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ORIGINAL ARTICLE

Cost Effectiveness of Adding Leflunomide to a 5-Year Strategy of Conventional Disease-Modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis

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Objective. **To estimate, from a public payer's perspective, the 5-year cost effectiveness of adding leflunomide (LEF) to a sequence of disease-modifying antirheumatic drugs (DMARDs) representative of a typical rheumatoid arthritis (RA) management approach adopted by Canadian rheumatologists.**

Methods. **A DMARD sequence including LEF was compared with one excluding it, using a 5-year simulation model where patients with RA cycle through different treatment regimens. Data were obtained through a systematic literature search (drug withdrawal rates, number and type of adverse events, American College of Rheumatology 20% responder status) and separately conducted surveys (choice of DMARD sequence, management of adverse events). Costs for adverse event management were calculated using the Ontario Schedule of Benefits, and monitoring costs were calculated according to official Canadian product monograph recommendations. Wholesale prices of all drugs were adjusted by the allowable markup and prescription fees. Utilities (as measured by the standard gamble [SG] and rating scale [RS] techniques) were obtained from 482 patients who participated in a 1-year randomized controlled trial that compared LEF, methotrexate, and placebo. Costs and utilities were discounted by 3%. Probabilistic sensitivity analysis was performed.**

Results. **Adding LEF to a conventional strategy of DMARDs increased the 5-year management costs by $1,231 compared with the strategy without LEF, which results in a cost-effectiveness ratio of $13,096 per additional year of response to treatment, and cost-utility ratios of $54,229 (RS) and $71,988 (SG) per quality-adjusted life-year gained.**

Conclusion. **Adding LEF as a new option to a conventional sequence of DMARDs extends the time patients may benefit from DMARD therapy at a reasonable cost effectiveness and cost utility. LEF data are limited to clinical trials; data from observational studies would be needed to corroborate these findings.**

KEY WORDS. Leflunomide; Cost effectiveness; Rheumatoid arthritis.

INTRODUCTION

An intense debate about appropriate treatment strategies in the management of rheumatoid arthritis (RA) has taken place throughout the last decade. A consensus seems to have emerged that patients with moderate or aggressive RA should be treated early and aggressively, if possible, by combining several disease-modifying antirheumatic drugs (DMARDs) (1–3). Fortunately, several new therapies have been approved for the treatment of RA, which expand the therapeutic options. In 1998, leflunomide (LEF) was the first DMARD approved in more than a decade by the US Food and Drug Administration. Soluble tumor necrosis factor α (TNFα) receptor and monoclonal anti-TNFα antibodies followed. Compared with existing therapies, which

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may cost as little as $300 per year, these new agents cost between $3,100 and $15,500 per year. In light of the ever-increasing need for justified allocation of health care budgets, the therapeutic potential of these agents needs to be assessed, not only based on their ability to slow or halt disease progression, but also by their relative impact on the costs of RA management.

The costs of illness associated with RA are compounded by the fact that RA often starts early in life. RA can lead to severe disability and may require hospitalization and intense medical and surgical treatment. The annual costs of RA vary, but have been estimated to be approximately $8,416 per patient in 1996 US dollars (4). Direct medical and nonmedical costs and indirect costs, such as losses in productivity all contribute to this sum. In Canada, the annual costs incurred by RA patients were calculated to average approximately US $7,847 in 1994 (5), with direct costs responsible for 74% of the total and prescription drugs for ~20% of the direct costs.

The relationship between costs and effectiveness of old or new antirheumatic therapies has been examined in only very few economic evaluations (6–9), and all of these compared one therapy to another over a short time period. There have been 2 attempts to model the disease over longer time horizons (10,11), but both studies were conducted without the required efficacy data to study the costs and benefits within a realistic treatment algorithm. The present study is an attempt to examine the incremental cost effectiveness and cost utility of adding LEF to a sequence of conventional DMARDs modeled over a 5-year time horizon in patients with active RA. The analysis is conducted from a Canadian payer's perspective.

METHODS

We developed a 5-year decision analysis model to compare 2 sequences of DMARD treatment, 1 that includes LEF and 1 that excludes it. For each sequence, the model simulated the response to treatment of a cohort of patients with RA severe enough to require treatment with methotrexate (MTX). Incremental cost effectiveness, defined as the additional cost of the DMARD strategy including LEF divided by its additional clinical benefit, was calculated from a public payer's perspective (Ontario Ministry of Health). Future costs and quality-adjusted life-years (QALYs) were discounted at an annual rate of 3%. All variables were varied over their reasonable ranges in a sensitivity analysis.

Model overview. The DMARD sequence emulates a conventional treatment strategy in which patients use different DMARD treatment regimens whenever they encounter toxicity or lack or loss of efficacy. Patients may experience 3 types of events during each 6-month treatment period: They continue therapy, they stop therapy because of adverse events, or they stop therapy because treatment is lacking or losing efficacy (Figure 1). Continuing patients may respond to treatment by at least 20% in 5 of 7 clinical measures (American College of Rheumatology 20% response criteria [ACR20]) and they may experience adverse events minor enough to continue therapy.

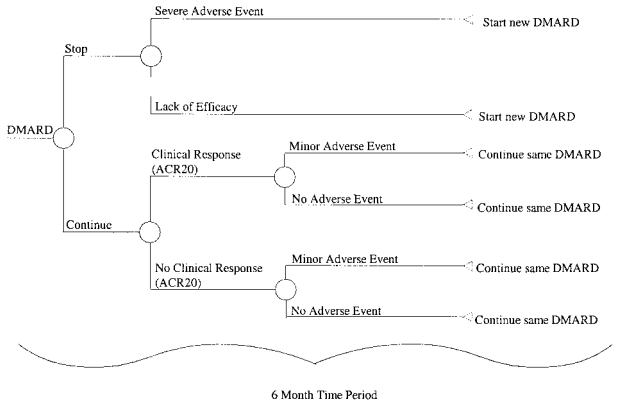

Figure 1. Decision analysis tree representing the conditions under which patients move from one branch (i.e., treatment) to another within a 6-month treatment cycle. DMARD = disease-modifying antirheumatic drug.

Strategies to be compared. The conventional sequence of DMARDs excludes LEF and was based on the responses of US and Canadian rheumatologists to case scenarios presented in a mailed survey (12). In this treatment strategy, patients start with MTX followed by combinations of MTX and sulfasalazine (SSZ), followed by triple therapy (MTX, SSZ, and hydroxychloroquine [HCQ]) (Figure 2). Those who develop toxicity to the MTX-based regimens at any time during this sequence will continue with gold sodium aurothiomalate (GST) and finally cyclosporin A (CSA). To this conventional strategy, we compared one where LEF was added as a new option before GST.

Clinical data. Outcome information for each DMARD was derived through a systematic search of the MEDLINE database from 1966 to 1997 by combining the key words "rheumatoid arthritis" with text words and key words for

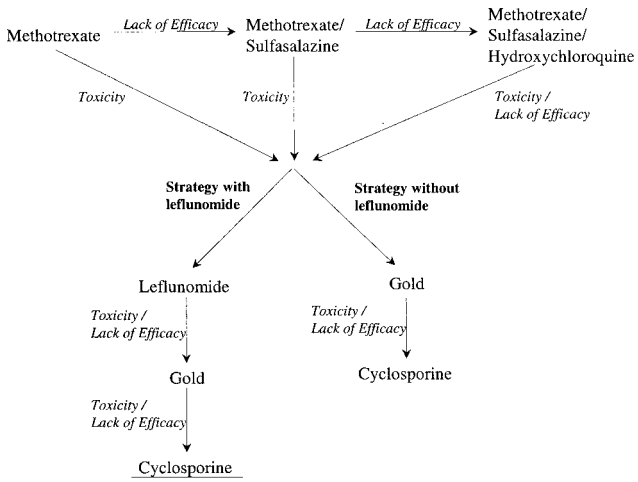

Figure 2. Sequence of disease-modifying antirheumatic drugs for patients with aggressive rheumatoid arthritis. The full strategy is shown on the left side and includes leflunomide, whereas a strategy without leflunomide is shown on the right.

MTX, GST, HCQ, CSA, and other DMARDs, including their synonyms. The search set was complemented by references from a literature search conducted by the RA subgroup of the Cochrane Musculoskeletal Review Group.

Treatment termination rates were abstracted from all observational studies and randomized controlled trials (RCTs) of DMARDs. Combined results of single DMARD therapy with MTX, SSZ, HCQ, and GST were published elsewhere (13). We retained studies that documented the experience of patients from the first day therapy was initiated, and that provided withdrawal information for the therapies of interest. Information on treatment withdrawals was abstracted according to a standardized questionnaire. Combined withdrawal rates and 95% confidence intervals were obtained using parametric regression, assuming an exponential hazard function. Withdrawal rates were converted to 6-month treatment withdrawal probabilities for use in the decision analysis model.

All observational studies and RCTs published after 1990 were searched for the use of explicit response criteria. Possible response criteria included the ACR preliminary criteria for 20%, 50%, and 70% improvement (14); the Paulus criteria for 20%, 50%, and 70% improvement (15); and the European League for Rheumatism (EULAR) criteria for good response (16) which are based on disease activity scores (DAS). Studies reporting any of the abovementioned criteria were retained. Intent-to-treat values were abstracted for the therapies of interest, due to the varying time horizons of some studies.

Studies that provided withdrawal information were also screened for the reporting of adverse events, in particular the number and percentage of patients suffering 1 or more adverse event(s). Both the number of adverse events and the number of patients experiencing at least 1 adverse event were abstracted. Adverse events from all studies were combined, by DMARD or combination of DMARDs, and classified according to broad clinical categories. Incidences per 1,000 person-years were calculated for all adverse events from studies with known lengths of followup time.

Utilities. Generic standard gamble (SG) and rating scale (RS) utilities were obtained from the MTX and LEF treatment groups of an RCT comparing LEF to MTX and placebo (17). Utilities were estimated for the following health states: treatment termination, treatment continuation as an ACR20 responder, and treatment continuation as an ACR20 nonresponder. Utilities for not being on any treatment were estimated from placebo patients who withdrew during the trial.

Costs. Costs of managing averse events were estimated by asking 2 community and 3 academic rheumatologists how they would typically manage adverse events occurring with MTX, GST, SSZ, HCQ, and CSA. To reflect the model, adverse events were categorized into 2 classes of severity: severe enough to cause treatment withdrawal, or mild adverse event not necessitating treatment withdrawal. Rheumatologists provided information on the management of 219 adverse events (MTX: 28 withdrawal events/38 continuations; gold: 27/23; SSZ 23/18; HCQ 7/20; CSA: 17/19). Specifically, they were asked to indicate 1) whether they would deal with each type of adverse event over the phone, see the patient in the office, or recommend immediate hospitalization; 2) what type of instructions they would give to the patient, including prescriptions of medications and change of antirheumatic medication; 3) which investigations or tests they would order; and 4) whether they would refer to other specialists or plan followup, and how often they would do so in their own practices. Costs of physician visits, procedures, and laboratory tests were derived from the Ontario Schedule of Physician and Laboratory Benefits, September 1999 version (18). Costs of hospitalizations were provided by the Ontario Case Costing Project database based on the International Classification of Diseases, Ninth Revision, Clinical Modification code for the respective adverse event (19).

Costs for each adverse event were averaged across the 5 respondents. The associated cost of each adverse event was then weighted by the fraction of its incidence relative to the total incidence to obtain an average cost per nature of adverse event, i.e., those events that lead to withdrawal and those that are mild enough for patients to continue therapy. Lowest and highest management costs were used as confidence limits. Costs for the management of adverse events associated with DMARD combinations were calculated by assuming that physicians' management of an adverse event on DMARD combination would be identical to the same adverse event reported for single drugs. Costs for managing adverse events on LEF were calculated based on the management of the same type of adverse event on MTX.

Costs of monitoring patients taking DMARDs were calculated based on directions issued for each drug in the Canadian Compendium of Pharmaceuticals and Specialties. Monitoring costs were divided into baseline monitoring costs, i.e., one-time costs necessary to implement the medication and check for absence of contraindications, and routine monitoring costs. Costs of physician services, procedures, and laboratory services were derived from the Ontario Schedules of Benefit for physician and laboratory services (18). Monitoring for combinations of DMARDs were combined and all overlapping monitoring items were eliminated.

Costs of drugs were derived from the wholesale price catalog of a supplier to the majority of hospital-based pharmacies in Toronto. A maximum markup of 10% allowable for patients insured under the Ontario Drug Benefit Plan was added to the price of each drug, as was a maximum allowable prescription fee of $8.12. The average price per month was based on the recommended dosage to be given to patients. High and low drug costs were calculated depending on the maximal and minimal therapeutic dosage for each drug. All Canadian costs were converted to US dollars by using a conversion factor of 1.255, the Purchasing Power Parity for Health and Medical Care for the year 1998 (20).

Analysis. Cost effectiveness for the DMARD strategy with LEF was compared with the conventional DMARD strategy in terms of the cost per additional year of ACR20

response and the cost per additional QALY, according to the RS and SG methods. Uncertainty was addressed by calculating the expected cost-effectiveness ratios based on 10,000 second-order Monte Carlo simulations, where sets of values for clinical outcome probabilities and costs were randomly chosen at each cycle from each variable's distribution of possible values. Distributions for cost items were specified to be triangular in shape with the mean value to be the most likely and the minimum and maximum values to be the least likely. Distributions for probabilities and utilities were assumed to approximate the normal distribution shaped by the standard deviation for each respective value. The Monte Carlo method then proceeds such that a value is picked from the distributions whereby values around the average are picked more frequently than values at the extremes of the distributions. Costs and utilities were discounted by 3%. Incremental cost-effectiveness ratios were classified according to whether they fell into one of the following categories: 1) more costly and more efficacious, 2) more costly and less efficacious, 3) less costly and more efficacious, and 4) less costly and less efficacious than the conventional strategy. Additionally, we calculated the percentage of incremental cost-effectiveness ratios that fell in category 1 and below a threshold of $100,000 per QALY gained.

RESULTS

Probabilities and costs used in building the model will be presented first, followed by cost-effectiveness results.

Probabilities. A total of 126 studies, including 119 from the single DMARD metaanalysis (13), provided information on withdrawal rates. Probabilities of withdrawal from therapy and the subset of toxicity withdrawals were combined across studies for each drug (Table 1). Percent response was obtained and combined across studies from the intent-to-treat findings of relevant RCTs of the respective therapies. In RCTs, adverse events are generally reported as the number of events and sometimes as the number of patients with events. We used the former as an upper limit for the percentage of adverse events and the latter as the lower limit.

Costs. Questionnaires collecting data on the management of adverse events with GST, MTX, SSZ, HCQ, and CSA were completed by all 5 rheumatologists. Costs are presented separately for adverse events mild enough not to lead to treatment withdrawal and for severe adverse events that cause treatment withdrawal (Table 1). Costs for baseline and routine monitoring were relatively similar for all treatments evaluated in the model.

Utilities. Of the 364 patients in the LEF and MTX treatment arms in the North American study, there were 329 and 332 patients, respectively, who participated at the SG utility and RS assessments. Of those, 129 and 131 were defined as treatment withdrawals; 134 and 135 as treatment success by ACR20 criteria; and 66 and 66 as not a success by ACR20 criteria but who completed the treatment regimens. There were 71 patients in the placebo group who terminated treatment prematurely and who provided SG and RS utilities for their health states. We could observe a clear increase in RS utilities from the worst health state (placebo, terminate treatment) to the best health state (continue active treatment as ACR20 responder). However, this gradient was not observed with the SG utilities, which were able only to distinguish between continuing and terminating patients, but not between responders and nonresponders (Table 2).

Cost-effectiveness and cost-utility results. Cost-effectiveness and cost-utility results are based on expected value calculations that use the point estimate for each model variable. Comparisons over the 5-year period, i.e., 10 6-month cycles, show that the conventional DMARD strategy would cost $8,467 per 5-year period. Addition of LEF would increase costs by $1,231 to $9,698 over the 5-year period (Table 3) Patients in the sequence of DMARDs that includes LEF would, on average, be in a state of response for 2.8 years over the 5-year period, gaining an extra 34 days compared with patients in the conventional strategy, who would be in a state of response for 2.7 years. These findings translate into a cost-effectiveness ratio of $13,096 for each additional year of response. Similarly, the patients in the strategy that includes LEF would gain 1 week of "perfect health," which translates into a cost-utility ratio of $54,229 per RS QALY gained or $71,998 per SG QALY gained. Monte Carlo simulations for the strategy including LEF compared with the strategy excluding LEF showed that the strategy including LEF is more costly and more efficacious in 68.1% and 67.2% of the simulations with RS and SQ QALYs, respectively; more costly and less efficacious in 31.6% and 32.4%; and either less costly and more efficacious or less costly and less efficacious in 0.3% and 0.4% of the simulations. Nearly 57% and 54% of the cost-effectiveness ratios fell below a threshold of $100,000 per RS and SG QALY gained, respectively.

Sensitivity analysis was also performed assuming the withdrawal rate of LEF to be equal to that of MTX, as in the original trial. The 5-year costs of the strategy with LEF would increase to $10,202 and the incremental gains in RS and SG QALYs would increase to a difference of 0.055 and 0.025, respectively, compared with baseline. The resulting cost-effectiveness ratios would be $31,680 and $68,198 per RS and SG QALY gained.

DISCUSSION

This evaluation shows that augmentation of a conventional DMARD strategy with LEF increases the 5-year management costs by $1,231 compared with the strategy without LEF, with a cost-effectiveness ratio of $13,096 per additional year of ACR20 response to treatment, and cost-utility ratios of $54,229 and $71,998 per RS and SG QALY gained. Adding LEF as a new option to a conventional sequence of DMARDs extends the time patients may benefit from DMARD therapy at a reasonable cost effectiveness and cost utility.

Table 1. Data used in the model for each disease-modifying antirheumatic drug*

6-month data	MTX	MTX & SSZ	TRIPLE	LEF	GST	CSA
Clinical data						
All terminations, % (SE)	13.5 (2.8)	12.5 (4.0)	3.6 (1.3)	31.6 (7.3)	26.0 (4.3)	19.3 (4.4)
Toxicity terminations, % (SE)	6.6 (1.3)	7.6 (2.2)	0.8 (0.4)	15.9 (3.5)	14.4 (2.8)	9.1 (2.0)
Total adverse events, % low†–high‡	18.3	38.4	16.9	16.5	25.2	36.6
Maximum adverse events per patient, n	1.7	1.5	1.5	4.5	1.4	1.7
ACR20 response rate, % (SE)	64.2 (6.3)	69.4 (8.9)	78.0 (8.2)	49.8 (5.5)	47.1 (11.7)	33.3 (10.9)
Costs						
Drug, US $ (range)	162 (85–265)	522 (270–801)	808 (417–1,087)	2,417 (n/a)	651 (330–651)	2,947 (1,037–4,124)
Baseline monitoring, US $	172	254	334	176	79	294
Routine followup monitoring, US $ (range)	290 (196–383)	295 (200–389)	334 (200–469)	215 (157–272)	526 (482–570)	363 (309–417)
Adverse event costs if termination US $ (range)	364 (191–602)	176 (153–207)	56 (50–72)	318 (251–371)	183 (60–291)	333 (85–502)
Adverse event costs if continuation US $ (range)	113 (36–195)	109 (75–162)	122 (94–156)	105 (87–128)	79 (21–136)	127 (40–261)
	0.742	0.794	0.809	0.728	0.636	0.413

* MTX = methotrexate; SSZ = sulfasalazine; HCQ = hydroxychloroquine; LEF = leflunomide; GST = gold sodium thiomalate; CSA = cyclosporin A; ACR20: American College of Rheumatology criteria of 20% improvement.
† Number of patients with adverse events.
‡ Number of adverse events.

Table 2. Patients' standard gamble and rating scale utilities

Utilities	
Standard gamble: response (SD)	0.823 (0.281)
Standard gamble: no response (SD)	0.882 (0.131)
Standard gamble: terminate treatment (SD)	0.783 (0.258)
Standard gamble: placebo, terminate (SD)	0.695 (0.290)
Rating scale: response (SD)	0.768 (0.222)
Rating scale: no response (SD)	0.706 (0.189)
Rating scale: terminate treatment (SD)	0.568 (0.236)
Rating scale: placebo, terminate (SD)	0.463 (0.217)

This model-based cost-effectiveness approach was selected to evaluate the added value of LEF when introduced in a management approach adopted by Canadian rheumatologists in their usual management of patients with active RA. We emulated the management of RA patients in real life where they usually cycle through different treatment regimens when experiencing toxicity or lack of efficacy. There are several advantages to this type of analysis. The modeling approach allows estimation of the expected performance of the drug in the real world and theoretically provides a better estimate of the cost effectiveness of new interventions. Furthermore, the impact of LEF can be assessed over a time horizon that exceeds the limited time horizons adopted in clinical trials. Within that more realistic framework, the addition of LEF as a new treatment alternative for patients requiring a new therapy extends the time patients may benefit from DMARDs.

The choice of the strategy was based on a separately conducted survey of Canadian rheumatologists (12). Different rheumatologists will opt for different treatment sequences; we are therefore aware that the adopted sequence is only one among many chosen by rheumatologists to treat patients with more aggressive RA. The choice of sequence was also constrained by technical considerations, which were imposed by the Markov modeling assumptions, and the limited availability of information in the literature. For example, the survey of Canadian rheumatologists identified the combination of MTX and HCQ to be more frequently used than that of MTX and SSZ. However, the combination of MTX and HCQ could not be modeled because there is no study reporting ACR20 response rates for this treatment strategy. Because the MTX-HCQ combination is perceived in practice to be equally efficacious to the methotraxate-sulfasalazine combination, the substitution of one for the other in the model was not expected to change the conclusions of the analysis. The TNFα blockers were also excluded from this analysis because they were not approved when this evaluation was undertaken.

Table 3. Cost-utility and cost-effectiveness results*

	Excluding leflunomide	Including leflunomide
Cost, US $	8,467	9,698
Incremental cost, US $		1,231
Effectiveness		
Years in ACR20 response	2.729	2.823
RS QALYs	3.339	3.362
SG QALYs	3.868	3.885
Incremental effectiveness		
Years in ACR20 response		0.094
RS QALYs		0.023
SG QALYs		0.017
Incremental cost effectiveness ratios		
ACR20 response, US $		13,096
RS, US $		54,229
SG, US $		71,988

* ACR20 = American College of Rheumatology criteria of 20% improvement; QALYs = quality-adjusted life-years; RS = rating scale; SG = standard gamble.

The results are influenced by the very positive findings of the 2 studies of triple therapy in RA (21,22). Even though patients were evaluated under clinical trial conditions, the withdrawal rates on triple therapy were so low that many patients stay on this therapy for quite a while when going through the model. However, data for combination therapy with MTX and SSZ are quite encouraging too, pointing to a clear relationship between the number of drugs used in combination and the decrease in withdrawal rates.

Even though the analysis was conducted over a 5-year time horizon, only 2-year information was available for LEF. Having to extrapolate from the 2-year data is a limitation of the model that does not favor LEF. For example, long-time experience with MTX showed that approximately 14% of patients discontinue during a 6-month period. When referring to the North American trial comparing LEF to MTX, the clinical trial setting points to a discontinuation rate of 32%, with no difference in discontinuation rates between the 2 agents (17). Further observational studies of LEF in routine clinical care settings may change the cost-effectiveness results in favor of LEF.

The cost-utility results based on the RS- and SG-derived QALYs were relatively similar, even though the findings from the RCT were very inconsistent, at least between responders and nonresponders. It might be that there is not sufficient clinical difference between nonresponders and responders who decide to continue therapy, and this lack of a difference is reflected in the utility values. However, the RS utilities show a clear increasing trend from terminating patients to nonresponders and responders. The evaluation of SG utilities within a clinical trial might very well be a method that is too insensitive to be used in clinical trial settings.

We would have liked to model other outcomes, such as improvement in ACR criteria by 50%. This is especially important because the newer DMARDs may be more potent and qualitatively superior to existing therapies, however, very few studies in the literature report on ACR50 outcomes. Although there is little reason to suspect qualitatively superior responses among the comparators used in the present study, this cannot be entirely excluded, and would likely bias against leflunomide.

Direct medical costs estimated for the purpose of the model-based comparison are only an approximation of the costs likely to be encountered in real life. It is conceivable that costs will be lower in real life. First, monitoring costs

were derived from monitoring recommendations provided in the product monographs. In real life, physicians will likely monitor less once they gain experience with each drug. Similarly, costs of managing adverse events were derived from a literature-based survey of 5 Toronto rheumatologists. Costing of the adverse events was based on the answers provided in the survey, which may deviate from physicians' behavior in real practice. Physicians responding to the questionnaire may have adopted a more cautious approach, not knowing the precise clinical circumstances accompanying the adverse event.

The majority of data supporting the model-based comparison was derived from the literature. The literature, however, is sparse for much of the data needed. For example, only 35% of the observational studies on maintenance of DMARDs provide data needed for the model. Similarly, only approximately 30% of RCTs or observational studies provide information on the number of patients with 1 or more adverse events. Explicit response criteria have only recently been used in RCTs and are seldom used in observational studies. For these reasons, the data used in our model do not represent all studies that were conducted with the respective drugs.

Research into the economics of DMARDs is complicated by the chronic nature of RA. There is not a single drug used to treat RA, but a multitude; and all of them have declining effectiveness over time. This makes modeling more complicated, particularly if combinations of drugs are used. Of further importance for modeling RA is the severity and stage of the disease, as a differential response may be expected from patients with mild RA or those who try MTX as first drug or after previous failure of other drugs, such as SSZ or HCQ. These details were impossible to consider in the present modeling framework.

The results of this study confirm that LEF has a place in the management of patients with RA and that its integration into the therapeutic armamentarium comes at reasonable cost. The exact therapeutic value of LEF in the routine management of patients with RA needs to be further established. As rheumatologists gain more experience with LEF, the drug's effectiveness will likely improve and further enhance its economic profile.

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