CADTH Therapeutic Review Panel

Final Recommendations

Biological Response Modifier Agents for Adults with Rheumatoid Arthritis

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July 2010

RECOMMENDATIONS

The Therapeutic Review Panel (TRP) recommends that in adult patients with rheumatoid arthritis with an inadequate response on optimal doses of disease-modifying antirheumatic drugs (DMARDs), one of the following biologics: abatacept, adalimumab, etanercept, golimumab, or infliximab could be used in combination with methotrexate or other DMARDs.

- Based on the results of a Canadian Agency for Drugs and Technologies in Health (CADTH) mixed treatment comparison (MTC) meta-analysis of 13 placebo-controlled trials in methotrexate-experienced patients, statistically significant differences in the American College of Rheumatology (ACR) 50 response could not be detected among the following biologics: abatacept, adalimumab, etanercept, golimumab, or infliximab.
- The TRP did not recommend the following biologics in patients who had an inadequate response on optimal doses of DMARDs for the following reasons:
  - Anakinra, unlike other biologics, did not demonstrate a clinically meaningful improvement in the Health Assessment Questionnaire-Disability Index (HAQ-DI) compared with placebo.
  - The quality of the three certolizumab pegol trials included in the CADTH therapeutic review was considered to be limited.
  - Rituximab's Health Canada indication is for patients with an inadequate response or intolerance to one or more tumor necrosis factor (TNF)-alpha inhibitor therapies and so was not considered by the TRP for use in patients with an inadequate response on optimal doses of DMARDs alone.

TRP recommends that for the TNF-alpha inhibitors listed, if no response or a loss of response is observed, the dose of the biologic should not be increased beyond the lowest approved dose.

- There was insufficient evidence of a benefit associated with escalating doses of TNF-alpha inhibitors beyond the lowest Health Canada recommended dose to justify the increased costs associated with higher doses of TNF-alpha inhibitors.
- There were four randomized controlled trials (RCTs) designed to evaluate dose escalation in non-responders or partial responders to a TNF-alpha inhibitor. A statistically significant benefit of dose escalation was not demonstrated in one of the three trials evaluating infliximab and the quality of the other two infliximab trials was limited. The one trial evaluating etanercept found no benefit of an increased frequency of dosing.
- A review of dose escalation of biologics with other mechanisms of action was outside the scope of this therapeutic review.

TRP recommends that following failure of or intolerance to a first TNF-alpha inhibitor, patients may be switched to abatacept or rituximab.

- Two RCTs in patients with an inadequate response to an initial TNF-alpha inhibitor demonstrated that patients taking rituximab or taking abatacept had statistically significantly greater ACR 50 responses compared with placebo.
- There was insufficient RCT evidence to support switching from one TNF-alpha inhibitor to another because in the one RCT that evaluated a TNF-alpha inhibitor, approximately half of the patients had not previously discontinued a TNF- alpha inhibitor due to lack of effectiveness.
- The Panel noted that this recommendation was based on fewer trials compared with the large number of available trials evaluating biologics in patients with an inadequate response to DMARD therapy.

Of Note

- The Panel noted that RCTs evaluating biologics for rheumatoid arthritis are short-term trials with low event rates for serious harms and often provide limited details on the type of serious adverse events observed. During post-market surveillance, serious events, such as progressive multifocal leukoencephalopathy (PML), serious infections, lymphoma, lupus and lupus-like disorder, demyelinating disease, and congestive heart failure have been observed in patients receiving biologics for rheumatoid arthritis. The Panel considered that there were insufficient data on harms to detect differences between biologics.
- The Panel noted that when considering the optimal use of biologics in RA, combination DMARD therapy is the most relevant comparator. Trials are currently ongoing evaluating triple combination DMARD therapy compared with biologic plus methotrexate.
- In patients with an inadequate response on optimal doses of disease-modifying antirheumatic drugs (DMARDs), the Panel noted that when comparing the relative cost-effectiveness of biologics, based on the CADTH economic analysis, adalimumab may be more cost-effective than the other biologics.
- In patients failing a TNF-alpha inhibitor:
    - The Panel considered that switching may be an option for patients who are intolerant but that there are no good quality data reporting on differences in efficacy based on reason for discontinuing initial therapy.
    - The Panel considered that there are observational studies demonstrating that in patients failing a TNF-alpha inhibitor, switching to a different TNF-alpha inhibitor may have some benefit, but that there are limitations associated with the interpretation of observational data.
    - There is no RCT evidence evaluating optimal treatment strategies in patients failing two or more biologics.

BACKGROUND

The CADTH therapeutic review evaluated the comparative effectiveness, harms, and cost-effectiveness of the eight biologics indicated for the treatment of rheumatoid arthritis in Canada at the time of the therapeutic review, as noted in the following table:

Table 1: Health Canada Rheumatoid Arthritis Indications of Biologics Included in the CADTH Therapeutic Review

Biologic	Health Canada Indications*	Health Canada Recommended Dosage and Route of Administration
TNF-alpha inhibitors		
Adalimumab	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.	40 mg **SC** every 2 weeks†
Certolizumab pegol	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.	400 mg **SC** at weeks 0, 2, and 4, then 200 mg every 2 weeks or 400 mg **SC** every 4 weeks
Etanercept	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.	25 mg **SC** biweekly or 50 mg **SC** weekly
Golimumab	For reducing signs and symptoms in adult patients with moderately to severely active RA, in combination with MTX.	50 mg **SC** monthly
Infliximab	For use in combination with MTX for the reduction in signs and symptoms, inhibition of the progression of structural damage, and improvement in physical function in adults with moderately to severely active RA	3 mg/kg **IV** at week 0, 2, and 6, then 3 mg/kg **IV** every 8 weeks‡
T-cell (CD28) co-stimulatory modulators		
Abatacept	For reducing signs and symptoms, inducing clinical response, 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 antagonists or to both.	500 mg **IV** (< 60 kg), 750 mg **IV** (60 kg to 100 kg), or 1g **IV** (> 100 kg) at weeks 0, 2, and 4, and then every 4 weeks
IL-1 antagonists		
Anakinra	For reducing the signs and symptoms of active RA in patients ≥ 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.	100 mg **SC** daily
CD20+ B-lymphocyte inhibitors		
Rituximab	In combination with MTX, rituximab is indicated to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis 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

CADTH = Canadian Agency for Drugs and Technologies in Health; DMARD = disease-modifying antirheumatic drug; IV = intravenous; MTX = methotrexate; RA = rheumatoid arthritis; SC = subcutaneous; TNF = tumor necrosis factor.
*Indications are for use in rheumatoid arthritis. Some biologics also have an indication for use in methotrexate naive patients, but these are not listed as they were not the focus of the TRP recommendations on biologics for rheumatoid arthritis.
†When treated with adalimumab as monotherapy, some patients with rheumatoid arthritis 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 of adalimumab every week.
‡For patients who have an incomplete response to infliximab, consideration may be given to adjusting the dose up to 10 mg/kg and/or treating as often as every four weeks.

SUMMARY OF APPROACH AND EVIDENCE

Clinical Effectiveness

1) Biologics for Rheumatoid Arthritis in Methotrexate-Experienced Patients

The Panel considered a CADTH systematic review of RCTs of biologics for rheumatoid arthritis and an analysis of the relative cost-effectiveness of biologics for rheumatoid arthritis in patients who had failed treatment with non-biologic DMARDs, such as methotrexate (see the Cost and Cost-Effectiveness section).

Outcomes were defined a priori in the CADTH systematic review protocol. Outcomes considered the most important to the Panel included radiographic progression, ACR 50 response, ACR 70 response, functional outcomes as measured by the HAQ-DI, death, and serious adverse events (including malignancies, serious infections, autoimmune disorders, and congestive heart failure). Of these outcomes, MTC meta-analyses were conducted on ACR 50 and ACR 70.

Of the 35 RCTs included in the CADTH systematic review, 25 were conducted in DMARD- experienced patients. All trials were placebo-controlled. Thirteen RCTs were homogenous enough to allow pooling in a MTC meta-analysis and formed the basis of the Panel's discussion. These 13 RCTs were conducted in patients receiving concomitant methotrexate at mean or median doses of ≥ 15 mg per week and evaluated a biologic 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, 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 with no concomitant DMARD, background DMARD therapy may not have consistently included methotrexate or low concomitant methotrexate doses.

The Panel considered that the 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 biologics, the quality of evidence was considered lowest for certolizumab pegol; withdrawals were as high as 87% in the control group of one trial.

Efficacy

- Statistically significant differences between biologics could not be detected based on estimates of ACR 50 response obtained through the CADTH MTC meta-analyses. 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 2: MTC Results for ACR 50 Comparing Biologic plus MTX versus Placebo plus MTX

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, 14.39)	6.72 (3.93, 11.48)
Etanercept	2	548	3.83 (2.03, 11.95)	5.62 (0.99, 31.83)
Golimumab	1	222	3.79 (1.26, 11.66)	3.76 (1.95, 7.26)
Infliximab	2	449	2.6 (1.18, 6.09)	2.52 (1.56, 4.08)
T-CELL (CD28) Co-Stimulatory Modulators				
Abatacept	3	1,138	3.34 (1.84, 6.25)	3.28 (2.44, 4.41)
IL-1 ANTAGONISTS				
Anakinra	2	654	3.04 (1.4, 8.15)	2.95 (1.37, 6.36)
CD20+ B-Lymphocyte Inhibitors				
Rituximab	1	244	3.41 (1.14, 10.42)	3.35 (1.76, 6.40)

CI = confidence interval; CrI = credible interval; MTC = mixed treatment comparison; MTX = methotrexate; OR = odds ratio.

- Absolute mean differences in 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 biologic over control. The mean treatment difference was lowest in one of the trials evaluating anakinra, Cohen 2004 (Δ = –0.11, 95% 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, Cohen 2002.
- 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 biologics 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.
- The Panel considered that there were three certolizumab pegol trials included in the CADTH systematic review but not in the MTC meta-analysis. Although ACR 50, HAQ-DI, and radiographic progression results appeared to be within the range of efficacy estimates for other biologics, interpretation of these data is limited by high withdrawal rates.

Harms

- Serious harms were considered for all 35 trials included in the therapeutic review. The Panel considered that interpretation of the harms data was limited by the short duration of trials, different definitions of serious adverse events, high and differential proportions of withdrawals between treatment groups with inadequate follow-up in patients who withdrew, 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 a serious adverse event were low and details on the types of serious adverse events were often lacking.
- For all of the biologics, 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.

2) Dose Escalation of Biologics for Rheumatoid Arthritis

The Panel considered a CADTH systematic review of RCTs evaluating the effects of dose escalation in patients who were non-responders or who had lost an initial response to a TNF-alpha inhibitor, observational data available from systematic reviews, and the costs associated with increased doses of biologics (see the Cost and Cost-Effectiveness section). A review of dose escalation of biologics with other mechanisms of action was outside the scope of this therapeutic review.

There were four RCTs designed to evaluate dose escalation in the CADTH therapeutic review, three evaluating infliximab and one evaluating etanercept. The Panel considered that the quality of 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 3: RCTs Evaluating Dose Escalation of Biologics

Study	Intervention	Efficacy	Harms
INFLIXIMAB			
Pavelka 2009 141 partial responders or with 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 eight 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 *54 Weeks*	IFX 3 mg/kg (n = 99) IFX 6 mg/kg (n = 104) IFX 10 mg/kg (n = 104) Administered every eight weeks MTX at a stable dose between 6 to 8 mg/week	ACR-N (mean % improvement): 3 mg/kg: 51.3% 6 mg/kg: 53.8% 10 mg/kg: 58.3% Differences only statistically 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 weeks 0,2,6, and 14 109 of 329 patients 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	No statistically significant difference in SAEs

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

Results from uncontrolled data from two additional RCTs that were not specifically designed to evaluate dose escalation demonstrated the following:

- There was no improvement in ACR 20 response when adalimumab was increased from every other week to weekly dosing.
- Dose escalation of golimumab from 50 mg to 100 mg did not confer an additional benefit.

A number of systematic reviews and health technology assessments were also summarized, some of which provided evidence for dose escalation based on observational studies; however, these studies were not the focus of the Panel's deliberations.

c) Biologics for Rheumatoid Arthritis after Failure of a TNF-alpha Inhibitor

The Panel considered a CADTH systematic review of RCTs, a summary of 31 observational studies that were included in a recent National Institute for Health and Clinical Excellence (NICE) technology appraisal on biologics after failure of a TNF-alpha inhibitor, and a CADTH cost-effectiveness analysis of biologics in TNF-alpha inhibitor experienced patients (see the Cost and Cost-Effectiveness section).

Four RCTs were included in the CADTH therapeutic review that evaluated biologics in patients failing an initial TNF-alpha inhibitor.

The Panel considered that the quality of these data was limited by the following factors: the small number of trials conducted in patients failing TNF-alpha inhibitors, the evaluation of patients with less severe rheumatoid arthritis in the golimumab trial and limitations of data from trial subgroups.

Table 4: RCTs Evaluating Biologics 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)	2.8 (1.3, 6.1)	Mean Difference: −0.14	Not measured

ABAT = abatacept; ACR = American College of Rheumatology; ADAL = adalimumab; ETAN = etanercept; GOL = golimumab; HAQ-DI = Health Assessment Questionnaire-Disability Index; IFX = infliximab; OR = odds ratio; PL = placebo; RTX = rituximab.

*One additional RCT 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 Panel did not consider this study any further because of limitations in the data.

** The minimal clinically important difference for HAQ-DI is considered 0.22 in patients with rheumatoid arthritis.

The Panel considered that interpretation of pre-specified subgroup analyses from the above trials was limited as they were based on small numbers and only reported ACR 20 responses.

A summary of a NICE technology appraisal that evaluated biologics (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 in the appraisal. 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; as well, 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 biologics included in the CADTH therapeutic review are provided in the table below. At the lowest Health Canada recommended doses, the annual cost of biologics is relatively similar. Increased costs are associated with dose escalation of biologics.

Table 5: Costs of Biologics Included in CADTH Therapeutic Review

Drug	Price ($)	Health Canada Recommended Doses		1st Year Annual Cost ($)	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)

Table 5: Costs of Biologics Included in CADTH Therapeutic Review

Drug	Price ($)	Health Canada Recommended Doses		1st Year Annual Cost ($)	Subsequent Year Annual Cost ($)
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.

Cost-Effectiveness in Methotrexate-Experienced Patients

The focus of this economic analysis was the relative cost-effectiveness of biologics in patients who had failed treatment with traditional DMARDs such as methotrexate. Abatacept, adalimumab, etanercept, infliximab, and golimumab were included in the analysis.

The time horizon of the economic model was five years with a cycle length of three months and the analysis was conducted from the perspective of the health care payer. The primary outcome in the economic analysis was the time with an ACR 50 response, which was based on ACR responses and withdrawal rates from the CADTH MTC meta-analysis. It was assumed that when patients discontinued therapy the costs associated with biologics would no longer accrue. The economic model estimates show that among the biologics, patients receiving adalimumab had the longest time with an ACR 50 response and patients receiving etanercept had the next longest time. Based on time with an ACR 50 response, the incremental cost-effectiveness ratio (ICER) for adalimumab compared with methotrexate was $41,899. Other TNF-alpha inhibitor therapies were associated with less clinical benefit in terms of ACR 50 response and higher costs or less clinical benefit and higher ICERs compared with adalimumab and methotrexate. These results were considered robust as they varied little when subjected to extensive sensitivity analyses (e.g., drug costs, administration costs, cost of supportive care, time horizons).

Cost-Effectiveness in Patients after Failure of a TNF-Alpha Inhibitor

An economic analysis was conducted to compare the relative cost-effectiveness of biologics in patients with rheumatoid arthritis who are TNF experienced. The primary outcome in the economic analysis was the time with an ACR 50 response, which was based on ACR responses and withdrawal rates from a CADTH MTC meta-analysis of three trials evaluating biologics in TNF-alpha inhibitor experienced patients (golimumab, abatacept, rituximab). It was assumed that when patients discontinued therapy the costs associated with biologics would no longer accrue. Based on the economic evaluation, time with an ACR 50 response was longest for rituximab, followed by abatacept. When compared with abatacept, rituximab appeared more cost-effective.

ADDITIONAL CONTEXT AND PANEL DISCUSSION POINTS

Clinical Outcomes

- The Panel discussed the clinical significance of data demonstrating inhibition of radiographic progression associated with biologics. A range of minimal clinically important differences have been cited and the Panel noted that the value of 4.6 units on the van der Heijde modified Sharp scale represented the smallest detectable difference between radiographs and that clinically important differences may be greater.

Switching Biologics

- The Panel noted that despite a lack of RCT evidence, in clinical practice, clinicians often switch patients to a second TNF-alpha inhibitor if the first TNF-alpha inhibitor was discontinued because of intolerance or loss of effect. Clinicians may consider using a second TNF-alpha inhibitor if there was not a response to the first TNF-alpha inhibitor, but there is less evidence to support this practice.

Dose Escalation

- It was noted that in clinical practice dose escalation is most frequently observed with infliximab.
- The Panel noted that patients and clinicians have suggested that dose escalation may be effective in some patients.

Concomitant DMARDs

- It was noted that when biologics are used in combination with methotrexate, methotrexate dosing should be optimized.
- It was noted that most of the trials included in the CADTH therapeutic review evaluated biologics in combination with methotrexate, but that other DMARDs are available and may be used in clinical practice.

Additional Points Discussed by the Panel

- The Panel discussed that the Canadian Expert Drug Advisory Committee (CEDAC) has made recommendations to list abatacept, adalimumab, golimumab, and rituximab for rheumatoid arthritis. Current CEDAC recommendations indicate that response to therapy should be assessed after 14 to 16 weeks and discontinued if an adequate response has not been observed.
- It was noted that the route of administration may be an important consideration for clinicians and patients. Some patients may prefer subcutaneous injections while other patients may not be able to administer subcutaneous injections and so an intravenous option is required.
- It was noted that the generalizability of clinical trials and their enrolled patient populations to real-world clinical practice is limited and many patients treated in practice do not meet trial inclusion criteria. Further, evidence from clinical trials provides population level data and does not provide adequate insight on the treatment of individual patients in clinical practice.
- The Panel noted that some patients are concerned about adverse events associated with biologics, which may influence their choice of therapy.

EVIDENCE GAPS RELATED TO BIOLOGICS IN RHEUMATOID ARTHRITIS

- The Panel discussed key evidence gaps related to the use of biologics for rheumatoid arthritis and noted that more evidence may become available to address these gaps in the future.
- The Panel considered that evidence on the use of biologics relative to non-biologic DMARDS is insufficient to make a recommendation on the use of biologics in methotrexate-naive patients at this time. Trials are currently ongoing evaluating triple combination DMARD therapy compared with biologic plus methotrexate.
- There was insufficient evidence for the Panel to provide a recommendation on discontinuation of TNF-alpha inhibitors in patients achieving remission. There are no RCTs comparing the effects of discontinuing biologic therapy with continuing biologic therapy in patients who have achieved remission. Based on uncontrolled data, in patients with early rheumatoid arthritis, there was some evidence to suggest that some patients achieving remission (based on Disease Activity Score) may be able to discontinue infliximab without disease flare. There is no evidence of the effects of discontinuation on radiographic progression or disease progression. There is no consensus on the definition of remission and definitions used in research studies may differ from those applied in clinical practice.
- There is limited RCT evidence evaluating treatment strategies in patients with loss of an initial response or no response to an initial TNF-alpha inhibitor, including studies comparing dose escalation with switching biologics; studies evaluating sequencing of biologics; and studies that evaluate whether or not patients with loss of an initial response should be treated the same or differently from those with no initial response.

Participating TRP Members:

TRP Co-Chairs: Dr. Robert Peterson and Dr. Lisa Dolovich

TRP Members: Dr. G. Michael Allan, Dr. Michael Allen, Dr. Bruce Carleton, Dr. Doug Coyle, Dr. Scott Klarenbach, Dr. Laurie Mallery, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

TRP Public Members: Ms. Cathy MacNutt and Mr. Brad Neubauer

TRP Specialist Expert Members: Dr. Jacob Karsh and Dr. Stephanie Ensworth.

Conflict of Interest:

Dr. Lisa Dolovich was co-investigator in studies on behaviour change interventions funded by Merck Frosst Canada Ltd., GlaxoSmithKline Inc., Sanofi-Aventis Pharma Inc., Eli Lilly Canada Inc. and Crystaal Corporation.

Dr. Bruce Carleton has received research support for a national program to improve adverse drug reaction reporting and identification of genetic determinants of drug risk in children: “Canadian Pharmacogenomics Network for Drug Safety”. Funding has been provided by the Canadian Institutes of Health Research (CIHR) and Canada Foundation for Innovation (CFI) from January 2009 to 2013. The University of British Columbia has also received funds from Pfizer Canada that will be used as part of the grant provided by CIHR and CFI. Funding for the period 2004-2008 was primarily provided by Genome Canada with some support from Genome BC, Merck Frosst Canada, Pfizer Canada, Eli Lilly Canada and Janssen-Ortho that provide pooled funds matching government funds for this grant. The pharmaceutical industry has no formal or informal role in this program of research.

Dr. Jacob Karsh has received honoraria for educational lectures from Abbott Canada, Amgen Canada, Bristol-Myers Squibb Canada, Merck Frosst Canada Ltd., Pfizer, Roche Canada, Schering-Plough, and UCB Pharma Canada Inc. He has also received compensation for consulting or advisory services from Abbott Canada, Amgen Canada, Bristol-Myers Squibb Canada, Merck Frosst Canada Ltd., Pfizer, Roche Canada, Schering-Plough, and UCB Pharma Canada Inc.

Dr. Scott Klarenbach is a member of a research group funded by an unrestricted grant from Amgen Canada and Merck Frosst Canada Ltd to the Alberta Kidney Disease Network.

Dr. Peterson received unrestricted funding from Celgene Corporation to lecture on drug safety in China.

Dr. Coyle acted as a consultant on this review and this conflict of interest was resolved in consultation with CADTH.

Based on the CADTH Conflict of Interest Guidelines, no other members had conflicts of interest.

About this Document:

Therapeutic Review Panel Recommendations or Advice are formulated following a comprehensive evidence-based review of the medication’s efficacy or effectiveness and safety and an assessment of its cost-effectiveness. Therapeutic review clinical and economic reports are based on published information available up to the time that the TRP made its recommendation. Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations is considered in the preparation of this recommendation document.

The TRP is a panel of the Canadian Agency for Drugs and Technologies in Health (CADTH). The TRP was established to make recommendations and provide advice to Canadian jurisdictions based on therapeutic reviews completed as part of the therapeutic review pilot project. It is made up of experts in drug evaluation and drug therapy and public members.

The Therapeutic Review Panel Recommendation or Advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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