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SUMMARY WITH CRITICAL APPRAISAL

Triple Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs for the Management of Rheumatoid Arthritis: A Review of Cost-Effectiveness

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Abbreviations

cs	conventional synthetic
DMARD	disease-modifying anti-rheumatic drug
EQ-5D	EuroQol 5-dimensions questionnaire
ETN	entanercept
HAQ	health assessment questionnaire
HCQ	hydrocholoroquine
LEF	leflunomide
MTX	methotrexate
RA	Rheumatoid arthritis
RACAT	rheumatoid arthritis comparison of active therapies
QALY	quality-adjusted life year
QoL	quality of life
SSZ	sulfasalazine
TEAR	Treatment of early aggressive rheumatoid arthritis
WTP	willingness-to-pay

Context and Policy Issues

Rheumatoid arthritis (RA) is an inflammatory, chronic disease of the joint that is characterized by activation of autoantibodies against immunoglobulin G and anticitrullinated protein antibodies.[1] Activated immune cells cause synovial accumulation that leads to cartilage and bone erosion.[2] The prevalence of RA in urban Quebec between 1992 and 2008 was estimated to be as high as 995 per 100,000 females aged 45 years and older and 994 per 100,000 males in the same age group.[3] The prevalence was estimated to be 205 per 100,000 females younger than 45 years, and 73 per 100,000 males younger than 45 years.[3] The prevalence values were lower in age-matched rural populations except for females aged 45 years and older.[3] In Ontario, the prevalence in 2010 was estimated to be 784 (with a 95% confidence interval of 779 to 789) per 100,000 people.[4] Patients with RA have a shorter life expectancy than the general population and are at higher risk of experiencing cardiovascular events.[2]

Methotrexate (MTX), a conventional synthetic disease modifying anti-rheumatic drug (csDMARD), is a folic acid antagonist and is the drug that is most commonly used to treat RA.[5] Some patients may be intolerant of or may not respond adequately to MTX monotherapy, therefore alternate forms of therapy have emerged. Other csDMARDs such as sulfasalazine (SSZ), leflunomide (LEF), and hydroxychloroquine (HCQ) are available and are offered as monotherapy or in combination with other csDMARDs or biologics. For patients who are intolerant of specific csDMARDs[6] or whose RA is inadequately controlled with one or more csDMARDs,[7] biologic therapies such as tumor necrosis inhibitors, T-cell stimulation inhibitors, CD20 inhibitors, IL-6 inhibitors, or JAK inhibitors, are increasingly being recommended.[7] However, given that biologics are significantly more costly than csDMARDs,[8] there are renewed efforts to determine whether combinations of csDMARDs may be more cost-effective.

The aim of this report is to summarize the cost-effectiveness evidence on triple csDMARDs therapy (specifically, methotrexate, sulfasalazine, hydroxychloroquine) relative to other pharmacologic options for the management of RA in North America.

Research Question

What is the cost-effectiveness of triple conventional synthetic disease-modifying anti-rheumatic drugs compared with other pharmacologic options for the management of rheumatoid arthritis?

Key Findings

Two relevant publications comprising cost-effectiveness analyses were identified; one involved patients with rheumatoid arthritis (RA) that could not be adequately controlled by methotrexate (MTX) monotherapy and the other was relevant to patients with early aggressive RA.

One evaluation found that in patients with MTX monotherapy-resistant RA, triple conventional synthetic disease-modifying anti-rheumatic drug therapy (consisting of a combination of MTX, sulfasalazine, and hydroxychloroquine) was cost-effective relative to a combination of etanercept and MTX (ETN-MTX combination therapy) over 24 weeks or 48 weeks. Under the best-case scenario, the projected incremental cost-effectiveness ratio (ICER) for ETN-MTX combination therapy over triple therapy was $137,000 per quality adjusted life-years (QALYs) gained over a lifetime horizon of 50 years. For the ICER to fall below an assumed willingness-to-pay threshold of $100,000 per QALYs gained, the price of ETN would have to fall by two-thirds. The second evaluation found that triple therapy offered immediately was likely to be cost-effective relative to immediate ETN-MTX combination therapy, step-up ETN-MTX combination therapy, and step-up triple therapy in patients with early aggressive RA. The ICER for immediate ETN-MTX therapy compared with triple therapy was $12.5 million per QALY gained. The ICER for the best case scenario was reported as $5.6 million per QALY gained while $14 million per QALY was the ICER for the worst case scenario. The results from the two evaluations are not comparable as they involve different populations, models, inputs, and assumptions.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) Embase, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and February 26, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with moderate to severe rheumatoid arthritis
Intervention	Triple conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs): methotrexate, sulfasalazine, hydroxychloroquine (given in combination)
Comparator	Other drugs for the management of rheumatoid arthritis : - double csDMARDs (any combination of two: methotrexate, sulfasalazine, hydroxychloroquine, leflunomide) - TNF-alpha inhibitors (infliximab, adalimumab, certolizumab pegol, golimumab, etanercept) - T-cell stimulation inhibitor (abatacept) - CD20 inhibitor (rituximab) - IL-6 inhibitors (tocilizumab, sarilumab) - JAK inhibitors (tofacitinib, baricitinib)
Outcomes	Cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they did not involve patients in North America, if they were duplicates or if they were published prior to 2014. Relevant systematic reviews were excluded if all of the primary studies were reported in other relevant systematic reviews. Economic evaluations that reported only on costs without an assessment of costs relative to clinical benefits were excluded.

Critical Appraisal of Individual Studies

The economic evaluations were critically appraised by one reviewer using the Drummond checklist.[9] Summary scores were not calculated; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 551 citations were identified in the literature search. Following screening of title and abstracts, 541 citations were excluded and 10 potentially relevant reports from the electronic search were retrieved for full-text review. Nine potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 19 potentially relevant articles, 17 publications were excluded for various reasons. Two publications met the inclusion criteria and were considered in this report. Appendix 1 presents the PRISMA[10] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study characteristics are summarized below and details are available in Appendix 2, Table 2.

Study Design

Two cost-effectiveness studies were included in this review.[11,12] One was published in 2017 and was based on patients enrolled in the Rheumatoid Arthritis Comparison of Active Studies (RACAT) trial;[11] the other was published in 2016 and was based on patients enrolled in the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial.[12] Both evaluations reported the output as ICERs i.e., the difference in public payer and/or societal costs divided by the difference in health-related quality-adjusted life years (QALYs) between the intervention and the comparator(s).

The 2017 economic evaluation reported on the incremental cost-effectiveness of ETN-MTX combination therapy relative to triple therapy (i.e., MTX+SSZ+HCQ therapy) in patients with MTX-resistant RA at stable doses of 15 to 25 mg per week of MTX for at least 12 weeks.[11] The authors reported the costs from the perspectives of the society and Medicare – a US public payer program – and extracted the QALYs from the RACAT trial. Two sets of analyses were conducted: a within-trial analysis based on measurements taken at 24 weeks and 48 weeks in the RACAT trial, and a lifetime analysis based on a sampling decision analytic model that extrapolated outcomes to a 50 year time horizon.

For the within-trial analysis, base case costs included drug costs (estimated from dosages) and costs associated with outpatient visits, diagnostic tests, joint procedures, hospitalizations, and productivity losses (through absenteeism). Unit costs for the base case were derived from the US Medicare schedule (i.e., the public payer perspective) and productivity losses (i.e., the societal perspective). Productivity losses were calculated from average wages of men and women of the corresponding age as reported by the US Bureau of Labor Statistics. QALYs were estimated on a scale of 0 (representing death) to 1 (representing full health) using the Health Assessment Questionnaire (HAQ), the EuroQol 5-dimensions questionnaire (EQ-5D), and the Sharp score. The HAQ measured inflammatory and radiographic elements of functional disability with scores ranging from 0 (representing no disability) to 3 (representing severe disability); the EQ-5D measured health-related quality of life (QoL) with scores ranging from 0 (representing death) to 1 (representing full health); while the Sharp score measured radiographic disease progression. The Sharp scale was not described. Deterministic sensitivity analyses were conducted around the base case using various scenarios, including but not limited to: varying the patient withdrawal rate from triple therapy, the cost of triple therapy and biologics, duration of triple therapy, baseline HAQ, HAQ progression, radiographic progression, cohort age, sex, and the standardized mortality ratio. The model was validated by comparing estimated outcomes with those reported in the published literature.

For the lifetime analysis costs and QALYs were extrapolated out to a lifetime horizon of 50 years. Future resource use and productivity costs were estimated as a function of HAQ scores and adjusted to 2014 US dollars. All costs were discounted at 3% per year. The probability of switching treatments was estimated with a Weibull model of data from the RACAT trial. Projected mortality rates were based on the 2009 US life table adjusted for RA standardized mortality ratios.

The 2016 study evaluated the cost-effectiveness of immediate triple therapy relative to immediate ETN-MTX combination therapy, step-up triple therapy, and step-up ETN-MTX combination therapy in patients with early aggressive RA (not defined).[12] The study took a societal cost perspective and projected outcomes over a time horizon of five years using a Markov model for a hypothetical cohort of patients similar to those enrolled in the TEAR trial. A longer time horizon was not evaluated as the authors indicated that it would be

challenging to make model predictions for longer time horizons because patients switch medications. Costs included direct drug and non-drug costs, additional annual direct costs calculated as a function of HAQ, and productivity losses also calculated as a function of HAQ. Costs were adjusted to 2013 US dollars and discounted at 3% per year. The sources of clinical inputs were the TEAR trial, supplemental clinical data from a cohort of 2459 RA patients treated over the span of seven years at a private clinic, and published literature. QALYs for the hypothetical cohort were estimated through HAQ scores derived from the disease activity scores in 28 joints (DAS28) of the supplemental cohort. Utility functions were calculated that defined the relationship between HAQ and QoL and the relationship between HAQ and mortality rates. One-way deterministic and probabilistic sensitivity analyses were conducted by varying the costs of ETN and triple therapy, the QoL utility function, treatment discontinuation rates, indirect costs, median annual wages, and additional direct cost per HAQ. The deterministic sensitivity analysis also included adjustments to the cohort's mean starting age and the annual discount rate.

Country of Origin

The 2017 economic evaluation was written by authors in Canada (British Columbia and Ontario) and the US (California, Nebraska, and Massachusetts).[11] It involved six treatment centres, including tertiary-care hospitals in Canada and the US and Veterans Affairs health care centres in the US.[11] The 2016 evaluation was written by authors in the US (Pennsylvania, Nebraska, Alabama, and Kansas) and it enrolled patients in the US only.[12]

Patient Population

The 2017 economic evaluation involved 324 patients with active RA that remained uncontrolled after 12 week of MTX therapy.[11] Patients were enrolled in the RACAT trial and received MTX at a mean baseline dose of 19.6 mg per week (i.e., a range of 15 to 25 mg per week). The average age of the patient cohort was 56.8 years.

The 2016 economic evaluation modelled a base case of a hypothetical cohort of patients with early aggressive RA similar to those enrolled in the US-based multicenter, double-blinded randomized TEAR trial.[12] Disability scores were extracted from a supplemental cohort of 2459 patients who were treated at a private clinic. The average age of the patient cohort was 50 years at the start of treatment.

Interventions and Comparators

In the study involving patients with active MTX-resistant RA, authors assumed a cohort where 163 patients with an average age of 56.3 years were randomized to ETN-MTX combination therapy while 161 patients with an average age of 57.3 years were randomized to triple therapy.[11] Mandatory blind switching following 24 weeks of therapy was modelled for patients in either group who did not achieve at least a 1.2-point decrease in their DAS28 score. A total of 26.7% of patients who initially received ETN-MTX therapy switched to another biologic while 27.0% of those who initially received triple therapy switched to a biologic and MTX. The lifetime analysis allowed patients being treated with MTX and a biologic to switch to other biologics as needed and those starting on triple therapy to switch to biologics as needed.

For patients with early aggressive RA, four sets of treatments were considered: immediate triple therapy (i.e, MTX+SSZ+HCQ in combination), immediate ETN-MTX therapy, step-up triple therapy after 24 weeks of MTX monotherapy, and step-up ETN-MTX therapy after 24 weeks of MTX monotherapy.[12] Patients with persistent disease (i.e., in health states S4

through S7 as determined with DAS28 scores greater than 3.2 but less than or equal to 6.0) had step-up therapy after being on MTX monotherapy for 24 weeks.[12] The number of patients in each group was not reported.

Outcomes

The 2017 economic evaluation reported on ICERs in 2014 US dollars per QALY.[11] A cost-effectiveness (or willingness-to-pay) threshold of $100,000 per QALY gained was used.[11] The 2016 economic evaluation reported on ICERs in 2013 US dollars per QALY and multiple cost-effectiveness thresholds were considered.[12]

Summary of Critical Appraisal

A summary of the critical appraisal of the studies is summarized below and details are available in Appendix 3, Table 3.

The economic evaluations[11,12] were assessed using the Drummond checklist.[9] Common strengths were that the intervention and comparator(s), the physical units of costs and consequences, and the incremental analysis were appropriate and costs and consequences were adjusted for differential timing through discounting.

With regard to limitations, comparisons were restricted to ETN in combination with MTX, although other biologics, csDMARDS, and combination therapies are available for patients with RA. Additional comparators may have been appropriate suggesting that the evaluations could have been more comprehensive. Allowances were made for uncertainty in the estimates of clinical and cost data; however, the sensitivity analyses varied in breadth and methodology.

The differences in the sensitivity analyses and notable methodological limitations preclude synthesis of the findings. Both evaluations accounted for variation in the rates of discontinuation or withdrawal, drug costs, and cohort age; however, only one accounted for uncertainty in response rates, male to female ratio, baseline HAQ, and standardized mortality ratio,[11] while the other accounted for variation in quality of life parameters, additional direct and indirect costs, discount factor, and annual wages.[12] Additionally, the evaluations established effectiveness of the intervention and comparator(s) from one clinical trial each. The small number of studies suggests that the sources of clinical inputs may have been artificially restricted. In fact, neither of the studies included a systematic review to identify other published studies with clinical inputs objectively. The authors of both evaluations did not provide justification for their sources of clinical and cost data. It is unclear whether all relevant costs were included in the base cases or whether they were credibly valued (particularly in reference to the Canadian context). Some projected costs were estimated from HAQ scores that were extrapolated from US patients.[12]

Summary of Findings

Appendix 4, Table 4 presents the main study findings and authors' conclusions.

The ICER for treating MTX-resistant RA patients with ETN-MTX over triple csDMARDS therapy was $2.67 million per QALY gained after 24 weeks of treatment and $0.978 million per QALY gained after 48 weeks, suggesting that, in the short-term, ETN-MTX was not cost-effective relative to triple therapy in MTX-resistant patients at a willingness to pay threshold of $100,000.[11] Over a lifetime of 50 years, the ICER for ETN-MTX compared with triple therapy was $521,520 with the best-case scenario projected to be $137,000 per

QALY gained and the worst-case scenario was that ETN-MTX would be dominated by triple therapy. The ICERs' lower bound was achieved when the probability of switching from triple therapy to biologic was doubled from the base case while the upper bound was achieved when the probability was halved. In the reference case, for the ICER to fall below the assumed willingness-to-pay (WTP) threshold of $100,000 per QALY gained, the price of biologics would have to fall by two-thirds.

For patients with early aggressive RA, immediate ETN-MTX was not likely to be cost-effective relative to immediate triple therapy given the ICER over a five-year period was estimated to be $12.5 million per QALY gained.[12] Deterministic sensitivity analyses suggested that the model was most sensitive to changes in the cost of ETN. At an annual cost of ETN of $12,000 the ICER could decrease to $5.6 million per QALY gained and at an annual cost of $30,000, it could increase to as high as $14 million per QALY gained. Step up triple therapy and step up ETN-MTX resulted in lower QALYs at higher costs and as such were also not likely to be cost-effective relative to immediate triple therapy. Immediate triple therapy remained the most cost-effective therapy and the dominant therapy at WTP thresholds lower than $5.6 million per QALY gained. Step up ETN-MTX was dominated by the other strategies at all WTP thresholds examined.

Although both evaluations compared ETN-MTX to triple therapy, their patient populations, model inputs, assumptions, and time horizons were different. As such, the ICERs that were calculated could not be compared.

Limitations

The body of evidence on the cost-effectiveness of triple therapy over other pharmacologic options for the management of moderate to severe RA has limitations that warrant caution when interpreting the results of the report. Indirectness of the evidence, variability in the analyses, the small size of the body of evidence, and the lack of Canadian sources are all limitations that are worth highlighting.

With regard to indirectness of the evidence, neither evaluation specifically covered patients with *moderate to severe* RA; one referred to patients with MTX-resistant RA[11] while the second referred to patients with early aggressive RA while extracting data from an external group of patients whose RA was not described.[12] The differences in patient populations, model inputs, assumptions, and time horizons for the base cases make it challenging to compare the outcomes. Each evaluation was based on one trial each and data on viable comparators were missing as neither of the studies reported on the use of biologics other than ETN, single csDMARDs other than MTX, or on the use of combinations other than ETN-MTX therapy.

Despite being conducted by authors out of the US and Canada and being based on a clinical trial enrolling patients in both countries, the sensitivity analysis conducted by Bansback et al., did not explicitly cover the Canadian context.[11] Unit drug costs were estimated from the US' Medicare schedule and productivity losses were based on average wages in the US. The study by Jalal et al., focused exclusively on patients in the US.[12] Information from more Canadian sources or country-specific analyses may have improved the generalizability of the findings to patients with moderate to severe RA in Canada.

Conclusions and Implications for Decision or Policy Making

One economic evaluation conducted by authors based in the US and Canada, found that triple therapy was cost-effective relative to ETN-MTX in MTX-resistant patients at a presumed willingness-to-pay threshold of $100.000 per QALY,[11] while another evaluation found that immediate triple therapy was cost-effective relative to immediate ETN-MTX combination therapy, step up triple therapy and step up ETN-MTX combination therapy in patients with early aggressive RA at willingness-to-pay thresholds up to $5.6 million per QALY.[12] Each evaluation was based on one trial, viable comparators were not included in the analyses, and little or no data was derived from Canadian sources. Consequently, it is not possible to make conclusions about the cost-effectiveness of triple therapy relative to all other pharmacologic options for the management of moderate to severe RA in Canada.

Further research addressing the effectiveness of triple therapy relative to other therapies such as other csDMARDs in combination or as monotherapies or biologics that have been approved for use in Canada may be useful, along with more research assessing differences in adverse effects of RA therapy.[1,11] More evidence on outcomes such as radiographic progression rate, probability of switching therapy, direct quality of life measurements, and treatment withdrawal rates due to adverse events is also needed.

When contemplating the cost-effectiveness of triple therapy in Canada, decision-makers may need to consider, among other things, the rate at which new csDMARDs and other therapies are being developed,[1] the potential for an increase in the availability and lower costs of biosimilars,[2] and differences in health care reimbursement between the US and Canada.

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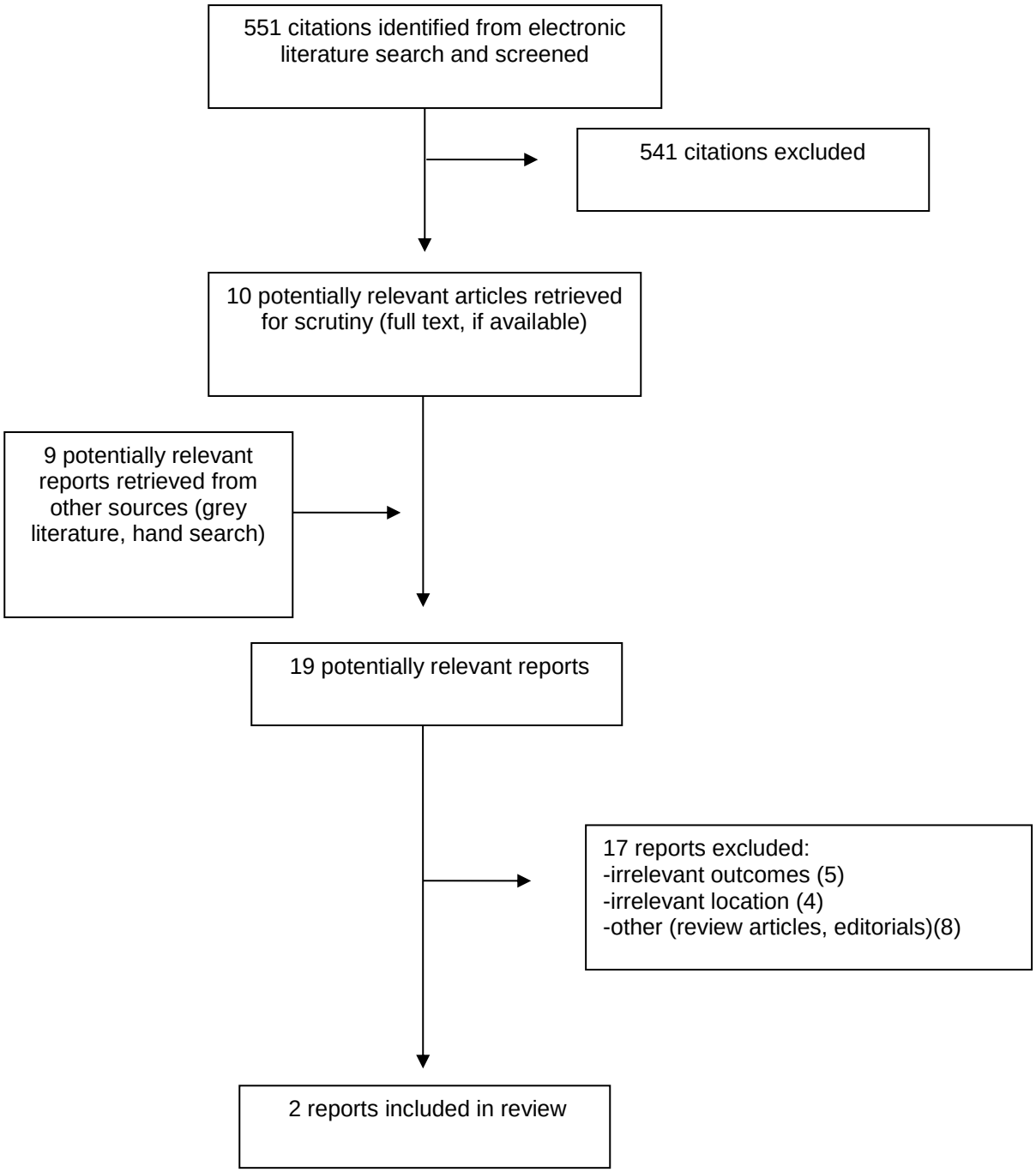
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Bansback, 2017,[11] Canada and United States	Cost-effectiveness analysis, 24 weeks, 48 weeks and lifetime time horizon, societal and US public payer (Medicare) perspective	To analyze the cost-effectiveness of ETN-MTX over triple therapy for RA following ≥ 12 weeks of 15 to 25 mg per week of MTX therapy	324 patients with active RA despite ≥ 12 weeks of 15 to 25 mg per week of MTX therapy; enrolled in the RACAT study Mean age at treatment: 56.8 years	Intervention: ETN-MTX therapy (n = 163) Comparator: MTX+SSZ+HCQ triple therapy (n = 161)	Within-trial analysis: Observational data Deterministic sensitivity analysis Lifetime analysis: Decision analytic model that extrapolated costs and QALYs to a lifetime time horizon	Clinical data HAQ, EQ-5D, and Sharp scores from the RACAT trial Cost data Drugs, outpatient health care visits, diagnostic tests, surgical joint procedures, hospitalizations, and productivity costs	• Lifetime time horizon was 50 years • Discount rate was 3% per year • Willingness-to-pay threshold was $100,000 per QALY • Drug costs were estimated from dosages • Costs were adjusted to 2014 dollars
Jalal, 2016,[12] United States	Cost-effectiveness analysis, 5-year time horizon, societal perspective	To analyze the cost-effectiveness of first-line ETN-MTX therapy, step-up triple therapy, and step-up ETN-MTX over immediate triple therapy as first line therapy for RA	A hypothetical cohort of patients with early aggressive RA similar to those enrolled in the TEAR study Mean age: 50 years (range, 40 to 60)	Intervention: first-line MTX+SSZ+HCQ triple therapy (n = 132) Comparators: first-line ETN-MTX therapy (n = 244), step-up triple therapy after 24 weeks of MTX (n = 124), step-up ETN-MTX therapy after 24 weeks of MTX (n = 255)	Markov cohort model; 7 disease activity states and one absorbing state of death; transition probabilities among disease states was estimated from the TEAR study One-way	Clinical data Computed HAQ disability indices/scores for TEAR patients from DAS28 scores of 2459 RA patients seen over 7 years at a private clinic Estimated RA-	• Time horizon was 5 years • Discount rate (for costs and QoL) was 3% per year • Discontinuation rates were 40.8% for triple therapy and-MTX therapy 25% for ETN • Costs were adjusted to 2013 dollars

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
					deterministic and probabilistic sensitivity analyses	specific mortality rates from HAQ and 2006 US Life Tables; derived QoL from HAQ scores <u>Cost data</u> Direct drug and non-drug costs; indirect costs from productivity losses and/or mathematical relationships to HAQ	

ETN = etanercept; DAS28 = disease activity score in 28 joints; HAQ = Health Assessment Questionnaire; HCQ = hydroxychloroquine; MTX = methotrexate; QoL = quality of life; RA = rheumatoid arthritis; RACAT = RA Comparison of Active Therapies; SSZ = sulfasalazine; TEAR = treatment of early aggressive RA

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Economic Studies using the Drummond Checklist[9]

Strengths	Limitations
Bansback, 2017[11]	
• The study examined the cost-effectiveness of ETN-MTX in comparison with triple therapy as a first-line strategy. Patients had been on MTX for ≥ 12 weeks and had failed to adequately recover • The perspective was stated as societal and Medicare (a US-based public coverage program) • The intervention and comparator were adequately described and appropriate • Costs were measured in appropriate physical units and adjusted to 2014 US dollars • Future costs were discounted by 3% • An incremental analysis of the costs and consequences was conducted • The type of cost analysis used was appropriate • Allowance was made for uncertainty in withdrawal rates, changes to drug costs, and uncertainty in response rates by conducting sensitivity (i.e., multiple scenario) analyses	• Clinical data for the base case were extracted primarily from one study (i.e., the RACAT trial) • The authors presented the intervention as a first-line therapy, yet patients had been on MTX for ≥ 12 weeks prior to enrollment • It is unclear whether all relevant costs were included • It is unclear whether the costs and consequences were credibly valued. • Justification for the discount rate was not provided
Jalal 2016[12]	
• The study examined the cost-effectiveness of triple therapy in comparison with ETN-MTX, step-up triple, and step –up ETM-MTX • The perspective was stated as societal • The intervention and comparators were adequately described and appropriate • Costs were measured in appropriate physical units and adjusted to 2013 US dollars • Future costs were discounted by 3% • An incremental analysis of the costs and consequences was conducted • The type of cost analysis used was appropriate • Allowance was made for uncertainty in discontinuation rates, cost of therapy, quality of life parameters, additional direct costs, productivity losses, discount factor, and age, by conducting sensitivity analyses with a Markov model	• The effectiveness of the intervention and comparators was established using conversion factors based on clinical data from a cohort of patients that was not adequately described • It is unclear whether all relevant costs were included • It is unclear whether the costs and consequences were credibly valued. • Some projected costs were indirectly estimated from HAQ scores. • Justification for the discount rate was not provided

ETN = entanercept; HAQ = health assessment questionnaire; MTX = methotrexate; RACAT = rheumatoid arthritis comparison of active therapies

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Economic Evaluations

Main Study Findings	Authors' Conclusion
Bansback, 2017[11]	
Within-trial analysis (base case) **ETN-MTX (n=163) vs. triple therapy (n=171) at 24 weeks (following ≥ 12 weeks of MTX monotherapy)** Cost of drugs ($): 11,295 vs. 343 Total costs ($): 12,002±2656 vs. 1225±2558[a] Increase in total costs ($): 10,786 (CI, 10,163 to 11,353)[b] Change in EQ-5D (QALY): 0.358±0.075 vs. 0.353±0.075 QALYs gained: 0.004 (CI, -0.004 to 0.012) ICER ($/QALYs gained): 2.67 million (CI, 0.87 to infinity);[c] suggesting that ETN-MTX is clinically superior to triple therapy but the clinical gains come at a high cost. ETN-MTX is not cost-effective at a WTP threshold of $100,000 per QALY gained. **ETN-MTX (n=163) vs. triple therapy (n=161) at 48 weeks (following ≥ 12 weeks of MTX monotherapy)** Cost of drugs ($): 19,634 vs. 3680 Total costs ($): 21,611±6756 vs. 6328±14,108[a] Increase in total costs ($): 15,233 (CI, 12,204 to 17,275)[b] [Increase in other health care and productivity costs ($): <800] Change in EQ-5D (QALY): 0.743±0.147 vs. 0.726±0.145 QALYs gained: 0.016 (CI, -0.007 to 0.039) ICER ($/QALYs gained): 0.978 million (CI, 0.39 to infinity);[c] suggesting that ETN-MTX provides clinical benefits at a high cost Lifetime analysis (base case) over 50 years **ETN-MTX (n=163) vs. triple therapy (n=161) over a lifetime of 50 years (following ≥ 12 weeks of MTX monotherapy)** Total costs ($): NR Increase in total costs ($):77,290 Change in HAQ scores (QALY): NR QALYs gained: 0.148 (CI, 0.01 to 0.31) ICER ($/QALYs gained): 521,520 (CI, 137,000 to dominated) Sensitivity and scenario analysis Best possible ICER ($/QALYs gained): 350,000 with worst possible radiographic progression and change in HAQ in the triple therapy group For the ICER to fall below 100,000 $/QALY gained, the price of biologics would have to fall by 2/3	*"…in patients who have RA not adequately controlled by methotrexate alone, we found that the additional costs associated with using ETN–MTX before triple therapy do not provide good value. Even from a long-term perspective, under optimistic scenarios, first-line therapy with ETN–MTX or other biologics likely is not a cost-effective use of resources compared with using triple therapy first."* (p 14)
Jalal 2016[12]	
Lifetime analysis (base case)[d]	*"…[immediate triple therapy] is highly CE in early aggressive RA*

Main Study Findings	Authors' Conclusion
Immediate ETN-MTX vs. immediate triple therapy over a 5-year time horizon[e] Total costs ($): 148,800 vs. 52,600 Increase in total costs ($): 96,200 Change in HAQ scores (QALY): 3.4831 vs. 3.4755 QALYs gained: 0.0076 ICER ($/QALYs gained): 12.5 million; suggesting that although immediate ETN-MTX is marginally more clinically effective than immediate triple therapy, that benefit comes at a cost so high that the therapy is not cost-effective relative to triple therapy Step up triple therapy and step up ETN-MTX resulted in lower QALYs at higher costs and as such were not cost-effective relative to immediate triple therapy <u>Deterministic sensitivity analysis</u>[f] ICER range ($/QALY gained): 5.6 to 14 million for ETN-MTX over triple therapy, as annual ETN cost changes from $12,000 to $30,000 Other modifiable parameters included utility function converting HAQ to QoL, annual discontinuation rates, cost of triple therapy, direct and indirect cost factors, discount rate, and annual wage. <u>Probabilistic sensitivity analysis</u> Immediate triple therapy is likely to be the most CE strategy and the dominant strategy at WTP thresholds < $6 million/QALY gained Between $6 million/QALY gained and $12.5 million/QALY gained, the probability of first-line triple therapy being the most CE strategy is < 50% but it remains the optimal strategy Step up triple therapy is less CE than immediate triple therapy at all WTP thresholds examined Step up ETN-MTX is dominated by other strategies at all WTP thresholds examined	*in the first 5 years of disease, and a substantial reduction in biologic agent cost is required for it to be cost-effective at these WTP thresholds."* (p 1755)

CE = cost-effective; CI = 95% confidence interval; EQ-5D = EuroQol 5-dimensions questionnaire; ETN = etanercept; HAQ = health assessment questionnaire; ICER = incremental cost-effectiveness ratio; MTX = methotrexate; NR = not reported; QALY = quality-adjusted life years; WTP = willingness-to-pay

[a] Based on multiple imputation results

[b] Adjusted for baseline HAQ score and sex

[c] Adjusted for baseline EQ-5D score

[d] ICERs at year 1 and 2 are not reported in this review

[e] Results from 1 year and 2 year time horizons are not reported in this review

[f] Results from the value of information analysis are not reported in this review

Appendix 5: Additional References of Potential Interest

Non-North American cost-effectiveness studies (in reverse chronological order)

The Netherlands

de Jong PH, Hazes JM, Buisman LR, et al. Best cost-effectiveness and worker productivity with initial triple DMARD therapy compared with methotrexate monotherapy in early rheumatoid arthritis: cost-utility analysis of the tREACH trial. *Rheumatology*. 2016 Dec;55(12):2138-2147.

Sweden

Eriksson JK, Karlsson JA, Bratt J, et al. Cost-effectiveness of infliximab versus conventional combination treatment in methotrexate-refractory early rheumatoid arthritis: 2-year results of the register-enriched randomised controlled SWEFOT trial. *Ann Rheum Dis*. 2015 Jun;74(6):1094-1101.

United Kingdom

Patel A, Heslin M, Scott DL, Stringer D, Birrell F, Ibrahim F. Cost-effectiveness of combination disease-modifying antirheumatics vs. tumour necrosis factor inhibitors in active rheumatoid arthritis: TACIT trial. *Arthritis Care Res (Hoboken)*. 2019 Jan 10;10:10.

Wailoo A, Hernandez Alava M, Scott IC, Ibrahim F, Scott DL. Cost-effectiveness of treatment strategies using combination disease-modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis. *Rheumatology.* 2014 Oct;53(10):1773-1777.