ORIGINAL RESEARCH

Annals of Internal Medicine

# Triple Therapy Versus Biologic Therapy for Active Rheumatoid Arthritis

## A Cost-Effectiveness Analysis

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**Background:** The RACAT (Rheumatoid Arthritis Comparison of Active Therapies) trial found triple therapy to be noninferior to etanercept–methotrexate in patients with active rheumatoid arthritis (RA).

**Objective:** To determine the cost-effectiveness of etanercept–methotrexate versus triple therapy as a first-line strategy.

**Design:** A within-trial analysis based on the 353 participants in the RACAT trial and a lifetime analysis that extrapolated costs and outcomes by using a decision analytic cohort model.

**Data Sources:** The RACAT trial and sources from the literature.

**Target Population:** Patients with active RA despite at least 12 weeks of methotrexate therapy.

**Time Horizon:** 24 weeks and lifetime.

**Perspective:** Societal and Medicare.

**Intervention:** Etanercept–methotrexate first versus triple therapy first.

**Outcome Measures:** Incremental costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs).

**Results of Base-Case Analysis:** The within-trial analysis found that etanercept–methotrexate as first-line therapy provided marginally more QALYs but accumulated substantially higher drug costs. Differences in other costs between strategies were negligible. The ICERs for first-line etanercept–methotrexate and triple therapy were $2.7 million per QALY and $0.98 million per QALY over 24 and 48 weeks, respectively. The lifetime analysis suggested that first-line etanercept–methotrexate would result in 0.15 additional lifetime QALY, but this gain would cost an incremental $77 290, leading to an ICER of $521 520 per QALY per patient.

**Results of Sensitivity Analysis:** Considering a long-term perspective, an initial strategy of etanercept–methotrexate and biologics with similar cost and efficacy is unlikely to be cost-effective compared with using triple therapy first, even under optimistic assumptions.

**Limitation:** Data on the long-term benefit of triple therapy are uncertain.

**Conclusion:** Initiating biologic therapy without trying triple therapy first increases costs while providing minimal incremental benefit.

**Primary Funding Source:** The Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development, Canadian Institutes for Health Research, and an interagency agreement with the National Institutes of Health–American Recovery and Reinvestment Act.

*Ann Intern Med.* 2017;167:8-16. doi:10.7326/M16-0713 **Annals.org**

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This article was published at Annals.org on 30 May 2017.

* For a list of Cooperative Studies Program (CSP) 551 RACAT (Rheumatoid Arthritis Comparison of Active Therapies) Investigators, see the **Appendix** (available at Annals.org).

The American College of Rheumatology recommends that biologic therapy be initiated in patients with rheumatoid arthritis (RA) whose disease is not controlled by a combination of conventional disease-modifying antirheumatic drugs (DMARDs) (1). Consequently, biologic drugs, such as the anti–tumor necrosis factor agents etanercept, adalimumab, infliximab, golimumab, and certolizumab, have become widely used. Biologics are expensive and consistently have been among the 10 top-selling drugs in the past 10 years (2), leading to huge increases in pharmaceutical expenditures (3). Some experts have suggested that the health benefits gained from using biologics justify their additional costs (4). However, the cost-effectiveness studies used as the rationale for this suggestion compared biologics with individual DMARDs instead of a combination of these agents in patients with RA not controlled by methotrexate monotherapy.

Recent studies demonstrated that the most effective DMARD combination is triple therapy with sulfasalazine, hydroxychloroquine, and methotrexate. In fact, triple therapy recently was shown to be neither inferior to nor less safe than adding a biologic to methotrexate (5, 6). As part of a large, multicenter, multinational, double-blind trial, the RACAT (Rheumatoid Arthritis Comparison of Active Therapies) study compared triple therapy with etanercept–methotrexate as a first-line strategy in patients with RA who had suboptimal responses to methotrexate monotherapy (7). This study's results support the findings of other trials of triple therapy (8), not only by confirming noninferiority but also by showing that patients who did not have meaningful improvement with etanercept–methotrexate after 24 weeks of treatment achieved favorable responses to triple therapy, and vice versa (7).

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*Web-Only*
Supplement

Despite this evidence, triple therapy is seldom initiated before biologics after DMARD monotherapy failure (9, 10), perhaps because questions remain about other costs potentially associated with triple therapy as well as the long-term consequences of the differences in secondary outcomes in the RACAT trial, such as radiographic progression (which was observed in the triple-therapy group). To address these remaining uncertainties, the present study considered the cost-effectiveness of implementing triple therapy first.

## METHODS

### Overview

The aim of the analysis was to determine the incremental cost-effectiveness ratios (ICERs) of etanercept–methotrexate versus triple therapy as first-line treatment for patients with active RA unresponsive to methotrexate monotherapy. The methods used are consistent with those of published methodological guidelines for undertaking economic evaluations (11, 12); all societal costs were considered in 2014 dollars and outcomes in terms of quality-adjusted life-years (QALYs). For the base-case analysis, we assumed a cohort of patients with RA who had demographic and other clinical characteristics similar to those of the RACAT trial population. We used 2 forms of analysis: a within-trial analysis based on comprehensive, observed data from RACAT trial participants over 48 weeks (allowing analyses of outcomes at weeks 24 and 48) and a lifetime analysis based on a decision analytic model using assumptions and external data to extrapolate costs and QALYs to a 50-year (that is, lifetime) time horizon. For detailed information about this analysis, see the **Supplement**, **Supplement Tables 1** through **11**, and **Supplement Figures 1** through **8** (available at Annals.org).

### Strategies

The within-trial analysis considered strategies from the RACAT study (7): Etanercept–methotrexate was compared with triple therapy as first-line treatment for patients with active RA that did not respond to methotrexate at stable doses of 15 to 25 mg/wk for at least 12 weeks; mandatory blind switching was done after 24 weeks for patients who did not achieve at least a 1.2-point decrease in 28-Joint Disease Activity Score (DAS28) (13). Patients in the RACAT trial received methotrexate at a mean baseline dosage of 19.6 mg/wk; the study found that triple therapy was noninferior to etanercept–methotrexate in terms of change in DAS28 and that similar proportions of patients switched from their randomly assigned therapy to the alternative regimen (27.0% of patients initially receiving triple therapy vs. 26.7% of those initially receiving etanercept–methotrexate).

For patients in whom methotrexate therapy failed, the lifetime analysis specifically compared 2 strategies: adding a biologic then switching to other biologics as needed versus starting with triple therapy then switching to other biologics as needed.

***Table 1.*** Demographic Characteristics of RACAT Trial Participants*

| Characteristic | Triple Therapy (*n* = 161) | Etanercept–Methotrexate (*n* = 163) |
|---|---|---|
| Mean age (SD), *y* | 57.3 (13.0) | 56.27 (13.3) |
| Female sex, *n (%)* | 68 (42.2) | 80 (49.1) |
| White race, *n (%)* | 147 (91.3) | 137 (84) |
| Current smoker, *n (%)* | 41 (25.5) | 40 (24.5) |
| Mean time since diagnosis (SD), *y* | 4.8 (7.8) | 4.9 (7.82) |
| Mean DAS28 (SD) | 5.8 (0.9) | 5.9 (0.84) |
| Mean patient's global assessment score (SD) | 5.4 (2.2) | 5.6 (1.91) |
| Mean physician's global assessment score (SD) | 6.0 (2.27) | 6.0 (1.98) |
| Mean swollen-joint count (SD), *n* | 11.0 (5.2) | 11.4 (5.23) |
| Mean tender-joint count (SD), *n* | 13.4 (6.7) | 13.2 (6.24) |
| Mean HAQ score (SD) | 1.3 (0.6) | 1.3 (0.61) |
| Mean erythrocyte sedimentation rate (SD), *mm/h* | 28.2 (21.4) | 29.7 (23.45) |
| Mean CDAI score (SD) | 35.9 (11.4) | 36.2 (11.15) |
| Mean modified Sharp score (SD) | 20.3 (29.7) | 16.6 (22.45) |
| Mean EQ-5D score (SD)† | 0.67 (0.18) | 0.7 (0.18) |
| Mean absenteeism (SD), *h* | 17.2 (65.36) | 11.0 (30.19) |
| Mean caregiver absenteeism (SD), *h* | 4.8 (21.28) | 12.8 (82.5) |
| Methotrexate‡ | | |
| Mean dose (SD), *mg/wk* | 19.84 (3.56) | 19.31 (3.3) |
| 10 or 12.5 mg/wk, *n (%)* | 3 (1.9) | 4 (2.5) |
| 15 or 17.5 mg/wk, *n (%)* | 50 (31.1) | 47 (28.8) |
| 20 or 22.5 mg/wk, *n (%)* | 71 (44.1) | 91 (55.8) |
| 25 mg/wk, *n (%)* | 37 (23.0) | 21 (12.9) |
| Oral corticosteroids, *n (%)* | 52 (32.3) | 56 (34.4) |

CDAI = Clinical Disease Activity Index; DAS28 = 28-Joint Disease Activity Score; EQ-5D = EuroQol 5-dimensions questionnaire; HAQ = Health Assessment Questionnaire; RACAT = Rheumatoid Arthritis Comparison of Active Therapies.
* 29 patients (17 in the triple-therapy group and 12 in the etanercept–methotrexate group) were excluded for not providing ≥1 follow-up visit.
† U.S. societal weights were applied to this instrument.
‡ Percentages may not sum to 100 due to rounding.

### Analysis

#### *Within-Trial 24- to 48-Week Analysis*

We included data from 324 patients from the RACAT trial (*n* = 353) who had at least 1 follow-up visit, allowing us to estimate economic outcomes (**Table 1**). Cumulative costs and QALYs were calculated for each treatment strategy. Missing data were estimated by using multiple imputation. Total costs and QALYs were then estimated by using separate regressions to account for differences between treatment groups (**Supplement**). The 24-week analysis considered first-line treatment with etanercept–methotrexate versus triple therapy without the possibility of switching, whereas the 48-week analysis considered which strategy was used first and accounted for switching.

#### *Lifetime Analysis Model*

For the lifetime analysis, we extrapolated the RACAT findings over the projected lifetime of patients. We adapted an existing individual sampling decision analytic model that simulates radiographic and functional disease in a cohort of patients through a sequence of treatments (14). For each treatment, we modeled the natural history of both the Health Assess-

*Table 2.* Model Variables for Within-Trial and Lifetime Analysis

| Variable | Mean (Confidence Limit) | Source |
|---|---|---|
| **Sharp score progression per 24 wk** | | Multivariate model based on RACAT data |
| Triple-therapy responders | 0.206 (0.037 to 0.375) | |
| Biologic responders | 0.042 (−0.108 to 0.191) | |
| Triple-therapy nonresponders* | 0.619 (0.138 to 1.100) | |
| Biologic nonresponders* | 0.385 (−0.036 to 0.806) | |
| **HAQ score progression†** | | |
| 0–24 wk (per 24 wk)‡ | | Multivariate model based on RACAT data |
| Triple-therapy responders | −0.494 (−0.589 to −0.399) | |
| Biologic responders | | |
| First biologic | −0.602 (−0.691 to −0.512) | |
| Second and subsequent biologics | −0.348 (−0.465 to −0.230) | |
| 24–48 wk (per 24 wk)‡ | | Multivariate model based on RACAT data |
| Triple-therapy responders | −0.211 (−0.282 to −0.14) | |
| Biologic responders (all) | −0.211 (−0.282 to −0.14) | |
| >48 wk (per year) | | |
| Triple-therapy responders | 0.018 (0.016 to 0.021) | Michaud et al (18) |
| Biologic responders (all) | 0.006 (0.002 to 0.013) | Michaud et al (18) |
| Per point change in Sharp score | 0.013 (0.005 to 0.021) | Smolen et al (19) |
| **Probability of switch (per 24 wk)§** | | Based on the Weibull model of RACAT data |
| 0–24 wk | | |
| From triple therapy to biologic | 0.293 (0.227 to 0.369) | |
| From biologic to biologic | 0.286 (0.221 to 0.360) | |
| 24–48 wk | | |
| From triple therapy to biologic | 0.165 (0.107 to 0.247) | |
| From biologic to biologic | 0.126 (0.076 to 0.202) | |
| >48 wk | From Weibull model | |
| **Increase in absences due to illness per point change in HAQ score per 24 wk, *h*‖** | 393.50 (276.05 to 560.91) | Multivariate model based on RACAT data |
| **Mortality¶** | | Estimated from U.S. life table 2009 (20) |
| Men (probability per year) | 0.008 (0.008 to 0.009) | |
| Women (probability per year) | 0.005 (0.004 to 0.005) | |
| Standardized mortality ratio for rheumatoid arthritis | 1.600 (1.200 to 1.800) | |
| **EQ-5D score per point change in HAQ score**** | −0.178 (−0.173 to −0.183) | Wailoo et al (4) |
| **Direct costs per point change in HAQ score, $** | 603.79 (544.66 to 662.92) | Wailoo et al (4) |
| **Drug costs per year, $** | | Medicare prices (21) |
| Etanercept–methotrexate group | 24 473 (17 000 to 35 000) | |
| Triple-therapy group | 744 (600 to 3000) | |

EQ-5D = EuroQol 5-dimensions questionnaire; HAQ = Health Assessment Questionnaire; RACAT = Rheumatoid Arthritis Comparison of Active Therapies.
* For a Sharp score of 18 at the beginning of a 24-wk cycle.
† During the period the patient received treatment.
‡ For a HAQ score of 1.3 (baseline HAQ score in the RACAT trial) at the beginning of a 24-wk cycle.
§ See **Supplement Table 3** (available at Annals.org) for the variables of the Weibull functions.
‖ See Validation section and **Supplement Table 8** (available at Annals.org) for the model equation and variables.
¶ From estimated function $e^{-9.814 + 0.088 \cdot age}$ for men and $e^{-10.950 + 0.098 \cdot age}$ for women if age is 56 y.
** The HAQ score has a fixed value of 0.5 at baseline, and all covariates have a fixed value at baseline. The change in EQ-5D score is observed as the HAQ score increases from 0.5 to 1.5.

ment Questionnaire (HAQ) (15) and radiographic (Sharp score) progression at 0 to 24, at 24 to 48, and after 48 weeks separately. The HAQ measures progression of functional disability with a score ranging from 0 (no disability) to 3 (severe disability). To reflect that the HAQ captures both inflammatory (reversible) and radiographic (irreversible) components of disability (16), we assumed that when a patient switches to the next treatment in the sequence, the inflammatory component of HAQ rebounds to the baseline value at the start of the most recent treatment; however, the radiographic component will have worsened irreversibly so that net HAQ disability worsens.

In both groups, patients whose RA was unresponsive to one biologic were switched to another that presumably cost the same and was as effective as etanercept (17). The time a patient continued to respond to treatment was extrapolated from RACAT study data, as was the HAQ and Sharp score progression for 0 to 48 weeks. Beyond 48 weeks, the inflammatory component of HAQ progression was estimated from a longitudinal observational study (18) in which the radiographic component was estimated from the extrapolated Sharp scores converted to HAQ on the basis of an established relationship (19). Mortality rates were based on U.S. life tables (20) adjusted for RA standardized mortality ratios.

The model is described further in the Supplement and depicted in Supplement Figure 1. Table 2 describes the variables used in the model.

### Resource Use and Costs

During the RACAT trial, data were collected routinely on medication use, nonprotocol visits to health professionals, tests, surgical procedures, and absences from paid and nonpaid work. Drug costs were estimated on the basis of the dosages reported in the study. We included visits, tests, and procedures related to RA, as well as the study treatments, in the primary analysis. Unit costs were derived from the Medicare schedule (21). Productivity losses were valued by using U.S. average wages of men and women of the corresponding age (Table 2). Future resource use was estimated on the basis of a previously established algorithm, which found that costs are greater with higher HAQ scores (4). A similar relationship was used to forecast productivity costs. Both these relationships were adjusted to 2014 dollars. All costs were discounted at 3% per year.

### Health-Related Quality of Life

Health-related quality of life was incorporated in terms of weights on a scale from 0 (death) to 1 (full health). The EuroQol 5-dimensions questionnaire (EQ-5D) was used in the RACAT trial, and we applied U.S. societal weights to this instrument (22). For the lifetime analysis, we used a previously established relationship with the HAQ (4). Estimates were combined with mortality to generate QALYs and discounted at 3% per year.

### Sensitivity and Uncertainty Analysis

To reflect the degree of uncertainty in our ICER estimates, we conducted a series of scenario analyses that considered alternative assumptions and sources of data around key variables. For example, we considered a scenario in which the withdrawal rate from triple therapy was greater than that observed in the trial, given concerns about patients' reluctance to maintain this multidose daily–weekly regimen. We also varied drug costs to consider the potential implications of "biosimilars" and drug tapering (Supplement). Because our primary analysis excluded the 29 patients who did not complete any follow-up visits, our sensitivity analysis assumed that the patients in the group that received etanercept–methotrexate first ($n$ = 12) responded to treatment and those who received triple therapy first ($n$ = 17) did not.

For the base-case and scenario analyses, we calculated 95% CIs around total costs, QALYs, and ICERs to reflect the underlying variable uncertainty. For the within-trial analysis, we calculated the value of total costs, QALYs, and ICERs at various percentile levels (for example, second percentile, 98th percentile) over 10 000 bootstrap samples (that is, multiple samples generated by sampling with replacement from observed data) (23). For the lifetime analysis, we combined bootstrap samples from RACAT-derived variables with samples from probability distributions assigned to non–RACAT-derived variables and conducted 10 000 Monte Carlo simulations (24).

### Model Validation

The lifetime model was externally validated by comparing predicted outcomes with those reported in the literature. The model predicted that patients would remain on triple therapy for a median of 1.45 years, compared with 2.04 years on biologic treatment—rates similar to those previously published (25)—and long-term radiographic and HAQ outcomes matched rates described in many studies.

### Study Oversight and Role of the Funding Source

The research protocol and documents for written informed consent were approved by the institutional review board at each participating site. This study was supported by the Cooperative Studies Program (CSP), Department of Veterans Affairs (VA) Office of Research and Development; the Canadian Institutes for Health Research; and an interagency agreement with the National Institutes of Health–American Recovery and Reinvestment Act. The funding sources had no role in the design, conduct, or analysis of the study or in the decision to submit the manuscript for publication.

## RESULTS

### Within-Trial Analysis

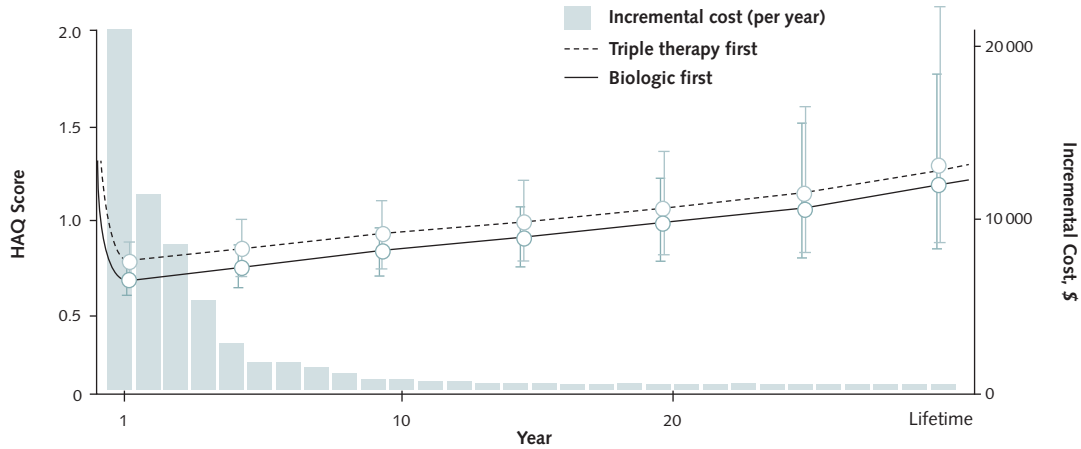
Both strategies showed substantial improvements in EQ-5D, with first-line etanercept–methotrexate providing marginally more accumulated QALYs: 0.358 versus 0.353 QALY (difference, 0.004 QALY [95% CI,

*Table 3.* Within-Trial 24- and 48-Week Analysis Results: Total Costs, QALYs, and ICERs

| Variable | 24 Wk | | | 48 Wk | | |
|---|---|---|---|---|---|---|
| | Mean Etanercept-Methotrexate (SD)* | Mean Triple Therapy (SD)* | Incremental (95% CI)† | Mean Etanercept-Methotrexate (SD)* | Mean Triple Therapy (SD)* | Incremental (95% CI)† |
| Total costs, $ | 12 002 (2656) | 1225 (2558) | 10 786 (10 163 to 11 353)‡ | 21 611 (6756) | 6328 (14 108) | 15 233 (12 204 to 17 275)‡ |
| QALYs | 0.358 (0.075) | 0.353 (0.075) | 0.004 (−0.004 to 0.012)§ | 0.743 (0.147) | 0.726 (0.145) | 0.016 (−0.007 to 0.039)§ |
| ICER, $‖ | – | – | 2 672 575 | – | – | 977 805 |

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
* Based on multiple imputation results.
† CIs were estimated by using the bootstrapping method.
‡ Adjusted for baseline Health Assessment Questionnaire score and sex.
§ Adjusted for baseline EuroQol 5-dimensions questionnaire score.
‖ Calculated from the mean of the ICERs for each multiple imputation simulation.

***Figure 1.*** Annual HAQ score and incremental cost over time.




| | | | | |
|---|---|---|---|---|
| **Cumulative difference in QALYs** | **0.0119** | **0.0937** | **0.1413** | **0.1482** |
| **Cumulative difference in cost, *$*** | **19 395** | **63 642** | **76 125** | **77 290** |
| **ICER, *$/QALY gained*** | **1 631 859** | **678 964** | **538 780** | **521 520** |

Error bars represent 95% CIs. HAQ = Health Assessment Questionnaire; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

−0.004 to 0.012 QALY]) over 24 weeks and 0.743 versus 0.726 QALY (difference, 0.016 QALY [CI, −0.007 to 0.039 QALY]) over 48 weeks for the etanercept–methotrexate and triple-therapy first-line strategies, respectively. The first-line etanercept–methotrexate strategy accumulated substantially higher drug costs, even after consideration of the switches between treatments at 24 weeks ($11 295 vs. $343 cumulative costs from 0 to 24 weeks [difference, $10 952] and $19 634 vs. $3680 cumulative costs from 0 to 48 weeks [difference, $15 954] for the etanercept–methotrexate and triple-therapy strategies, respectively). The differences in other health care and productivity costs between strategies were small (<$800 at 48 weeks). The resultant ICER for first-line etanercept–methotrexate versus triple therapy was $2.7 million (CI, $0.87 to infinity) per QALY gained over 24 weeks. Because at 24 weeks, 27% of patients in the triple-therapy group switched to biologics and 27% in the biologic group switched to triple therapy, the incremental cost and subsequent ICER at 48 weeks decreased to $0.98 million (CI, $0.39 to infinity) per QALY (**Table 3** and **Appendix Table**, available at Annals.org).

### Lifetime Analysis Model

**Figure 1** shows the considerable cost differences over time between the 2 strategies, increasing from nearly $20 000 in the first year to nearly $80 000 over a lifetime. The triple-therapy first-line strategy led to an increase in HAQ score (that is, more functional disability), which over a lifetime translated into 0.15 QALY (CI, 0.01 to 0.31 QALY) (or 55 days of perfect health) gained with biologics, with an ICER of $521 520 (CI, $137 000 to dominated) per QALY gained for the biologic versus the triple-therapy first-line strategy.

### Sensitivity and Scenario Analyses

The cost-effectiveness acceptability curve illustrates that the biologic-first strategy has a 0.1% probability of being cost-effective at a threshold ICER of $100 000 per QALY (**Supplement Figure 8**). Scenario analyses suggest that the cost-effectiveness of the biologic-first strategy remains more than $100 000 per QALY even for optimistic scenarios (**Figure 2**). For example, even if radiographic and HAQ progression in patients receiving first-line triple therapy are far higher than observed in the trial and at the extremes of what has been reported in the literature, the ICER for the biologic-first strategy is still $350 000 per QALY. Similarly high ICERs were found even if retention on triple therapy was shorter than that seen in the RACAT trial because of tolerability issues. We calculated that the annual acquisition cost of a biologic would have to be less than one third of its current price for it to be considered cost-effective at the threshold of $100 000 per QALY.

## DISCUSSION

This study examined the economic analysis of a trial of biologic therapy combined with methotrexate versus triple therapy in patients with active RA despite at least 12 weeks of methotrexate therapy. Triple therapy is a combination of drugs that has been promoted for more than a decade (26, 27) but currently is used far less than biologics as a first-line treatment after methotrexate failure (9, 10). The topic has relevance for clinicians, patients, and policymakers. The original trial suggested that triple therapy was noninferior to etanercept–methotrexate. This economic analysis sug-

gests that biologic therapy is superior but has a high ICER. Current guidelines and reimbursement permit the initiation of biologic therapy in such cases, but this approach may be an inefficient use of resources. Other studies in patients with active RA despite DMARD monotherapy found that biologic therapies yielded clinical outcomes similar to those of triple therapy 18 to 24 months later but with less associated radiographic progression (5, 6). This analysis attempts to estimate the benefit of that reduction in radiographic progression over the long term and suggests that it has little economic value.

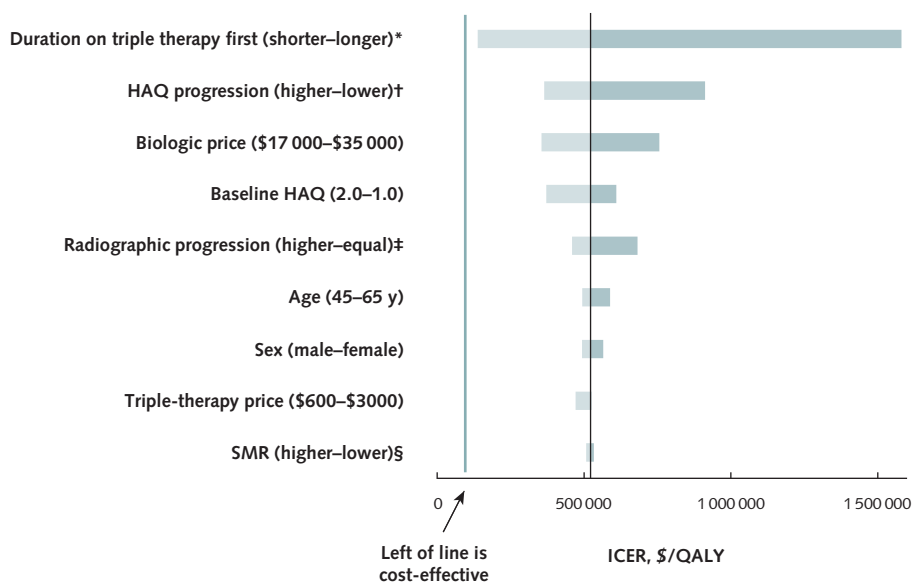
Of importance, the implication of this study is not that biologics should be withheld from patients with RA not completely controlled by methotrexate alone. Rather, the study demonstrates the cost savings that would result from prescribing triple therapy first, before a biologic, for such patients. This study shows that for every patient who tries triple therapy before a biologic, payers will save an average of $78 000 over the patient's lifetime, and most of that savings will accrue within the first 10 years.

The clinical effect of trying triple therapy first may be represented in terms of total QALYs over a patient's lifetime or in terms of HAQ scores at any given time. Specifically, patients who receive triple therapy before a biologic will miss out on a benefit of approximately 0.15 QALY over their lifetime or a benefit of approximately 0.05 HAQ point at any point in time. To put these numbers into perspective, total hip arthroplasty in a patient with osteoarthritis who is approximately the same age as an average patient with RA provides an additional 6.9 QALYs (28). In terms of HAQ score, only differences greater than 0.2 point are considered minimally important to patients (29).

Our findings are based on both a within-trial analysis of RACAT data (that is, observed data) and a decision analytic model (that is, extrapolated data). The results of our within-trial analysis agree with those of economic analyses of other trials studying combination therapy compared with biologics. A Swedish study calculated that infliximab would cost €20 916 more than triple therapy over a period of 21 months and provide only 0.01 additional QALY, resulting in an ICER of €2 404 197 per QALY (30). In a study from the United Kingdom, the use of adalimumab, etanercept, or infliximab cost $8586 more than DMARD combinations over a period of 12 months, but no difference in EQ-5D was observed (31).

An important limitation of the RACAT trial, and consequently our economic analysis, is that the potential long-term benefits of etanercept–methotrexate therapy might not be fully accounted for because of the trial's inherent shortcomings in terms of sample size and observation period. In theory, the small, non–statistically significant differences observed between triple therapy and etanercept–methotrexate in the RACAT trial might be shown to be statistically significant in a trial with a much larger sample size followed over a much longer period. However, a trial with the capacity to observe

***Figure 2.*** Tornado diagram for sensitivity analysis.




HAQ = Health Assessment Questionnaire; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SMR = standardized mortality ratio.
* Longer = double; shorter = half the probabilities of switch in Table 2.
† Higher = Sharp score radiographic progression (per 24 wk) with triple therapy for responders and nonresponders worsens by 0.058 and 0.33, that is, from 0.206 and 0.619 to 0.264 and 0.949, respectively; lower = short and long HAQ progression in 24 wk and after 48 wk for triple therapy is equal to that of biologic.
‡ Equal = treatment effect is zero for both responders and nonresponders; higher = radiographic triple-therapy treatment effect for responders and nonresponders is increased by 0.058 and 0.330.
§ Higher = 2; lower = 1.

whether a decrease in radiographic damage leads to a long-term reduction in disability would be prohibitively expensive and resource intensive. Addressing the unavoidable limitations of trial-based analysis is the purpose of the decision analytic model that we developed. Although a recent U.S. study extrapolated to 5 years the results from a trial of triple therapy versus etanercept in patients with early RA (32), it focused only on the inflammatory components of the HAQ, leaving questions about the longer-term effect of early radiographic changes unanswered. The key strength of our modeling approach is that by extrapolating radiographic scores and relating changes to HAQ scores and QALYs, we could demonstrate the effect of these differences on patients over the long term.

The RACAT trial, which provided the data for this economic analysis (33), has other limitations. It failed to reach the target sample size, and participants who did not have at least a 1.2-point decrease in DAS28 were required to switch to an alternative treatment at 24 weeks, which might not reflect clinical practice. Furthermore, because recruitment was largely through the VA system, the study included a higher proportion of men than is typical for the general population with RA. Finally, although patients had RA of relatively long duration, their disease had been treated only with methotrexate.

Our analytic approach also has limitations. Our model did not account for the possibility that certain adverse effects (such as common gastrointestinal symptoms, uncommon types of cancer, and infections) might differ between the 2 strategies. Our analyses were based only on a single trial, and by simulating an "average" RACAT patient, we could not fully account for the heterogeneity in the population. We were able to consider scenarios that challenged the influence of these limitations, such as considering baseline characteristics more generalizable to the overall population with RA rather than to patients who enroll in clinical trials. The results of these analyses suggest that our model findings generally are robust.

In light of its robust findings, this study has important health policy implications. Given the current very low use of triple therapy in the United States (9, 10), implementing a policy change requiring that triple therapy be prescribed before biologic use might save millions of dollars in health care expenditures. For example, a study of 2903 VA patients who received an RA diagnosis found that of the approximately 700 who initiated a biologic, only 2.5% had tried triple therapy first (10). Prescribing triple therapy first to just 75% of those patients would have saved up to $10 million in the first year of RA management in this population alone. The opportunity cost of this spending, which diverts resources from more cost-effective treatments and services that might provide much greater health improvements to the same population, will be an important consideration for the future.

Proposed strategies currently under investigation to reduce costs among patients with RA treated with biologics include tapering (that is, reducing the dosage, ostensibly with the same clinical benefit) and replacing biologics with biosimilars (that is, drugs that are almost identical to previously approved biologics but cost less). In this study, we did not directly model the effects of tapering or replacing biologics with biosimilars; however, assuming these strategies do not affect clinical benefit, our sensitivity analyses indicate that unless tapering or biosimilars reduce the total cost of biologic therapy to at least one third of its current price, a first-line strategy of triple therapy would still be more cost-effective.

In conclusion, in patients who have RA not adequately controlled by methotrexate alone, we found that the additional costs associated with using etanercept–methotrexate before triple therapy do not provide good value. Even from a long-term perspective, under optimistic scenarios, first-line therapy with etanercept–methotrexate or other biologics likely is not a cost-effective use of resources compared with using triple therapy first.

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**Note:** Dr. Bansback is a Canadian Institutes of Health Research New Investigator.

**Acknowledgment:** The authors thank Amgen for donating the placebo etanercept and Tima Mohammadi for her help with the lifetime model analysis.

**Disclosures:** Dr. Bansback reports grants from Canadian Institutes for Health Research during the conduct of the study. Dr. O'Dell reports nonfinancial support from the U.S. Department of Veterans Affairs during the conduct of the study. Dr. Keystone reports grants and personal fees from Abbott Laboratories, Amgen, AstraZeneca, Bristol-Myers Squibb, Hoffmann-La Roche, Eli Lilly and Company, Janssen, Novartis, Pfizer, and UCB; personal fees from Biotest, Crescendo Bioscience, Genentech, and Merck; and grants from Sanofi-Aventis, outside the submitted work. Dr. Mikuls reports personal fees from Pfizer and grants from Bristol-Myers Squibb and Roche Genentech outside the submitted work. Dr. Anis reports grants from Canadian Institutes for Health Research during the conduct of the study and grants and personal fees from Pfizer, personal fees from Sanofi, and grants from AbbVie outside the submitted work. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-0713.

**Reproducible Research Statement:** *Study protocol:* Not available. *Statistical code:* Available from Dr. Bansback (e-mail, nick.bansback@ubc.ca). *Data set:* Individual-level RACAT data are not available; statistical results are presented in the Supplement.

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# AD LIBITUM

## Counterclockwise

Lost in time
and the fog of bereavement
I'm startled to see the hands
of the clock by our bed
running backwards.
I confront it face to face,
shake it, but resist unplugging.

For days we track back
(the clock and I)
from now to then till suddenly I see
what Zen and physics say is true–
we live in a block universe,
all things in all time.
And with that, I unplug.

I no longer use the clock
but keep it closeted–
prophet in a cave–
silent reminder that
there's no such thing as a race
against time, no finish line
only this human finitude.

*Veneta Masson, RN, MA*
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***Appendix Table.*** Within-Trial 24- and 48-Week Analysis Results: Mean Accumulated Costs

| Variable | Costs at 24 Weeks | | | | | Costs at 48 Weeks | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Etanercept-Methotrexate | | Triple Therapy | | Difference (95% CI), $* | Etanercept-Methotrexate | | Triple Therapy | | Difference (95% CI), $* |
| | Resource Use, *n* (%)† | Mean (SD), $‡ | Resource Use, *n* (%)† | Mean (SD), $‡ | | Resource Use, *n* (%)† | Mean (SD), $‡ | Resource Use, *n* (%)† | Mean (SD), $‡ | |
| Total | 141 (100) | 12 002 (2656) | 142 (100) | 1225 (2558) | 10 786 (10 163 to 11 353)§ | 129 (100) | 21 611 (6756) | 130 (100) | 6328 (14 108) | 15 233 (12 204 to 17 275)§ |
| Drugs | 163 (100) | 11 295 (0) | 161 (100) | 343 (0) | 10 952 (10 952 to 10 952) | 163 (100) | 19 634 (4862) | 161 (100) | 3680 (4896) | 15 954 (14 938 to 16 971) |
| Etanercept-methotrexate | 163 (100) | 11 295 (0) | 0 (0) | 0 (0) | 11 295 (11 295 to 11 295) | 163 (100) | 19 547 (5031) | 44 (26.99) | 3088 (5051) | 16 460 (15 358 to 17 562)‖ |
| Triple therapy | 0 (0) | 0 (0) | 161 (100) | 343 (0) | −343 (−343 to −343) | 44 (27.33) | 94 (154) | 161 (100) | 599 (155) | −505 (−539 to −472) |
| Diagnostic testing | 54 (33.13) | 84 (248) | 63 (39.87) | 87 (258) | −4 (−60 to 51)‖ | 75 (47.47) | 169 (446) | 87 (58) | 211 (436) | −41 (−139 to 63)‖ |
| Outpatient visits | 35 (22.88) | 116 (246) | 53 (34.64) | 193 (526) | −77 (−176 to 1) | 55 (36.91) | 245 (466) | 70 (47.3) | 352 (758) | −107 (−245 to 15) |
| Rheumatologist | 9 (5.88) | 26 (102) | 16 (10.46) | 32 (100) | −6 (−28 to 15) | 16 (10.74) | 46 (154) | 24 (16.22) | 62 (160) | −16 (−50 to 17) |
| Other | 29 (18.95) | 90 (217) | 43 (28.1) | 161 (485) | −71 (−161 to −1) | 50 (33.56) | 199 (424) | 60 (40.54) | 289 (701) | −90 (−222 to 22) |
| Joint procedure | 11 (6.83) | 26 (107) | 19 (12.03) | 115 (473) | −88 (−174 to −18)‖ | 24 (15.19) | 129 (537) | 29 (18.95) | 166 (536) | −38 (−155 to 81)‖ |
| Hospitalizations | 3 (1.86) | 270 (2184) | 7 (4.38) | 275 (1548) | −5 (−416 to 409) | 7 (4.55) | 1131 (5021) | 9 (5.81) | 1518 (11 184) | −388 (−2985 to 1196)‖ |
| Absenteeism | 31 (20) | 210 (999) | 33 (21.57) | 211 (1344) | −1 (−292 to 256) | 39 (26.35) | 302 (1168) | 40 (27.59) | 401 (1797) | −99 (−476 to 217) |

* CIs were estimated by using the bootstrapping method.
† Based on observed data.
‡ Based on multiple imputation results.
§ Adjusted for baseline Health Assessment Questionnaire score and sex.
‖ The discrepancy between the difference between the 2 means and the reported difference is due to rounding.