)
CD20+ B-Lymphocyte Inhibitors				
Rituximab	1	244	3.41 (1.14 to 10.42)	3.35 (1.76 to 6.40)

Table A15: ACR 70, MTC Results versus Control, MTX-Experienced Patients				
Intervention	**Number of Trials**	**Number of Patients**	**MTC Estimate, OR (95% CrI)**	**Direct Estimate, OR (95% CI)**
TNF-alpha Inhibitors				
Adalimumab	3	664	5.67 (2.16 to 15.12)	6.34 (3.09 to 12.98)
Etanercept	2	548	3.97 (1.61 to 22.97)	4.91 (1.01 to 23.76)
Golimumab	1	222	4.75 (0.95 to 25.01)	4.56 (1.82 to 11.45)
Infliximab	2	449	3.8 (1.23 to 13.73)	3.56 (1.82 to 6.94)
T-cell (CD28) Co-Stimulatory Modulators				
Abatacept	3	1138	4.02 (1.81 to 11.42)	3.72 (2.02 to 6.84)
IL-1 Antagonists				
Anakinra	2	654	4.94 (1.4 to 30.8)	3.57 (1.35 to 9.38)
CD20+ B-Lymphocyte Inhibitors				
Rituximab	1	244	5 (1.01 to 26.23)	4.73 (1.86 to 12.05)

Table A16: WDAEs, MTC Results versus Control, MTX-Experienced Patients				
Intervention	**Number of Trials**	**Number of Patients**	**MTC Estimate, OR (95% CrI)**	**Direct Estimate, OR (95% CI)**
TNF-alpha Inhibitors				
Adalimumab	3	664	1.16 (0.2 to 3.82)	1.33 (0.51 to 3.45)
Etanercept	2	548	0.75 (0.16 to 4.15)	0.72 (0.42 to 1.25)
Golimumab	1	222	0.42 (0.02 to 4.78)	0.49 (0.1 to 2.47)
Infliximab	2	449	1.64 (0.34 to 10.28)	1.66 (0.22 to 12.66)
T-cell (CD28) Co-Stimulatory Modulators				
Abatacept	3	1152	1.29 (0.36 to 5.37)	1.13 (0.27 to 4.68)
IL-1 Antagonists				
Anakinra	2	706	1.23 (0.28 to 5.46)	1.21 (0.68 to 2.17)
CD20+ B-Lymphocyte Inhibitors				
Rituximab	1	341	NE	10.42 (0.58 to 186.47)

Table A17: Summary of Sensitivity Analyses for ACR 50 in MTX-Experienced Patients — MTC Estimate of Effect versus Control								
Analysis	**Adalimumab**	**Abatacept**	**Infliximab**	**Anakinra**	**Etanercept**	**Rituximab**	**Golimumab**	**Certolizumab**
Primary MTC analysis	7.03 (3.64 to 14.39)	3.34 (1.84 to 6.25)	2.6 (1.18 to 6.09)	3.04 (1.4 to 8.15)	3.83 (2.03 to 11.95)	3.41 (1.14 to 10.42)	3.79 (1.26 to 11.66)	NA
Meta-regressions adjusting for:								
Control group response rate	5.09 (2.77 to 9.73)	3.41 (2.18 to 5.38)	2.6 (1.34 to 4.98)	1.81 (0.8 to 4.24)	12.18 (3.98 to 56.36)	2.87 (1.21 to 7.05)	3.35 (1.4 to 8.09)	NA
Baseline duration of disease (years)	6.02 (3.13 to 12.66)	3.47 (1.96 to 6.44)	2.68 (1.22 to 6.01)	2.79 (1.34 to 7.63)	4.44 (2.24 to 12.74)	2.93 (0.97 to 8.79)	5.86 (1.78 to 21.45)	NA
Sensitivity analyses with removal of studies with:								
> 30% withdrawal in the control group	15.04 (5.68 to 49.04)	3.09 (2.24 to 4.32)	2.37 (1.36 to 4.27)	2.82 (1.71 to 4.83)	26.14 (4.35 to 723.2)	NA	3.82 (2 to 7.53)	NA
Data reported beyond 24 weeks	6.86 (4.55 to 10.57)	3.31 (2.47 to 4.48)	2.37 (1.37 to 4.25)	2.82 (1.7 to 4.82)	26.45 (4.24 to 806.5)	3.41 (1.81 to 6.7)	3.82 (1.99 to 7.51)	NA

Methotrexate-Naive Patients

The following tables are all based on random effect meta-analyses and include only trials conducted in methotrexate-naive patients. There were no trials evaluating certolizumab pegol, rituximab, or anakinra that met these inclusion criteria; therefore, they could not be included in this network analysis. The following trials were included in this analysis: PREMIER 2006, Bejarano 2008, COMET 2008, GO-BEFORE 2009, ASPIRE 2004, Quinn 2005, and AGREE 2009.

Table A18: ACR 20, MTC Results versus Control, MTX-Naive Patients				
Intervention	**Number of Trials**	**Number of Patients**	**MTC Estimate, OR (95% CrI)**	**Direct Estimate, OR (95% CI)**
TNF-alpha Inhibitors				
Adalimumab	2	673	1.87 (0.59 to 6.33)	1.82 (1.33 to 2.50)
Etanercept	1	499	3.02 (0.58 to 15.61)	3.00 (1.93 to 4.67)
Golimumab	1	319	1.65 (0.32 to 8.6)	1.65 (1.06 to 2.57)
Infliximab	2	645	1.54 (0.5 to 6.97)	1.46 (1.06 to 2.00)
T-cell (CD28) Co-Stimulatory Modulators				
Abatacept	0	0	NA	NA

Table A19: ACR 50, MTC Results versus Control, MTX-Naive Patients				
Intervention	**Number of Trials**	**Number of Patients**	**MTC Estimate, OR (95% CrI)**	**Direct Estimate, OR (95% CI)**
TNF-alpha Inhibitors				
Adalimumab	2	673	1.77 (0.47 to 6.48)	1.81 (1.33 to 2.45)
Etanercept	1	499	2.51 (0.4 to 15.64)	2.51 (1.74 to 3.63)
Golimumab	1	319	1.61 (0.26 to 10.1)	1.62 (1.02 to 2.58)
Infliximab	2	645	2.11 (0.7 to 12.77)	2.16 (0.92 to 5.06)
T-cell (CD28) Co-Stimulatory Modulators				
Abatacept	1	509	1.85 (0.3 to 11.55)	1.84 (1.29 to 2.62)

Table A20: ACR 70, MTC Results versus Control, MTX-Naïve Patients				
Intervention	**# trials**	**# patients**	**MTC Estimate, OR (95% CrI)**	**Direct Estimate, OR (95% CI)**
TNF-alpha Inhibitors				
Adalimumab	2	673	2.09 (0.55 to 7.52)	2.14 (1.56 to 2.94)
Etanercept	1	499	2.38 (0.38 to 14.47)	2.37 (1.63 to 3.43)
Golimumab	1	319	1.69 (0.27 to 10.71)	1.70 (0.97 to 2.97)
Infliximab	2	645	2.12 (0.68 to 12.35)	2.07 (1.00 to 4.29)
T-cell (CD28) Co-Stimulatory Modulators				
Abatacept	1	509	1.99 (0.32 to 12.16)	1.98 (1.36 to 2.87)

Table A21: WDAEs, MTC Results versus Control, MTX-Naive Patients				
Intervention	**Number of Trials**	**Number of Patients**	**MTC Estimate, OR (95% CrI)**	**Direct Estimate, OR (95% CI)**
TNF-alpha Inhibitors				
Adalimumab	2	673	1.45 (0.27 to 6.62)	1.54 (0.90 to 2.64)
Etanercept	1	542	0.78 (0.09 to 6.81)	0.78 (0.46 to 1.33)
Golimumab	1	318	7.12 (0.42 to 324.8)	5.20 (0.6 to 44.99)
Infliximab	2	661	3.77 (0.67 to 40.06)	3.18 (1.53 to 6.62)
T-cell (CD28) Co-Stimulatory Modulators				
Abatacept	1	509	0.7 (0.07 to 6.68)	0.71 (0.28 to 1.80)

Patients Who Are TNF-alpha Inhibitor Experienced

The following tables are all based on random effect meta-analyses and include only trials conducted in patients who are TNF-alpha inhibitor experienced. There were no trials evaluating infliximab, etanercept, adalimumab certolizumab pegol or anakinra that met these inclusion criteria, therefore, they could not be included in this network analysis. The following trials were included in this analysis: GO-AFTER 2009, ATTAIN 2005, REFLEX 2006.

Table A22: ACR 20, MTC Results versus Control, Patients Who Are TNF-alpha Inhibitor Experienced

Intervention	Number of Trials	Number of Patients	MTC Estimate, OR (95% CrI)	Direct Estimate, OR (95% CI)
TNF-alpha Inhibitors				
Golimumab	1	308	2.58 (0.2 to 33.3)	2.47 (1.46 to 4.19)
T-CELL (CD28) Co-Stimulatory Modulators				
Abatacept	1	389	4.24 (0.33 to 54.21)	4.18 (2.55 to 6.85)
CD20+ B-Lymphocyte Inhibitors				
Rituximab	1	499	4.81 (0.37 to 61.01)	4.77 (3.12 to 7.31)

Table A23: ACR 50, MTC Results versus Control, Patients Who Are TNF-alpha Inhibitor Experienced

Intervention	Number of Trials	Number of Patients	MTC Estimate, OR (95% CrI)	Direct Estimate, OR (95% CI)
TNF-alpha Inhibitors				
Golimumab	1	308	4.28 (0.31 to 59.76)	2.83 (1.31 to 6.12)
T-CELL (CD28) Co-Stimulatory Modulators				
Abatacept	1	389	7.02 (0.51 to 101.7)	6.53 (2.54 to 16.77)
CD20+ B-Lymphocyte Inhibitors				
Rituximab	1	499	7.31 (0.56 to 96.33)	7.01 (3.53 to 13.91)

Table A24: ACR 70, MTC Results versus Control, Patients Who Are TNF-alpha Inhibitor Experienced

Intervention	Number of Trials	Number of Patients	MTC Estimate, OR (95% CrI)	Direct Estimate, OR (95% CI)
TNF-alpha Inhibitors				
Golimumab	1	308	4.26 (0.3 to 63.89)	4.00 (1.44 to 11.07)
T-CELL (CD28) Co-Stimulatory Modulators				
Abatacept	1	389	8.89 (0.55 to 187.9)	7.40 (1.73 to 31.7)
CD20+ B-Lymphocyte Inhibitors				
Rituximab	1	499	16.59 (1.02 to 351.5)	13.67 (3.25 to 57.5)

Table A25: WDAEs, MTC Results versus Control, Patients Who Are TNF-alpha Inhibitor Experienced

Intervention	Number of Trials	Number of Patients	MTC Estimate, OR (95% CrI)	Direct Estimate, OR (95% CI)
TNF-alpha Inhibitors				
Golimumab	1	308	0.46 (0.03 to 7.55)	0.50 (0.12 to 2.02)
T-CELL (CD28) Co-Stimulatory Modulators				
Abatacept	1	389	0.96 (0.07 to 14.55)	0.93 (0.30 to 2.82)
CD20+ B-Lymphocyte Inhibitors				
Rituximab	1	499	3.23 (0.19 to 70.56)	2.76 (0.58 to 13.13)

APPENDIX 3: SWITCHING BETWEEN BIOLOGIC AGENTS

1. Objective

To review evidence for the clinical effectiveness of cycling between TNF-alpha inhibitors or switching to another biologic agent with a different mechanism of action in adult patients with rheumatoid arthritis who do not respond initially to TNF-alpha inhibitors (primary non-responders) or who have had an initial response and then failed a TNF-alpha inhibitor (secondary non-responders). This was addressed through a systematic review. The literature search covered the years 2004 to 2009, and was similar to the search for the primary research question in terms of language restrictions and databases searched. Regular alerts were established until therapeutic review recommendations were made.

2. Findings

Switching or Cycling Between TNF-alpha Inhibitors

Approximately one-third of patients with RA treated with TNF-alpha therapies fail to achieve a 20% improvement in the American College of Rheumatology criteria (ACR 20),[62] and are sometimes referred to as primary non-responders.[63] Other patients respond to initial treatment, but subsequently fail or experience a loss of effectiveness[62] and are known as secondary non-responders.[63] The strategy to try a second or third TNF-alpha inhibitor after the first has failed, or to increase the dose of the TNF-alpha inhibitor is relatively common in clinical practice. A retrospective analysis of a US insurance claims database to assess patterns of cycling between TNF-alpha inhibitors, dose escalation, and time to discontinuation of treatment was conducted.[64] The study reported that the frequency of cycling had increased and the treatment duration before switching had decreased over the period analyzed from 2000 to 2005. The rationale for cycling between TNF-alpha inhibitors with similar mechanisms of action may be the potential for differences in the bioavailability of the drugs or differences in the incidence of drug-neutralizing antibodies.[62]

A recent NICE technology assessment report conducted a systematic review of adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of RA after failure of a TNF-alpha inhibitor.[65] The systematic review included both randomized studies and non-randomized studies with ≥ 20 patients per treatment group. There were 36 studies identified: five RCTs, three comparative studies and 28 uncontrolled studies (Table A27). Due to heterogeneity, data were not pooled. Three of the five RCTs are summarized later in this CADTH review (ATTAIN, REFLEX and OPPOSITE) and two evaluated abatacept in combination with a TNF-alpha inhibitor, which is not recommended clinical practice and so these trials were not considered any further. Among the non-randomized studies, a prospective cohort from a British biologics registry reported a significantly greater reduction in HAQ-DI among patients who switch to a different TNF-alpha inhibitor compared with those who switched to a non-biologic DMARD. Another non-randomized study found no statistically significant differences for patients switching to rituximab compared with switching to a TNF-alpha inhibitor. Among the 28 observational studies, many of which were before-after designs, significant improvements were observed after switching to a TNF-alpha inhibitor compared with before the switch. Observational studies also suggested that efficacy of a subsequent TNF-alpha inhibitor may be associated with the reason for withdrawal of the prior TNF-alpha inhibitor (e.g., lower response if withdrawn due to efficacy versus a higher response if withdrawn due to an adverse event). These studies also found that the proportion of patients who respond to subsequent treatment decreases as the number of prior TNF-alpha inhibitors previously tried increases. Results from observational studies are necessarily confounded by factors such as baseline disease activity, prior therapy and methods of selecting and following up people. Overall, the NICE assessment concluded that in patients failing a TNF-alpha inhibitor there was a lack of good quality evidence directly comparing the effectiveness of biologic agents, although observational studies suggested that a different TNF-alpha inhibitor may have some benefit, although the magnitude of the benefit is uncertain.

A systematic review by Carmona et al. (2007)[66] evaluated the evidence regarding switching between biologic agents, including TNF-alpha inhibitors. All study designs other than narrative reviews were eligible for inclusion. A total of 33 studies (two RCTs) met inclusion. Although the review included studies evaluating diseases other than RA, only the RA-relevant data are presented here. A total of 3,487 patients with RA participated across all studies, which accounted for the majority of the total study participants. The majority of the studies used TNF-alpha inhibitors at their recommended doses. The authors reported that switches between monoclonal antibodies typically have lower effect sizes than that of the first biologic. However, if the impetus to switch is due to an adverse event with a TNF-alpha inhibitor, then the response rate may be better with the second agent. The authors recommended that patients with inadequate responses to a TNF-alpha inhibitor switch to a non–TNF-alpha inhibitor biologic; however, this suggestion appears to be based on limited supportive evidence. Further, the authors proposed that switching between TNF-alpha inhibitors may be best reserved for situations when patients are experiencing adverse events.

Suarez-Almazor et al. (2007)[67] reviewed the evidence regarding the use of etanercept and infliximab for the treatment of RA in a CADTH health technology assessment. The focus of the report was on the timing of therapy (as an initial therapy or after failure of another therapy other than a TNF-alpha inhibitor), changes in dosing, and switching between etanercept and infliximab. To be considered for inclusion, studies had to have one of the following designs: RCT, controlled clinical trial, quasi-randomized, cohort (prospective or retrospective), or case-control. The minimum sample size for observational studies was 30. Studies had to use the TNF-alpha inhibitors at recommended doses (infliximab, ≥ 3 mg/kg every eight weeks; etanercept, ≥ 50 mg/week), had a minimum duration of therapy and follow-up of one year, and had at least one of the following primary end points: DAS; ACR 20, ACR 50, ACR 70; health-related quality of life, radiological damage, and drug remission. A total of 23 studies regarding dose escalation and switching were included in the health technology assessment. With regard to cycling between TNF-alpha inhibitors, the authors stated that the majority of the studies in which patients had failed one or more TNF-alpha inhibitors, reported that the patients responded to another anti–TNF-alpha agent. The authors cautioned that most of the included studies were small uncontrolled case series, which may be subject to bias. Overall, the authors concluded that patients who failed to respond to one or more TNF-alpha inhibitors may respond to a different TNF-alpha inhibitor.

An open-label, US-based study (OPPOSITE study) evaluating the effectiveness of switching from etanercept to infliximab following an incomplete response was conducted by Furst et al. (2007).[68] The trial included 28 patients with RA who had experience an incomplete response to etanercept. One patient withdrew prior to randomization. Patients were randomized to receive 3 mg/kg infliximab at weeks zero, two, six, 14, and 22 (group one; n = 13) or to continue receiving 25 mg, once weekly (group two; n = 14) for 16 weeks. All patients continued to receive pre-study stable doses of methotrexate (7.5 mg to 25 mg, twice weekly). At week 16 (before early escape), ACR 20 responses were achieved in 61.5% and 28.6% of infliximab- and etanercept-treated patients, respectively. A total of 15.4% of IFX-treated and 7.1% of etanercept-treated patients had a DAS 28 score less than 2.6 and the per cent change from baseline in DAS 28 score was 28.6% and 24.2% respectively. These differences were not statistically different but the study was not powered to detect a difference. The authors concluded that their findings favoured infliximab treatment in patients who had failed previous etanercept treatment, although they noted that their findings would need to be confirmed in a larger study with a more rigorous design.

Smolen et al. (2009)[36] evaluated the effect of golimumab treatment in patients with RA who previously had been treated with at least one dose of a TNF-alpha inhibitor in GO-AFTER. Concomitant use of DMARDs was permitted. A total of 461 patients were stratified by DMARD use and randomized to receive either placebo (group one; n = 155), 50 mg golimumab (group two; n = 153), or 100 mg golimumab (group three; n = 153). Prior to the study, over 95% of patients had received at least four weeks of treatment with one or more TNF-alpha inhibitors: 115 (25%) patients had received two and 43 (9%) had received three TNF-alpha inhibitors. This included 222 (48.2%) patients treated with adalimumab, 222 (48.2%) with etanercept and 218 (47.3%) with infliximab. Previous TNF-alpha inhibitors were discontinued because of a lack of effectiveness (269 [58%] patients) or reasons

unrelated to effectiveness, such as intolerance or accessibility issues (246 [53%]); some patients discontinued TNF-alpha inhibitors for more than one reason. The primary outcome was the proportion of participants achieving ACR 20 at week 14 (group one, 18%; group two, 35%; and group three, 38%). The authors concluded that golimumab was effective at reducing the symptoms of RA in patients who had been previously treated with at least one TNF-alpha inhibitor. Pre-specified subgroup analyses based on the reason for discontinuation of the previous TNF-alpha inhibitor and on number of previous TNF-alpha inhibitors and are presented below for combined golimumab groups (50 mg and 100 mg). These analyses suggest that the reason for discontinuation of prior TNF-alpha inhibitor therapy may not influence effectiveness of golimumab and that golimumab is no more effective than placebo in patients who have received at least three prior TNF-alpha inhibitors, although small numbers reduce confidence in these findings.

It was also observed that the ACR 20 response for patients who had received one previous TNF-alpha inhibitor did not differ significantly whether the drug was adalimumab, etanercept, or infliximab:

Table A26: ACR 20 Response in Patients Receiving Only One Prior TNF-alpha Inhibitor Therapy

Prior TNF-alpha Inhibitor in Patients Receiving Only One Prior TNF-alpha Inhibitor Therapy	ACR 20 Response	
	Placebo (n = 71)	Golimumab 50 mg and 100 mg combined (n = 144)
Overall Response	8/39 (20.5%)	43/92 (46.7%)
Adalimumab	3/15 (20.0%)	10/29 (34.5%)
Etanercept	0/6 (0)	17/34 (50.0%)
Infliximab	5/18 (27.8%)	16/29 (55.2%)

Switching from a TNF-alpha Inhibitor to a Biologic with a Different Mechanism

Two randomized controlled trials were identified in which patients who had failed a TNF-alpha inhibitor initiated treatment with a biologic with a different mechanism of action: one trial evaluating rituximab, which included two study publications,[34,69] and one trial evaluating abatacept.[16]

Rituximab

Cohen et al. (2006)[34] evaluated the effectiveness of rituximab in patients with RA who had a previous inadequate response or who were intolerant to one or more TNF-alpha inhibitors. Study participants were enrolled in the Randomized Evaluation of Long-Term Efficacy of rituximab in RA (REFLEX) trial and had long-standing active disease. Included patients were those who had an inadequate response (not defined) to previous or current treatment with a TNF-alpha inhibitor or who were intolerant to at least one TNF-alpha inhibitor (90% to 92% and 8% to 10% respectively). Patients were randomized to receive placebo (n = 209) or 1,000 mg rituximab (n = 311) in combination with their pre-randomization stable dosage of methotrexate (10 mg to 25 mg/week). The primary end point was the proportion of study participants achieving an ACR 20 response by week 24. An early-escape option occurred at 16 weeks, in which patients treated with placebo could receive two infusions of 1,000 mg rituximab and standard-of-care was offered to rituximab-treated patients. Prior to study enrolment, 388 (60%) patients had received one TNF-alpha inhibitor, 159 (30.1%) had received two TNF-alpha inhibitors and 47 (9.1%) had received three TNF-alpha inhibitors. Of the study population, 90% to 92% had inadequate efficacy with a previous TNF-alpha inhibitor while the remainder were intolerant. Previous experience with TNF-alpha inhibitors included 388 (75.0%) patients receiving infliximab, 109 (21.1%) patients receiving adalimumab, and 272 (52.6%) patients receiving etanercept. Eighty patients in the placebo group received rescue therapy and one patient in the rituximab group. At week 24, 51% of rituximab-treated patients versus 18% of placebo-treated patients had an ACR 20 response. Significantly more rituximab -treated patients also achieved ACR 50 and ACR 70 than in the placebo group (27% and 12% versus 5% and 1%). The authors concluded that a single treatment with rituximab in patients who did not respond to one or more TNF-alpha inhibitors resulted in significant improvements in clinical outcomes. Post-hoc subgroup analyses suggested that efficacy of rituximab does not vary based on the reason for withdrawal or the number of prior TNF-alpha inhibitors that were tried (one versus > 1).

Additional results from REFLEX were provided by Keystone et al. (2009), who reported on subset of the population who had received at least a part of the first rituximab treatment and for whom at least one post-baseline radiograph was available.[69] At least one post-baseline radiograph was available for 186 patients in the placebo group and 277 in the rituximab group. Approximately 80% of patients in the placebo group had received at least one course of rituximab. By week 56, 27% of the patients randomized to the rituximab group had withdrawn. Reasons for withdrawal were not stated. At week 56, patients in the rituximab group had statistically significant improvements compared with placebo in the total Genant-modified Sharp score (1.00 versus 2.31), erosion score (0.59 versus 1.32), and joint space narrowing score (0.41 versus 0.99). The authors concluded that rituximab can inhibit the progression of joint damage in patients with and inadequate response to a TNF-alpha inhibitor.

Abatacept

In the ATTAIN study, Genovese et al. (2005)[16] examined the effectiveness of abatacept treatment in patients who had inadequate responses to TNF-alpha inhibitors. Patients were eligible for inclusion if they had been treated with a TNF-alpha inhibitor and an oral DMARD or anakinra for a minimum of three months. Of patients enrolled in the study, 153 (39.1%) were currently receiving a TNF-alpha inhibitor and 238 (60.1%) were former users of TNF-alpha inhibitors. There were 136 (34.8%) patients who had received etanercept, 255 (65.2%) who had received infliximab and 8 (2.0%) who had received adalimumab. Prior to randomization, all patients were required to refrain from etanercept or infliximab treatment for a minimum of 28 or 60 days, respectively. A total of 391 patients were randomized and treated with either abatacept (group one; n = 258; 500 to 1,000 mg) or placebo (group two; n = 133). Both groups received a stable dose of an oral DMARD. Two-hundred and twenty-three patients in group one and 99 patients in group two completed the six-month study. The two primary end points were the proportion of patients with an ACR 20 response and the proportion of patients with a minimum improvement in HAQ-DI score of 0.3. The authors noted that a minimally clinically important change is 0.22. At six months, 50.4% of the patients in the abatacept group versus 19.5% of the patients in the placebo group had achieved an ACR 20 response. The proportions achieving ACR 50 and ACR 70 were also significantly higher in the abatacept group. The mean improvement in HAQ-DI scores was also greater in the abatacept group (0.45 versus 0.11). The authors concluded that patients who had previously not responded to TNF-alpha inhibitor therapy had improved clinical outcomes when treated with abatacept. In addition, subgroup analyses did not find any statistically significant differences in abatacept efficacy based on the number of prior TNF-alpha inhibitors (one versus two) or based on the prior TNF-alpha inhibitor taken (etanercept versus infliximab).

One additional study was identified, which evaluated abatacept in patients failing TNF-alpha inhibitor therapy. This study did not meet the protocol inclusion criteria, because it was not randomized but was of interest to this review of abatacept.[70] Schiff et al. (2009) evaluated the effectiveness of abatacept therapy in patients who had failed TNF-alpha inhibitor therapy. The open-label study involved 1,046 patients and included a washout group (n = 449) and a direct-switch group (n = 587). Patients in the washout group had to be off anti–TNF-alpha therapy for at least two months. Patients in the direct-switch group received abatacept treatment at the time of their next scheduled anti–TNF-alpha treatment. The dose of abatacept was 10 mg/kg on days one, 15, 29, and every four weeks up to and inclusive of day 141. The study was six months in length. A total of 377 patients in the washout group and 483 in the direct-switch group completed the study. The clinical efficacy end points were DAS 28 (C-reactive protein) and HAQ-DI. The authors described a clinically meaningful improvement in disease activity as a decrease from baseline score by at least 1.2 units. A score < 3.2 was considered low disease activity and < 2.6 was considered DAS 28-remission. At six months, the proportion of patients that demonstrated improvements in DAS 28 and HAQ-DI did not differ between groups. The proportion of patients with low disease activity and with DAS 28-defined remission was also comparable between groups. The authors reported that abatacept showed clinical effectiveness in the treatment of RA patients who had previously failed anti–TNF-alpha therapy, if abatacept was administered following an anti–TNF-alpha washout period or if switched directly to from anti–TNF-alpha therapy to abatacept.

Limitations

There are several limitations associated with the published evidence regarding the treatment of RA patients who did not respond to anti–TNF-alpha therapy. Our literature search did not identify any head-to-head trials comparing non-responding patients who cycled through anti–TNF-alpha agents with those who switched to another biologic with a different mechanism. The included studies varied in terms of length of study duration (treatment and follow-up) which may limit the ability to detect less frequent adverse events. Several of the studies were open-label, or single-blinded in design. Limited blinding in a study may introduce bias. Overall, the included studies had differences in patients' baseline disease activity, disease duration, reporting of previous use of antirheumatic therapies, definitions of disease remission, and dosages of current therapies (e.g., methotrexate or glucocorticoids). A limited literature search was conducted, and it is possible that studies not cited in the databases searched were omitted or were not included in the health technology assessments or systematic reviews that are summarized. This report limited the inclusion of primary studies to RCTs.

3. Summary

Two RCTs were identified that evaluated switching between TNF-alpha inhibitors. One small RCT (N = 28), the OPPOSITE study, evaluated the effect of switching from etanercept to infliximab compared with remaining on etanercept in patients with an incomplete response; no statistically significant differences in efficacy were observed at week 16.[68] A second RCT, GO-AFTER (N = 461), evaluating golimumab in patients with previous exposure to at least one dose of a TNF-alpha inhibitor found golimumab to be more effective than placebo.[36] Subgroup analyses suggested that while golimumab is more effective than placebo in patients with exposure to one previous TNF-alpha inhibitor or two previous TNF-alpha inhibitors, there is no significant difference between golimumab and placebo in patients with prior exposure to three or more TNF-alpha inhibitors. Subgroup analyses also suggested that the efficacy of golimumab compared with placebo did not differ based on the reason for discontinuation of prior TNF-alpha inhibitor therapy (lack of effectiveness or unrelated to lack of effectiveness) or based on the TNF-alpha inhibitor to which a patient was exposed (adalimumab, etanercept, infliximab).

In addition, two large RCTs were identified that were conducted in patients who had failed a TNF-alpha inhibitor (infliximab, adalimumab or etanercept) and evaluated the efficacy of a biologic with a different mechanism of action. One of the RCTs, REFLEX (N = 520) evaluated the effects of rituximab and found that it was effective in improving ACR response, as well as inhibiting radiographic progression.[34,69] Similarly, the other RCT, ATTAIN (N = 393), which evaluated the effects of abatacept in patients who had failed infliximab or etanercept, found that it was effective in improving ACR response but effects on radiographic progression were not reported.[16] Subgroup analyses from these trials did not find significant differences in efficacy based on whether one or two TNF-alpha inhibitors had been previously tried.

A number of systematic reviews were also identified that addressed questions around switching biologic agents, including a recently published NICE technology assessment. This assessment was based on three RCTs, three non-randomized comparative studies and 28 observational studies. The NICE assessment only included three of the four RCTs summarized in the CADTH therapeutic review; GO-AFTER was not included. REFLEX evaluating rituximab, ATTAIN evaluating abatacept and OPPOSITE evaluating infliximab were included. According to the NICE assessment, in patients failing a TNF-alpha inhibitor there is a lack of good quality evidence directly comparing the effectiveness of biologic agents. It concluded that based on RCTs there is a benefit of either abatacept or rituximab in patients failing TNF-alpha inhibitors and that based on observational studies a different TNF-alpha inhibitor may have some benefit, although the magnitude of the benefit is uncertain.

Table A27: RCTs Evaluating Switching, Included Study Characteristics						
Study (Year)	**Treatment Groups (number of patients)**	**Mean MTX dosage**	**Mean Age in Years (SD), % Female**	**Disease Duration (years)**	**Swollen Joints, Tender Joints Baseline DAS**	**Primary Outcomes**
Switching between TNF-alpha Inhibitors						
Switching from a TNF-alpha Inhibitor to Golimumab						
Smolen et al. (2009)[36] GO-AFTER	PL (n = 155) Injections every 4 weeks	NR	54.0 (46.0 to 64.0) 85%	9.8	14.0, 26.0 6.3	<u>% achieving ACR 20 at week 14:</u> PL: 18% GOL 50 mg: 35%; P = 0.0006; versus PL GOL 100 mg: 38%; P = 0.0001; versus PL
	GOL 50 mg (n = 153)	NR	55.0 (46.0 to 63.0) 74%	9.6	14.0, 27.0 6.3	
	GOL 100 mg (n = 153)	NR	55.0 (47.0 to 61.0) 80%	8.7	13.0, 26.0 6.1	
Switching from Etanercept to Infliximab						
Furst et al. (2007)[68]	IFX (n = 13)	NR	54.1(13.5) 84.6%	9.6	20.7, 31.4 6.2 (mean)	<u>ACR 20 at week 16:</u> IFX: 61.5% ETN: 28.6% <u>ACR 50 at week 16:</u> IFX: 30.7% ETN: 14.3% <u>DAS 28 at week 16:</u> IFX: 1.5% ETN: 1.6%
	ETN (n = 14)	NR	52.2(14.5) 100%	12.1	20.1, 25.6 6.5 (mean)	
Switching from a TNF-alpha Inhibitor To a Biologic with a Different Mechanism						
Switching to Rituximab						
Cohen et al. (2006)[34] REFLEX	PL + MTX (n = 209)	16.7	52.8(12.6) 81%	11.7	22.9, 33.0 6.8	<u>% achieving ACR 20 at week 24:</u> PL + MTX: 18% RTX + MTX: 51%; P <0.0001 (versus placebo group)
	RTX + MTX (n = 308)	16.4	52.2(12.2) 81%	12.1	23.4, 33.9 6.9	
Keystone et al. (2009)[69] REFLEX	PL + MTX (n = 186)	NR	53.0 (NR) 80%	11.6	23.2, 33.2 6.8	Mean changes at week 56 in radiographic end points <u>Total Genant-modified Sharp</u> RTX + MTX (1.00) versus PL + MTX (2.31), P = 0.005 <u>Joint space narrowing:</u> RTX + MTX (0.99) versus PL + MTX (0.41), P <0.001 <u>Joint space narrowing:</u> RTX + MTX (1.32) versus PL + MTX (0.59), P = 0.011
	RTX + MTX 1,000 mg (n = 277) Day 1 and 15 Week 16, 20, 24, and 56	NR	52.5 (NR) 81%	12.0	23.2, 33.2 6.8	

Table A27: RCTs Evaluating Switching, Included Study Characteristics						
Study (Year)	**Treatment Groups (number of patients)**	**Mean MTX dosage**	**Mean Age in Years (SD), % Female**	**Disease Duration (years)**	**Swollen Joints, Tender Joints Baseline DAS**	**Primary Outcomes**
Switching to Abatacept						
ATTAIN 2005[16]	ABT (n = 258)	15.2	53.4(12.4) 77.1%	12.2	22.3, 31.2 6.5	<u>% achieving ACR 20 response at 6 months:</u> PL: 19.5% ABT: 50.4%; P <0.001 <u>% achieving an improvement of at least 0.3 from baseline in HAQ-DI</u> PL: 23.3% ABT: 47.3%; P <0.001
	PL (n = 133)	14.4	53.7(11.3) 79.7%	11.4	22.0, 32.8 6.5	

ABT = abatacept; ACR = American College of Rheumatology; GOL = golimumab; ETN = etanercept; IFX = infliximab; MTX = methotrexate; NR = not reported; PL = placebo.

Table A28: Observational Studies Evaluating Switching (as included in the NICE technology appraisal on biologic agents after a TNF-alpha inhibitor failure[65])

Study (sample size) duration	Study Design	Prior TNF-alpha Inhibitor (number)	Reason for Switching	Treatment Group (number of patients)	ACR 50, % (95% CI) DAS, mean change (SD) EULAR, % (95% CI) HAQ-DI, mean change (SD)
Adalimumab					
Bennett 2005 (n = 26) 52 weeks	Uncontrolled Prospective	IFX, ETAN, anakinra (1)	Primary (8) and secondary (13) failures, [all = IFX] AEs, other	ADA (n = 26)	Mean Δ DAS: –1.70 (–2.30) EULAR (good/moderate): 65.4% (4.3 to 82.8) EULAR(good): 19.2% (6.6 to 39.4) Mean Δ HAQ-DI: –0.31 (0.57)
Wick 2005 (n = 27) 24 weeks	Uncontrolled retrospective	IFX (1)	Secondary failure	ADAL (n = 27)	ACR 20: 70.4 (49.8 to 86.2) Mean Δ DAS: –1.30 (–1.80)
Nikas 2006 (n = 24) 52 weeks	Uncontrolled Prospective	IFX (1)	Lack of efficacy, AEs	ADAL (n = 24)	ACR 20: 75.0 (53.3 to 90.2) ACR 50: 50.0% (29.1 to 70.9) ACR 70: 33.3 (15.6 to 55.3) EULAR response: 70.8% (48.9 to 87.4)
Bombardieri 2007 (n = 899) 12 weeks	Uncontrolled Prospective	IFX, ETAN or both (≥1)	Primary and secondary failure, intolerance	ADAL (n = 899)	ACR 20: 60.1 (56.8 to 63.3) ACR 50: 33.0% (30.0 to 36.2) ACR 70: 13.0% (10.9 to 15.4) Mean Δ DAS: –1.90 (–1.40) EULAR(good/moderate): 99.0%(98.1 to 99.5) EULAR(good): 23.0 (20.3 to 25.9) Mean Δ HAQ-DI: –0.31 (0.57)
Van der Bijl 2008 (n = 41) 16 to 56 weeks	Uncontrolled Prospective	IFX (1)	Primary and secondary failure, intolerance	ADAL (n = 41)	ACR 20: 46.3 (30.7 to 62.6) ACR 50: 26.8% (14.2 to 42.9) ACR 70: 12.2 (4.1 to 26.2) Mean Δ DAS: –1.50 (1.60) EULAR(good/moderate): 78.0 (62.4 to 89.4) EULAR(good): 17.1 (7.2 to 32.1) Mean Δ HAQ-DI
Etanercept					
Haroui 2004 (n = 25) 12 weeks	Uncontrolled Prospective	IFX	Inefficacy, AEs	ETAN (25)	ACR 20:58.3 (36.6 to 77.9) ACR 50: 20.8% (7.1 to 42.2) ACR 70: Mean Δ HAQ-DI: –045 (NR)
Buch 2005 (n = 207) 12 weeks	Uncontrolled Prospective	IFX	Inefficacy	ETAN (25)	ACR 20: 72.0 (50.6 to 87.9) ACR 50: 64.0% (42.5 to 82.0) ACR 70: 20.0 (6.8 to 40.7)

Table A28: Observational Studies Evaluating Switching (as included in the NICE technology appraisal on biologic agents after a TNF-alpha inhibitor failure[65])					
Study (sample size) duration	**Study Design**	**Prior TNF-alpha Inhibitor (number)**	**Reason for Switching**	**Treatment Group (number of patients)**	**ACR 50, % (95% CI) DAS, mean change (SD) EULAR, % (95% CI) HAQ-DI, mean change (SD)**
Cohen 2005 (n = 24) 13 weeks	Uncontrolled retrospective	IFX	Inefficacy, AEs	ETAN (24)	DAS 28: –1.80 (1.60) EULAR(good):45.8 (25.6 to 67.2) EULAR(good/moderate): 58.3 (36.6 to 77.9)
Buch 2007 (n = 95) 12 weeks	Uncontrolled Prospective	IFX	Inefficacy, AEs	ETAN (95)	ACR 20:37.5% (26.4 to 49.7) ACR 50: 23.6% (14.4 to 35.1) ACR 70:15.3 (7.9 to 25.7) DAS 28: –1.47 (1.80) EULAR(good): 12.5 (5.9 to 22.4) EULAR (good/moderate): 61.1 (48.9 to 72.4)
Iannone 2007 (n = 37) 24 weeks	Uncontrolled retrospective	IFX	AEs	ETAN (37)	DAS 44 (3 months):–0.70 (NR) DAS 44 (6 months): –0.90 (NR) Mean Δ HAQ-DI (3 months): 0.15 (NR) Mean Δ HAQ-DI(6 months): 0 (NR)
Laas 2008 (n = 49) > 36 weeks	Uncontrolled Prospective	IFX	Inefficacy, AEs, non-medical reasons	ETAN (49)	DAS 28: –0.47 (2.06)
Bingham 2009 (n = 201) 16 weeks	Uncontrolled Prospective	IFX	Inefficacy	ETAN (201)	ACR 20: 42.3 (35.4 to 49.4) ACR 50: 18.4 (13.3 to 24.5) ACR 70: 8.0 (4.6 to 12.6) DAS 28: –1.60 (1.45) EULAR(good/moderate): 58.2 (51.1 to 65.1) Mean Δ HAQ-DI: –0.35 (NR)
Infliximab					
Ang 2003 (n = 24) NR	Uncontrolled retrospective	ETAN (1)	Inadequate response, toxicity	IFX (24)	NR
Hanasen 2004 (n = 20) NR	Uncontrolled retrospective	ETAN (1)	Lack of efficacy, drug shortage, patient concerns re: safety, thrombocytopenia	IFX (20)	NR
Yazici 2004 (n = 21) NR	Uncontrolled Prospective	ETAN (1)	inefficacy	IFX (21) IFX (41)	HAQ-DI: at 12 months patients improved significantly EULAR: at 12 months patients improved significantly

Table A28: Observational Studies Evaluating Switching (as included in the NICE technology appraisal on biologic agents after a TNF-alpha inhibitor failure[65])

Study (sample size) duration	Study Design	Prior TNF-alpha Inhibitor (number)	Reason for Switching	Treatment Group (number of patients)	ACR 50, % (95% CI) DAS, mean change (SD) EULAR, % (95% CI) HAQ-DI, mean change (SD)
TNF-alpha Inhibitors as a Class					
Hyrich 2009 (n =) > 6 months	Cohort	ETAN, IFX, ADAL	Inefficacy, AEs	TNF-alpha inhibitor (all switchers n = 534; stoppers = 202)	HAQ-DI (all switchers): –0.11 (0.77)
Gomez-Reino 2006 (n = 488) 104 weeks	Uncontrolled Prospective (Not just RA patients, also AS, PsA, etc.	IFX, ETAN	Lack of efficacy, AEs	TNF-alpha inhibitor (n = 448)	NR
Solau-Gervais 2006 (n = 70) > 13 weeks	Uncontrolled Prospective	ETAN (30 to 48), IFX (40 to 60), ADAL (10 to 12)	NR	TNF-alpha inhibitor (n = 70)	NR
Hjardem 2007 (n = 235) > 13 weeks	Uncontrolled retrospective	ETAN, IFX, ADAL	Inefficacy, AEs, other	TNF-alpha inhibitor (n = 235)	DAS: –1.0 (4.4) EULAR(good): 9.8% (6.3 to 14.3) EULAR (good/moderate): 31.5% (25.6 to 37.8)
Duftner 2008 (n = 109) Up to 208 weeks	Uncontrolled retrospective	IFX (27), ETAN, (22.3) ADAL (36.5)	Inefficacy, AEs, other	TNF-alpha inhibitor (n = 109)	NR
Karlsson 2008 (n = 337) 13 weeks	Uncontrolled retrospective	1st TNF-alpha inhibitor: ETAN (20), IFX (73), ADAL (7.7). 2nd TNF-alpha inhibitor: ETAN (58), IFX (8.3), ADAL (34)	Inefficacy, AEs, other	TNF-alpha inhibitor (n = 337)	ACR 20: 49.0% (43.5 to 54.4) ACR 50: 25.8% (21.2 to 30.8) ACR 70: 7.1% (4.6 to 10.4) DAS <3.2: 29.1% (24.3 to 34.2) DAS <2.6: 15.4% (11.7 to 19.7) EULAR (good):22.8% (18.5 to 27.7) EULAR(good/moderate):64.7% (59.3 to 69.8)
Blom 2009 (n = 197) 48 weeks	Uncontrolled retrospective	IFX, ETAN, ADAL	Non-response, loss of response, AEs	IFX, ETAN, ADAL (n = 197)	DAS (3 months): –0.86 (1.27) DAS (6 months): –0.92 (1.34) DAS < 3.2 (3 months): 14.2% (9.7 to 19.9) EULAR (good, 3 months):34.7%(21.7 to 49.6) EULAR (good, 6 months):36.7% (23.4 to 51.7) EULAR (good/moderate, 3 months): 31.5% (25.1 to 38.5) EULAR (good/moderate, 6 months): 32.5% (26.0 to 39.5)

Table A28: Observational Studies Evaluating Switching (as included in the NICE technology appraisal on biologic agents after a TNF-alpha inhibitor failure[65])					
Study (sample size) duration	**Study Design**	**Prior TNF-alpha Inhibitor (number)**	**Reason for Switching**	**Treatment Group (number of patients)**	**ACR 50, % (95% CI) DAS, mean change (SD) EULAR, % (95% CI) HAQ-DI, mean change (SD)**
Finckh 2009 11 months	Prospective cohort	Any (≥ 1)	Inadequate response	RTX (n = 155), different TNF-alpha inhibitor (n = 163)	DAS: –0.88 (1.82)
Rituximab					
Bokarewa 2007 (n = 48) 52 weeks	Uncontrolled Prospective	64% > 1 biologic agent	Lack of response	RTX (n = 48)	NR
Jois 2007 (n = 20) 26 weeks	Uncontrolled Prospective	Any (≥2)	Lack of response	RTX (n = 20)	Mean DAS 28 (3 months): 5.60 Mean DAS 28 (6 months): 5.50
Keystone 2007 (n = 158) 24 weeks	Uncontrolled retrospective	All had TNF-alpha inhibitor	NR	RTX (n = 155 to 158)	ACR 20: 65.2% (57.1 to 72.6) ACR 50: 32.9% (25.6 to 40.9) ACR 70: 12.3% (7.5 to 18.5) EULAR(good/moderate): 77.2%(69.9 to 83.5) EULAR (low disease): 13.3 (8.4 to 19.6) EULAR (remission): 5.7 (2.6 to 10.5) % HAQ-DI (achieving MCID): 71.8 (64.0 to 78.7)
Assous 2008 (n = 50) 26 weeks	Uncontrolled retrospective	any	Lack of response; contraindication	RTX (n = 50)	EULAR (good/moderate): 82.0% (68.6 to 91.4) EULAR (good): 36.0% (22.9 to 50.8) Mean DAS 28: 3.97
Thurlings 2008 (n = 30) 24 weeks	Uncontrolled Prospective	Any (≥ 1)	AEs, inefficacy	RTX (n = 30)	EULAR (good/moderate):73.3 (54.1 to 87.7) EULAR (good): 16.7% (5.6 to 34.7) Mean DAS 28: 5.00 (1.90)
Finckh 2009 11 months	Prospective cohort	Any (≥ 1)	NR	RTX (n = 155)	Mean Δ BL DAS 28: –1.61 (1.30)
Abatacept					
ARRIVE (n = 1,045) 24 weeks	Uncontrolled Prospective	Any (1 to 3)	Lack of efficacy, safety, intolerability	ABAT (n = 1,046)	Mean DAS 28: –2.00 (2.32)

ABAT = abatacept; ACR = American College of Rheumatology; AE = adverse events; DAS = disease activity score; EULAR = European League Against Rheumatism; GOL = golimumab; ETAN = etanercept; HAQ-DI = Health Assessment Questionnaire Disability Index; IFX = infliximab; MCID = minimal clinically important difference; MTX = methotrexate; NR = not reported; PL = placebo; RTX = rituximab.

APPENDIX 4: DOSE ESCALATION OF TNF-ALPHA INHIBITORS

1. Objective

To review evidence for the clinical effectiveness of increasing the dose of TNF-alpha inhibitors in adult patients with rheumatoid arthritis who do not respond initially to TNF-alpha inhibitors (primary non-responders) or who have had an initial response and then failed a TNF-alpha inhibitor (secondary non-responders). This was addressed through a systematic review. The literature search covered the years 2004 to 2009, and was similar to the search for the primary research question in terms of language restrictions and databases searched. Regular alerts were established until therapeutic review recommendations were made.

2. Findings

There were four RCTs identified that were designed to evaluate dose escalation, three evaluating infliximab and one evaluating etanercept. The trial data was limited by the following factors: small number of trials designed to evaluate dose escalation, suboptimal methotrexate dosing in a Japanese population and uncontrolled data.

Table A29: Randomized Controlled Trials Evaluating Dose Escalation of Biologic Agents

Study	Intervention	Efficacy	Harms
INFLIXIMAB			
Pavelka 2009 141 partial responders or reduced effectiveness despite IFX 3 mg/kg every 8 weeks for 1 year prior to randomization 12 Months	IFX 3 mg/kg (n = 71) IFX 5 mg/kg (n = 70) administered every 8 weeks	No statistically significant difference in DAS 28 or DAS 28 components	No statistically significant difference in SAEs, serious infections, or WDAEs between groups AEs were higher with 5 mg/kg versus 3 mg/kg (47.8% versus 28.2%, P = 0.02)
Takeuchi 2009 307 Japanese patients receiving IFX 3 mg/kg at weeks 0,2 and 6, regardless of response *Week 54*	IFX 3 mg/kg (n = 99) IFX 6 mg/kg (n = 104) IFX 10 mg/kg (n = 104) administered every eight weeks	ACR-N (mean % improvement): 3 mg/kg: 51.3% 6 mg/kg: 53.8% 10 mg/kg: 58.3% (only significant for 3 mg/kg versus 10 mg/kg)	No statistically significant difference in SAEs across all 3 groups
Rhaman 2007 non or partial responders to IFX 3 mg/kg at week 0,2,6, and 14 N = 109 of 329 were eligible for dose escalation	IFX dose escalation by 1.5 mg/kg at weeks 22, 30, 38 and 46 41% of patients had ≥1 dose escalation	≥ 20% improvement in tender or swollen joint counts 8 weeks after the last dose escalation • 77% (41/53) of non-responders • 83% (39/47) of partial responders	No statistically significant difference in SAEs
ETANERCEPT			
Weinblatt 2008 patients with a suboptimal response to an etanercept dose of 50 mg given once a week plus weekly MTX (a dose ≥ 15 mg/week), N = 200 12 weeks	ETAN 50 mg, twice weekly (n = 160) ETAN 50 mg once weekly (n = 40)	No statistically significant improvement in clinical outcomes	

ACR-N = American College of Rheumatology N; AE = adverse events; DAS = Disease Activity Score; ETAN = etanercept; IFX = infliximab; MTX = methotrexate; SAE = serious adverse events; WDAE = withdrawals due to adverse events.

TNF-alpha Inhibitors

Infliximab

Three randomized controlled trials were identified that evaluated the effectiveness of dose escalation with infliximab.

Pavelka et al. (2009)[71] evaluated the effect of a dose increase of infliximab in patients with RA. The study participants had been previously treated with infliximab (3 mg/kg every eight weeks for one year) and who were partial responders or who had experienced reduced effectiveness over the course of therapy. All included patients had initiated infliximab with a DAS 28 score greater than 5.1, had a positive response within the first three months of treatment (i.e., a reduction of 1.2 in DAS 28 compared with baseline) but did not have a DAS 28 score greater than 2.6 (i.e., remission) at entry into this study. Patients also did not have any contraindications to TNF-alpha inhibitor therapy. A total of 141 patients were enrolled and were randomized to either continue with the recommended dose of infliximab (3 mg/kg every eight weeks; n = 71) or to increase the infliximab dose (5 mg/kg every eight weeks; n = 70). After 12 months of treatment, there were no differences between the two groups based on DAS 28 or its components. In both groups, there was a DAS 28 reduction of approximately 0.65 to 0.67, respectively. The proportions of patients with serious adverse events (16.9% versus 15.9%), serious infections (5.8% versus 5.6%) and withdrawals due to adverse events (5.6% versus 7.1%) were similar between the two groups. Adverse events was higher in the high dose group (28.2% versus 47.8%, P = 0.02).

Takeuchi et al. (2009) reported results from a double-blind RCT, called the RISING study, that assessed the effect of increasing the infliximab dose in Japanese patients with rheumatoid arthritis.[72] The study evaluated the benefits and harms of different doses of infliximab in patients who received a dose of 3 mg/kg infliximab at weeks zero, two, and six. A total of 327 patients with active RA despite having been treated with methotrexate (6 mg/week or more; the approved maximum dose of methotrexate in Japan is 8 mg/week) for 12 weeks were included. Following the open-label portion of the study in which patients received a dose of 3 mg/kg infliximab at weeks zero, two, and six, regardless of response, patients (n = 307) were randomly assigned at week 10 to receive infliximab at a dose of 3 mg/kg (n = 99), 6 mg/kg (n = 104), or 10 mg/kg (n = 104). Treatment groups were balanced based on ACR 20 and ACR 50 responses at week 10. Infliximab was administered every eight weeks from week 14 to 46 and responses were assessed at week 54. The primary outcome was the mean percent improvement in ACR-N. Compared with the 3 mg/kg group, patients who received 10 mg/kg but not patients who received 6 mg/kg had a statistically significant mean percent improvement in ACR-N compared with baseline (51.3% versus 58.3% and 53.8%). The authors reported that there were no significant differences between the reported adverse events between groups and that an infliximab dose of 10 mg/kg was effective in patients who had been previously treated with 3 mg/kg. Pre-specified subgroup analyses for patients who had no EULAR response to 3 mg/kg of infliximab at week 10 were also conducted, indicating that in patients who are non-responders, infliximab dose escalation may be an effective strategy. By week 54, 90% (9 of 10) patients who continued to receive 3 mg/kg remained EULAR non-responders, 44% (7 of 16) patients who escalated to 6 mg/kg remained EULAR non-responders and 0% (0 of 11) patients who escalated to 10 mg/kg remained EULAR non-responders.

Rhaman et al. (2007)[73] evaluated the benefits and harms of dose escalation of infliximab in rheumatoid arthritis patients who had an inadequate response to 3 mg/kg of infliximab. This report details findings from one arm of the Safety Trial for rheumatoid Arthritis with Remicade Therapy (START) in which the dose escalation strategy was employed. The patients in the dose escalation arm (n = 360) received 3 mg/kg infliximab at weeks zero, two, six, and 14. At week 22, patients were assessed for dose escalation and were eligible if they were either non-responders or partial responders. There were 329 patients eligible for dose escalation and 220 of did not require dose escalation at any time. There did not appear to be any distinguishing baseline clinical characteristics for patients who require dose escalation compared with those who did not require dose escalation. A total of 100/109 patients eligible for a dose escalation were included in the analysis (nine patients received a dose escalation in error). Non-responders (n = 53) were patients who at week 14 had a less than 20% improvement from baseline in the combined tender joint count and swollen joint count.

Partial responders (n = 47) were patients who had a ≥ 50% reduction in improvement in the combined tender joint count and swollen joint count from baseline to the time at which response was initially achieved. Dose escalation occurred in increments of 1.5 mg/kg at weeks 22, 30, 38, and 46. 41% received more than one dose escalation. There were 77% (41 of 53) of non-responders and 83% (39 of 47) of partial responders who responded to dose escalation. Response was defined as patients who showed a 20% or more improvement from baseline in the total number of tender or swollen joints eight weeks after the last dose escalation. The authors reported that the rates of one or more serious adverse events did not differ between patients who received a dose escalation and those who did not (8.6% versus 12.8%, respectively). The authors concluded that in patients who did not respond to a dose of 3 mg/kg infliximab, a dose increase may be beneficial and is not associated with an increased risk of having a serious adverse event.

Adalimumab

Breedveld et al. (2006) evaluated the effect of adalimumab plus methotrexate compared with adalimumab alone and with methotrexate alone in patients with early RA who were methotrexate-naïve in the PREMIER study. Patients who had previously taken more than two DMARDs were excluded. Methotrexate dosing was initiated at a dose of 7.5 mg/week and increased up to 20 mg/week by week nine. Adalimumab was administered 40 mg every other week as per Health Canada-approved dosing. At week 16 and following, a rescue protocol was in place mandating that for patients who had not achieved an ACR 20 response, the injectable medication (adalimumab or placebo) be increased to weekly dosing after the dosage of the oral medication (methotrexate or placebo) had been optimized. Therefore, placebo patients never had a true change in their therapy while adalimumab patients had their dose increased to adalimumab every other week. The mean methotrexate dose in the adalimumab plus methotrexate group was 16.3 mg/week and was 16.9 mg/week in the methotrexate alone group. During year one, 11% (29/238) of combination therapy patients, 25% (69/274) of adalimumab monotherapy patients, and 20% (52/257) of methotrexate monotherapy patients underwent dose escalation. Of these, a number were non-responders who had never achieved an ACR 20 response at any time prior to dose escalation: 41% (12/29) of combination therapy patients, 29% (20/69) of adalimumab monotherapy patients, and 48% (25/52) of methotrexate monotherapy patients. Dose escalation had a minimal effect on these patients with 1% of combination therapy patients, 2% to 3% of adalimumab monotherapy patients and 4% of methotrexate monotherapy patients achieving an ACR 20 through years one and two. The authors reported that similar results were observed with patients who had achieved a prior ACR response, although data were not shown. The authors concluded that there is no benefit to increasing the dose of adalimumab from 40 mg every other week to 40 mg once weekly in either non-responders or partial responders.

Soubrier et al. (2009)[74] evaluated the effectiveness of adalimumab given in combination with methotrexate for the treatment of RA but also included dose escalation and switching protocols in an effort to develop a strategy of tight disease control. The study was an unblinded RCT and involved 65 patients with early (defined as less than six months) and active disease. At study entry, patients were naïve to both methotrexate and biologic therapy. Patients were randomized to either group one (methotrexate: 0.3 mg/kg/week to a maximum of 20 mg/week; n = 32) or to group two [methotrexate (0.3 mg/kg/week to a maximum of 20 mg/week) + adalimumab 40 mg/2 weeks; n = 33]. Treatment regimens were maintained for three months and then disease activity was assessed and treatment modifications made. For group one, if there was disease remission (defined as DAS 28_{ESR} < 2.6 for a minimum of six months), the methotrexate dose was tapered to 7.5 mg/week. Insufficient responses in group one were treated by the addition of adalimumab (40 mg/2 weeks) or etanercept (25 mg given twice a week) in combination with methotrexate. For group two, if there was disease remission, methotrexate was tapered. If there was an inadequate response (i.e., DAS 28 > 3.2), the dose of adalimumab was increased to 40 mg/week. If the increased dose of adalimumab failed, etanercept therapy (25 mg given twice a week) was initiated. At 12 weeks, if the DAS 28 was < 3.2, adalimumab could be stopped; no patients met this criterion after 12 weeks. Twenty-nine and 28 patients completed the first year of treatment in group one and 2 respectively. There were no differences in the number of visits in which the patients had low disease activity between groups. The number of patients requiring dose escalation of adalimumab from once every two weeks to every week in group

two was not reported; therefore, the effectiveness of this dose escalation strategy cannot be evaluated. Etanercept treatment occurred in four patients in group one and two patients in group two but again, the effectiveness of switching from adalimumab to etanercept was not specifically evaluated.

Etanercept

Weinblatt et al. (2008)[75] evaluated the effectiveness of increasing the dosing frequency of etanercept in patients with RA. Two-hundred patients with a suboptimal response to an etanercept dose of 50 mg given once a week plus weekly methotrexate (a dose ≥ 15 mg) were randomized to receive either etanercept 50 mg, twice weekly (n = 160) or etanercept 50 mg, once weekly plus a placebo (n = 40) for 12 weeks. Suboptimal responders were defined as those patients with active disease despite six months of therapy with optimized methotrexate (a stable dosage of ≥ 15 mg/week for at least four weeks prior to study) and etanercept once weekly and who had ≥5 swollen and ≥ 5 tender joints based on a 28-joint count. All patients were also treated with methotrexate at their pre-study stable dosage (≥ 15 mg). The primary outcome of the study was the proportion of patients with a good or moderate (as defined by the European Union League Against Rheumatism [EULAR] criteria) DAS 28 score at week 12. Secondary outcomes included ACR 20, ACR 50, and ACR 70 responses at week 12. A total of 187 patients completed 12 weeks of the study. At 12 weeks, there was no significant difference in the DAS 28 response and ACR responses between groups. The authors concluded that increasing the dosing frequency of etanercept to 50 mg twice a week did not improve responses after 12 weeks of treatment.

Golimumab

Two golimumab randomized controlled trials, GO-FORWARD and GO-AFTER,[36,37] were identified that reported dose escalation as part of a rescue therapy strategy.

Keystone et al. (2009)[37] reported results from the phase III GO-FORWARD study that examined golimumab for the treatment of patients with active RA. Patients were excluded if they had previously used any TNF-alpha inhibitor, rituximab, natalizumab or a cytotoxic agent. A total of 444 patients were randomized to one of four groups: placebo + methotrexate (n = 133); 100 mg golimumab + placebo (n = 133); 50 mg golimumab + methotrexate (n = 89); or 100 mg golimumab + methotrexate (n = 89). At week 16, the patients in groups 1, 2, and 3 who did not reach a 20% improvement in tender and swollen joint counts were eligible for early escape, and received either 50 mg + methotrexate (group one) or 100 mg golimumab + methotrexate (groups 2 and 3). The ACR 20 response at week 14 was 33.1% in the placebo group (group one), 44.4% in group two, 55.1% in group three, and 56.2% in group four. Approximately 17% (15/89) of the patients in group three received rescue therapy (a dose increase from 50 mg golimumab to 100 mg golimumab). Of these, only 20% (3/15) achieved an ACR 20 response at week 14. Among patients in group four (100 mg golimumab + methotrexate) who met early escape criteria but whose dose was not adjusted, 28.6% (4/14) had an ACR 20 response at week 24. Therefore, there appeared to be limited benefit of golimumab dose escalation from 50 mg to 100 mg.

Smolen et al. (2009)[36] evaluated the effect of golimumab treatment in patients with RA who previously had been treated with at least one dose of a TNF-alpha inhibitor in GO-AFTER. Concomitant use of DMARDs was permitted. A total of 461 patients were stratified by DMARD use and randomized to receive either placebo (group one; n = 155), 50 mg golimumab (group two; n = 153), or 100 mg golimumab (group three; n = 153). The primary outcome was the proportion of participants achieving ACR 20 at week 14 (group one, 18%; group two, 35%; and group three, 38%). Rescue therapy was offered to participants at week 16 who had less than 20% improvement from baseline in tender and swollen joint count. Participants in group one received 50 mg golimumab and those in group two received 100 mg golimumab. Approximately 46% of participants in group one and 27% of participants in group two received the rescue therapy. A separate analysis of patients who received escalated dose of golimumab was not provided therefore the effectiveness of this strategy is unknown.

Observational Data Regarding Dose Escalation

Suarez-Almazor et al. (2007)[67] reviewed the evidence regarding the timing, dose escalation and switching of infliximab and etanercept in rheumatoid arthritis in a CADTH health technology assessment report. Both randomized and non-randomized studies were included in the systematic review. With respect to dose escalation, a total of 12 studies were identified, all of which were observational; no randomized controlled trials evaluating dose escalation were identified. Of the 12 studies, six were conducted using administrative databases and only reported on patterns of dose escalation, not on impact of dose escalation (Harley et al, Gilbert et al, Stockl et al, George et al, Etemad et al, Ollendorf et al). Based on these studies, the authors reported that dose escalation of infliximab was common in clinical practice. The authors also noted that there were relatively few studies reporting on dose escalation of etanercept; however, they noted that this may be due to the differences in routes of administration. Etanercept is given subcutaneously, and it may not be as convenient for patients to be given multiple subcutaneous injections; whereas infliximab is given as an infusion and dose adjustments can be made easily.

There were six observational studies conducted in a clinical setting that evaluated the impact of dose escalation. Summaries of these studies, as included in the CADTH health technology assessment report are provided below:

- Geborek et al. conducted a two-year study in seven centres in Sweden comparing ETN, infliximab, and LEF treatment in patients with RA who had failed at least two DMARDs, including methotrexate. During the study, 166 patients received etanercept, 135 received infliximab, and 103 received LEF. Patients were evaluated according to ACR and DAS 28 criteria. The initial dose for etanercept was 25 mg twice weekly, and the initial dose for infliximab was 3 mg/kg at weeks zero, two, six, and 12, and every eight weeks thereafter. If the response to infliximab was insufficient, then the dose could be tailored by recommended total dose increments of 100 mg (vial dose), up to a maximum of 500 mg, with the same dosing intervals. If dose increments failed, then more frequent dosing was permitted, down to intervals of four weeks between treatments. Of the patients on infliximab, 57% required increased dosage or shortened treatment intervals. Compared to patients on infliximab, patients on etanercept had significantly better ACR 50 scores at three months ($P < 0.05$). No difference was found at other time points. This suggests that the infliximab dose increase in 57% of the patients had a clinically beneficial impact.
- Abarca et al. studied 244 patients with RA who were treated with infliximab or etanercept between 1999 and 2002 and who were enrolled from rheumatology practices in the US. The authors used chart review to examine the dosing patterns involved in the use of etanercept and infliximab. Patients on etanercept had a mean follow-up of 19.3±14.1 months, and patients on infliximab had a mean follow-up of 14.8 ± 6.9 months. For the 128 patients on etanercept who continued receiving therapy until the end of the study, no significant variation in dose was generally observed. The mean initial dose was 25.0 mg, and the mean last dose was 25.8 mg ($P = 0.16$). For the 56 patients (out of an original 89) on infliximab who continued receiving therapy until the end of the study, significant variation in dose was generally observed. The mean initial dose was 3.38 mg/kg, and the mean last dose was 4.51 mg/kg ($P < 0.001$).
- Sidiropoulos et al. conducted a study of 68 patients with RA who received treatment with IFX to determine the impact of dose adjustments. Patients were studied over the course of 12 infliximab infusions of 3 mg/kg at weeks zero, two, and six, and every eight weeks thereafter. The findings were based on individual responses for 12 infusions. Of the 68 patients in the study, 55 (81%) continued taking methotrexate when switching to infliximab but discontinued other DMARDs, six took other DMARDs with infliximab, and seven received only infliximab. The discontinuation of treatment occurred in 20 patients (29%). The frequency of infliximab injections increased to at least once every six weeks for 73% of the patients. The methotrexate dose was increased for 20% of the patients. In 21% of the patients, the initial dose of infliximab or methotrexate was not modified during follow-up. The response was determined using the DAS. Patients who required a dose adjustment were more likely to have a higher DAS than those who did not ($P < 0.01$). Patients who did intensify treatment had a significant mean decrease in DAS ($P < 0.002$).
- Stern et al. reported two studies. The first study was a retrospective cohort study of infliximab in two clinical practices. The study followed 394 RA patients for up to four infusions. Patients completed a questionnaire about infliximab use. The average infliximab dose increased rapidly

until the end of the first year, then stabilized. The average dose increase over the two years was 41%. Dosage increases occurred in 61% of patients. More than 95% of infusions occurred in an eight-week interval. The average improvement in HAQ disability score was 0.28; 75% of patients continued using infliximab two years after the treatment onset. The second study was a cross-sectional self-report survey of 1,324 patients receiving infliximab. The mean dose after 1.5 years of treatment was 5 mg/kg. Dosage increases occurred in 56% of patients. Higher doses were more frequent in patients with more severe disease, comorbidities, and fibromyalgia.

- Van Vollenhoven et al. conducted a study of 124 patients with RA. The authors compared 44 patients on infliximab with dose increases, 44 patients on infliximab without dose increases, and 36 patients on etanercept. The study used information taken from the Stockholm TNF-alpha follow-up registry. A statistically significant improvement from 3 mg/kg to 5 mg/kg to 7 mg/kg, based on DAS 28 and 28 SJC values, was observed in the dose-increase group. Similar patterns of improvement were observed in the other two groups, making the impact of dose increase questionable. The authors concluded that more study of infliximab at doses > 3 mg/kg is required to draw definitive conclusions about dose increases.
- Durez et al. examined 511 patients with active RA who were being treated with infliximab and followed them for 62 weeks. All patients who continued on methotrexate were treated with 3 mg/kg infliximab at weeks zero, two, and six, and every eight weeks thereafter, up to week 22. At week 22, a clinical judgment was made whether to increase the dose by 100 mg. In total, 22% of the patients received the increased dose because of partial loss of response, and on average, the baseline disease activity was higher for patients who received the increase in dosage versus those who did not (P <0.001). In the group that partially lost response in the initial 22 weeks, the increased dosage was likely beneficial, based on improvement in the ACR criteria. Because of issues related to study design, it was possible that results were due to a regression-to-the-mean effect.

Overall, the CADTH health technology assessment[67] concluded that the evidence regarding dose escalation is limited and that the limitations associated with the observational study designs did not permit evaluation of benefits or harms associated with the dose escalation.

Ariza-Ariza et al. (2007)[76] conducted a systematic review to estimate the proportion of patients with rheumatoid arthritis and on TNF-alpha inhibitors (infliximab, etanercept or adalimumab) who require dose escalation. Of the 15 studies meeting the inclusion criteria, five reported data on the efficacy of dose escalation (Durez 2005, Edrees 2005, Sidiropoulos 2004, van Vollenhove 2004, van Vollenhoven unpublished data from STURE), all of which evaluated infliximab and which were non-randomized uncontrolled studies. ACR 20 responses to dose escalation strategies ranged from 27% to 36%. An ACR 50 response of 13% was reported in one study and the DAS improvement ranged from –0.46 to –0.66 between two studies. The authors reported that dose escalation may result in improved clinical outcomes but that findings may be limited by the lack of high-quality studies included in their review and that not all of the 15 included studies reported any changes in clinical outcomes following dose escalation.

Limitations

There are several limitations associated with the published evidence regarding the treatment of RA patients who did not respond to anti–TNF-alpha therapy. The included studies varied in terms of length of study duration (treatment and follow-up) which may limit the ability to detect less frequent adverse events. Several of the studies were open-label, or single-blinded in design. Limited blinding in a study may introduce bias. Overall, the included studies had differences in patients' baseline disease activity, disease duration, reporting of previous use of antirheumatic therapies, definitions of disease remission, and dosages of current therapies (e.g., methotrexate or glucocorticoids). A limited literature search was conducted, and this report limited the inclusion of primary studies to RCTs.

3. Summary

Three RCTs evaluating infliximab dose escalation were identified.[71-73] With the exception of one of the RCTs,[71] this body of evidence suggested that dose escalation of infliximab up to 10 mg/kg can be an effective treatment strategy in either partial responders or non-responders. One RCT reported that increasing the frequency of etanercept dosing from once weekly to twice weekly did not result in an improvement in clinical outcomes.[75]

Similarly, results from uncontrolled data from two additional randomized controlled trials that were not specifically designed to evaluate dose escalation demonstrated. The PREMIER study evaluating adalimumab and the GO-FORWARD study evaluating golimumab did not observe a benefit in dose escalation among non-responders or partial responders. There was no improvement in ACR 20 response when adalimumab was increased from every other week to weekly dosing in the PREMIER study. Dose escalation of golimumab from 50 mg to 100 mg did not confer an additional benefit in the GO-FORWARD study.

No randomized controlled trial evidence was found evaluating the benefits of dose escalation of certolizumab pegol.

Additional systematic reviews and health technology assessments on dose escalation have been conducted that include observational studies but due to limitations in the designs of the included studies, strong conclusions on the effectiveness of dose escalation could not be made.[67,76,77]

APPENDIX 5: SUMMARIES OF SUPPLEMENTAL INFORMATION

A. Discontinuation of the TNF-alpha Inhibitors in Patients Achieving Remission

Three randomized controlled trials were identified that provided uncontrolled data from one treatment group on the effects of discontinuing TNF-alpha inhibitors: the BeSt study and Quinn 2005, which were conducted in patients with early RA and ATTRACT 2000, which was conducted in patients with established RA.[20,22,78,79]

The original aim of BeSt was to evaluate four different treatment strategies in patients with early RA, only one group of which was initially randomized to biologic therapy (initial combination therapy of infliximab plus methotrexate). In BeSt, tapering of infliximab therapy was initiated in patients sustaining a DAS ≤ 2.4 for at least six months. Clinical remission was defined as DAS <1.6. Drug-free remission was defined as a sustained DAS < 1.6 with no DMARD or biologic therapy. Authors of the BeSt study concluded that initial combination therapy of infliximab and methotrexate with possible dose escalation allows for the discontinuation of infliximab and tapering of methotrexate in some patients. At two years of follow-up, a subgroup analysis demonstrated that initial combination therapy resulted in discontinuation of infliximab in 67% patients after a median treatment duration of 9.9 months. Flares requiring re-initiation of treatment occurred in only 13% of these patients, most of whom subsequently achieved remission with re-initiation of infliximab, although sometimes at higher doses. At four years of follow-up there were no differences in drug-free remission rates between the four treatment groups in the BeSt study with 18% of infliximab plus methotrexate patients achieving drug-free remission.

Quinn 2005 and ATTRACT 2000,[20,22] evaluated discontinuation of infliximab therapy in patients who had enrolled in randomized controlled trials and who were responders to therapy. Both analyses were observational in nature and followed patients who discontinued therapy. In Quinn 2005, conducted in patients with early RA, maintenance of response was maintained in the majority of patients for one year following discontinuation of therapy. In ATTRACT 2000, conducted in patients with established RA, disease flares requiring re-initiation of treatment occurred in almost all patients within 15 weeks. In ATTRACT 2000, patients who re-initiated therapy were able to obtain a response similar to their first response on infliximab indicating no adverse effects associated with discontinuation of infliximab for an interval of several months.

Differences in response to infliximab discontinuation across studies may be related to differences in the enrolled patient populations.

B. Additional Harms Information

Additional harms information was reviewed through identification of regulatory and manufacturer-issued harms warnings, long-term extension data from randomized controlled trials, as well findings from systematic reviews and meta-analyses reporting on harms associated with biologic agents for rheumatoid arthritis.[5,80-106]

A review of recent regulatory warnings yielded the following findings related to TNF-alpha inhibitors as a drug class: a warning of an association between TNF-alpha antagonist use and an increased risk of systemic lupus erythmatosus and various neurologic harms; and a warning of potentially increased risks of infection, malignancy, and cardiovascular disorders. In addition, a number of warnings were identified specific to select biologic agents: a warning of a third case of progressive multifocal leukoencephalopathy in a RA patient treated with rituximab; a warning of a potential association between etanercept use and an increased risk of uveitis, and also an increased risk of fungal infections including histoplasmosis, coccidiodomycosis, blastomycosis, candidiasis,

aspergillosis, pneumocystosis. Other warnings summarized in the Cochrane Overview included the following: an association between TNF-alpha inhibitor use and risk of opportunistic infections, reactivation of tuberculosis and sepsis; risk of pancytopenia, aplastic anemia, autoantibodies, and lupus-like syndrome associated with adalimumab and etanercept use; risk of infusion and hypersensitivity reactions and also an increased risk of hospitalization and mortality for worsening heart failure associated with infliximab therapy; an increased risk of exacerbations, cough, rhonchi, and dyspnea in COPD sufferers treated with abatacept.

Despite regulatory warnings for TNF-alpha inhibitors, there are conflicting results in the published literature regarding the increased risk of malignancy and infection associated with use of Health Canada-approved doses of TNF-alpha inhibitors and other biologic agents used in the treatment of RA. Long-term uncontrolled extension phases that were reviewed have not identified any increase in serious harms relative to that reported in the original double-blind randomized controlled phases of studies. To date, 57 cases of PML following rituximab therapy in HIV-negative patients have been identified, the majority of which occurred in patients with hematologic malignancies.

C. Efficacy of Biologic Agents Compared with Combination DMARD Therapy

Randomized controlled trials evaluating the relative efficacy of DMARD combination therapy compared with biologic therapy in patients with rheumatoid arthritis were reviewed.

Three recent randomized controlled trials evaluating DMARD combination therapy compared with biologic therapy were identified that were of interest: the SWEFOT study,[107] the TEAR study,[108] and the BeSt study.[78]

Combination DMARD therapy (sulfasalazine, hydroxychloroquine and methotrexate) is an effective treatment option for patients with early rheumatoid arthritis who have not had a sufficient response to methotrexate monotherapy but the relative efficacy and harms for TNF-alpha inhibitor therapy compared with combination DMARD therapy are uncertain. Infliximab has been evaluated in the one-year Swefot study (ongoing to two-years) and etanercept has been evaluated in the two-year TEAR study. At six months, as measured by ACR response in the Swefot Study and at 12 months as measured by EULAR response in the TEAR study, differences favouring TNF-alpha inhibitor therapy were observed. At two years, as measured by DAS 28 in the TEAR study, no significant differences were observed between TNF-alpha inhibitor and combination DMARD therapy. Two-year data from the Swefot study will be of interest when available to determine if differences between TNF-alpha inhibitor therapy and combination therapy remain or if they are consistent with findings from the TEAR study where no differences were observed at two years. Four year radiologic data from the BeSt treatment strategy study suggested that joint damage progression remained lower after initial combination therapy with infliximab compared with initial DMARD monotherapy and step up DMARD combination therapy.

APPENDIX 6: PHARMACOECONOMIC REVIEW SUMMARY

Objectives

- To examine the comparative cost-effectiveness of the biologic agents in the treatment of adults with RA.
- To examine the cost-effectiveness of the sequential use of biologic agents in RA based on non-response and treatment failures.

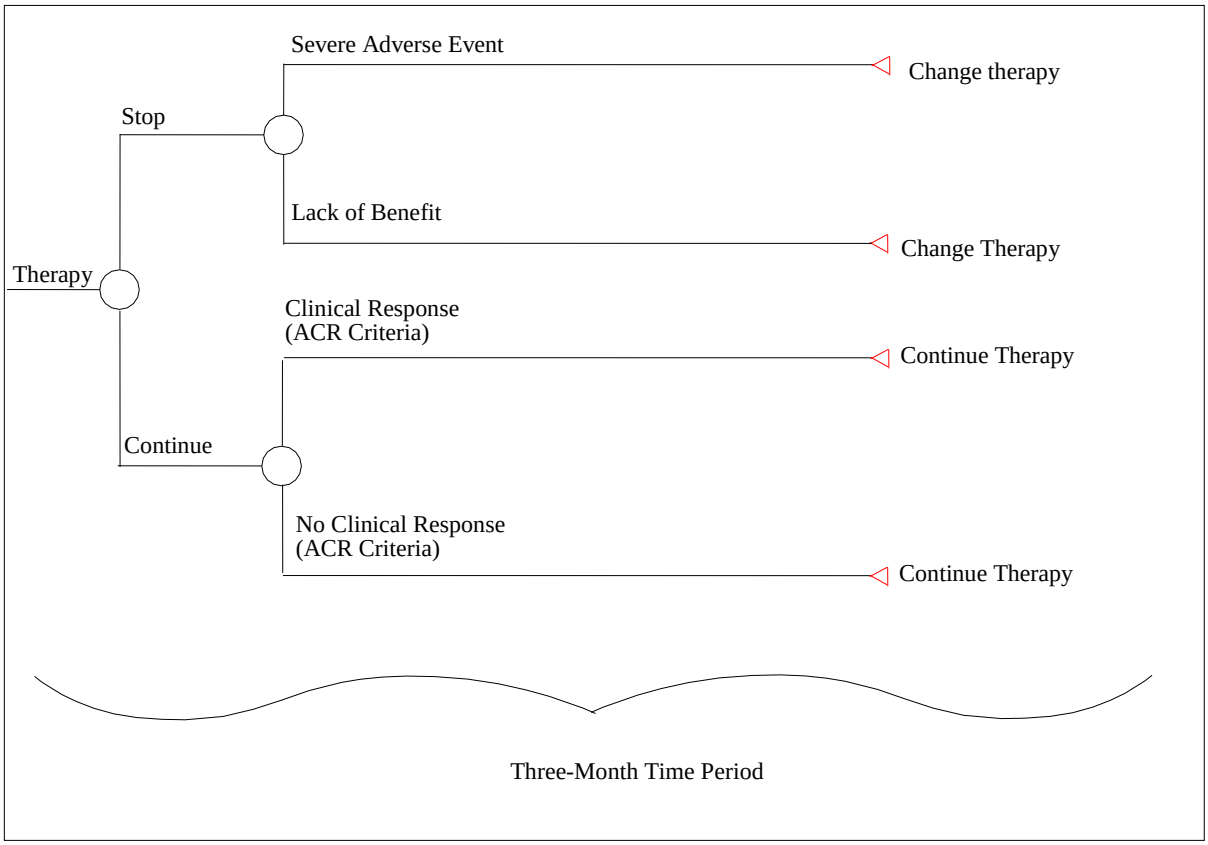
Methods

The primary analysis was a cost-effectiveness analysis conducted within the framework of a decision analytic model to compare the cost-effectiveness of first-line biologic agents in RA in patients who had failed treatment with traditional DMARDs (e.g., methotrexate). The cost-effectiveness of the biologic agents was calculated using supportive care, which consisted of methotrexate as the comparator. The five biologic agents included were abatacept, adalimumab, etanercept, infliximab, and golimumab. Rituximab was not included within this analysis as it is only indicated after failure of a biologic agent. Two further biologic agents were omitted from the analysis. Anakinra was not included in the primary analysis as it is not recommended as a preferred agent based on ACR guidelines;[56] however, it was included in a sensitivity analysis. For the primary analysis, focus was on clinical trial data relating to patients with prior methotrexate use and no previous use of anti–TNF-alpha agents. Trials also had to include adequate methotrexate dosage. Certolizumab pegol was not included in the analysis as there were no relevant RCTs meeting these criteria.

A model was created that simulates a population of RA patients over a course of five years with a cycle length of three months. With each cycle, patients may transition between three states, which include continuing therapy (with either no response or some degree of response to treatment), withdrawal due to adverse events, and withdrawal due to other reasons (e.g., non-response). The results of the MTCs within the CADTH clinical report were used as inputs into the model to inform the transitions of patients from one state to another for each of the medications. Patients continuing with treatment are classified by the extent of their response (no response, ACR 20, ACR 50, and ACR 70) to treatment. The primary outcome measure was the time with an ACR 50 response, as it was assumed to be an appropriate level of response before changing therapy. Costs from appropriate published Canadian sources, including physician and laboratory service fee schedules and provincial drug formularies, were incorporated within the model. The analysis was conducted from the perspective of the health care provider. In addition, an exploratory cost-utility analysis was conducted. There are several different approaches with the literature for calculating utility values based on either their HAQ scores or ACR responses. In this report the method developed by Kielhorn et al.[57] was used for the primary cost-utility analysis; two alternative methods were considered in the sensitivity analysis.[58,59]

A second analysis was conducted that examined the sequencing of biologic agents in the treatment of RA. Within the initial analysis, patients who were withdrawn from biologic therapy were transitioned to supportive care, which consisted of treatment with methotrexate. Within the sequencing analysis, the optimal sequence post–first-line therapy was determined through a net-benefit analysis using a threshold value for willingness-to-pay of $50,000 per quality-adjusted life-year (QALY). The optimal sequence was determined to be adalimumab, followed by golimumab, abatacept, and rituximab. Models were then developed allowing patients to be transitioned to the next biologic agent within the sequence upon withdrawal of the previous biologic, rather than transition direct to supportive care. With each successive model, one additional biologic agent was added to the sequence. The results were reported as the incremental cost per QALY gained of the current sequence in comparison with the prior sequence with one less biologic agent.

Figure A9: Schematic of Markov Model



Key Results and Interpretations

Based on the economic model, the most effective biologic agent, in terms of time with an ACR 50 response, of those indicated as a first-line biologic therapy, was adalimumab. Abatacept, infliximab, and golimumab were all less expensive than adalimumab, but they are also less effective (Table A30). When compared with methotrexate, abatacept, infliximab and golimumab are all subjected to extended dominance through adalimumab and methotrexate — associated with less time with an ACR 50 response and with incremental cost-effectiveness ratios (ICERs) that exceed adalimumab compared with methotrexate. Etanercept is more expensive than adalimumab and less effective and is therefore dominated by adalimumab. Adalimumab was associated with an ICER of $41,899 per time with an ACR 50 response compared with methotrexate. A sensitivity analysis using different rates of response and adopting different parameter values within the model yielded results that were consistent with the ACR 50 response.

Table A30: Cost-Effectiveness Analysis Based on ACR 50 Response				
	Cost ($)	**Time with ACR 50**	**ICER versus Methotrexate ($)**	**Dominance**
Methotrexate	2,784	0.00		
Adalimumab	39,704	0.88	41,899	
Dominated* therapies				
Infliximab	33,503	0.32	95,433	Extended dominance† through adalimumab and methotrexate
Abatacept	37,285	0.48	72,553	Extended dominance through methotrexate and adalimumab
Golimumab	39,087	0.61	59,282	Extended dominance through methotrexate and adalimumab
Etanercept	51,897	0.74	66,476	Dominated by adalimumab

ACR = American College of Rheumatology; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
∗Dominated = less costly and greater QALYs; †Extended dominance = the combination of two other alternatives dominates the treatment.

The results were robust to most changes in the input parameters within the deterministic sensitivity analysis, for example, with costs associated with adverse events, discount rate, proportion of patients requiring home assistance, increasing and decreasing the costs of supportive care, and different time horizons. When anakinra was included in the model, it resulted in an incremental cost per year with ACR 50 response of $65,641 versus methotrexate; consequently, anakinra is subject to extended dominance through adalimumab and methotrexate.

Based on a secondary analysis, the incremental cost per QALY of adalimumab compared with methotrexate was $115,000, while infliximab, abatacept, and golimumab were subjected to extended dominance. The incremental cost per QALY for etanercept versus adalimumab was $409,946. The results were sensitive to the method of estimating utilities: results based on the Chiou method were similar to that of the primary cost-utility analysis with an incremental cost per QALY gained for adalimumab compared with methotrexate of $120,000; while the results using the method derived by Marra, showed that adalimumab and etanercept were dominated by golimumab.

With respect to the sequencing of biologic agents, the optimal sequence was found to be adalimumab, followed by golimumab, abatacept, and then rituximab. When the sequence of two biologic agents, adalimumab followed by golimumab, was compared with adalimumab alone, the incremental cost per QALY was $106,603 (Table A31). When three biologic agents, adalimumab and golimumab, followed by abatacept, were compared with the sequence of two biologic agents, the incremental cost-utility ratio was $134,595. A sequence of four biologic agents compared with three resulted in an incremental cost-utility ratio of $176,665.

Table A31: Incremental Cost per QALY Gained from Adding Biologic Treatment to Sequence				
Step	**Sequence**	**QALY**	**Costs ($)**	**ICER ($)**
1	ADAL→STC	1.36	44,258	
2	ADAL→GOL→STC	1.90	102,402	106,603
3	ADAL→GOL→ABAT→STC	2.14	134,674	134,595
4	ADAL→GOL→ABAT→RTX→STC	2.28	159,693	176,665

ABAT = abatacept; ADAL = adalimumab; GOL = golimumab; ICER = incremental cost-effectiveness ratio; RTX = rituximab; STC = standard care; QALY = quality-adjusted life-year.

Based on an analysis of second-line therapies using only data from trials with patients who had failed previous TNF-alpha inhibitor therapy, abatacept, rituximab, and golimumab were compared with each other and methotrexate. The results of the modelling exercise showed that in comparison with methotrexate, abatacept resulted in an ICER of $97,000 per additional year spent with an ACR 50 response or $153,000 per QALY. Other drugs were less cost-effective in comparison.

Study Limitations

The key limitation of this study is the lack of clinical data for some model parameters. The CADTH MTC combined data from trials with differences in study populations, primarily as a means of allowing comparison across as many biologic agents as possible. The interpretation of the MTC is difficult given the high degree of heterogeneity across the clinical trials. Fewer trials reported outcomes such as ACR 70 and HAQ scores, which limited some of the analyses that could be conducted. In addition, the high rate of withdrawals in clinical trials leads to concerns about the reliability of the comparisons made.

There is limited clinical evidence relating to the use of biologic agents sequentially after failure on a biologic. Thus, analysis after previous TNF-alpha inhibitor agent use was restricted to only the three biologic agents for which such data exists.

Although methotrexate was used as the comparator within the model in order to provide a consistent baseline, as patients had failed methotrexate before entering the clinical trials, the model conservatively assumed that patients on methotrexate did not have a response to treatment. This assumption should not affect the comparison between biologic agents; however, as the assumption provides a conservative estimate regarding the potential benefits of methotrexate, the true ICERs for biologic agents versus methotrexate may be higher than estimated.

Conclusions

An economic evaluation was conducted to examine the relative cost-effectiveness of biologic agents (abatacept, adalimumab, etanercept, infliximab, and golimumab) in patients who had failed treatment with traditional DMARDs, such as methotrexate. It should be emphasized that the clinical inputs for the economic evaluation were based on the results of the MTC meta-analyses, in which clinically meaningful differences in ACR between the biologic agents were not observed. Consequently, the Therapeutic Review Panel focused their deliberations on the cost of biologics rather than the cost-effectiveness estimates derived from the MTC meta-analyses and economic model.

Nevertheless, based on the economic evaluation, adalimumab was found to be the most effective of the biologic agents for use in the treatment of RA after failure of traditional DMARD therapy, as it is associated with the highest rates of ACR response. All other biologic therapies were associated with less clinical benefits and higher total costs (dominated) or associated with less clinical benefits and higher ICERs when compared with adalimumab versus methotrexate (extended dominance). The ICER for adalimumab versus methotrexate, with respect to time with an ACR 50 response, was $41,899. This result may be considered robust as it varied little when subjected to extensive sensitivity analyses.

An analysis of the use of sequential biologic agents found that the sequential use of adalimumab, followed by golimumab, was associated with an incremental cost per QALY of $106,603 when compared with adalimumab alone. The incorporation of additional biologic agents to the sequence resulted in steadily increasing ICERs, indicating that adding treatments to a sequence becomes increasingly less cost-effective as more biologic agents are used. It should be noted that there was limited clinical evidence to inform this analysis.

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