Cost-Effectiveness Estimates Reported for Tumor Necrosis Factor Blocking Agents in Rheumatoid Arthritis Refractory to Methotrexate – A Brief Summary

ANDREAS MAETZEL

ABSTRACT. In a climate of rising healthcare expenditures the economic evaluation of new therapies becomes increasingly important in decision-making by health authorities. This article highlights some of the considerations regarding the economic assessment of drug treatments as they relate to rheumatic diseases, with emphasis on new biologic therapies such as tumor necrosis factor inhibitors. (J Rheumatol 2005;32 Suppl 72:51-53)

Key Indexing Terms:
BIOLOGIC THERAPY
ARTHRITIS
COST-BENEFIT ANALYSIS

Healthcare expenditures are rising in most industrialized nations due to an aging population and technological advances, which challenge governments' capacities to accommodate such expenditures from general revenues. Interestingly, actual budgets for healthcare spending are often scattered regionally or institutionally, often across many government agencies or paying institutions. Therefore, decisions to grant reimbursement status in one case and refusal to do so in another are often deliberate, and subject to particular circumstances, including the unique makeup of the experts sitting on formulary committees[1].

Experience with such formulary committees shows that the size of the clinical benefit of a new application has a decisive influence on final approval status, moreso than the price[2]. However, it has become common practice and is now generally recommended to assess "value for money" for new drugs and health interventions[3]. This is irrespective of the payer's ability to actually "afford" such new medications, since relatively inexpensive medications reimbursed for a large proportion of the population may stress healthcare budgets more than expensive medications for rare disorders. Explicit considerations of "value for money" are thus an essential component of a new drug's application for reimbursement status; they assist policymakers in their decisions on whether to grant such status.

To evaluate the economics of a new therapy, in particular biologic response modifiers for the treatment of rheumatoid arthritis (RA), a comprehensive accounting of the treatment and disease costs and an unbiased documentation of the health benefits of treatment are needed. Such information is needed for the new biologics and the existing treatments. Economic evaluations require detailed documentation of costs and cost savings in many areas directly and indirectly affected by the delivery of healthcare. Medical care costs include costs for drug treatments, laboratory tests, visits to physicians and nurses, hospitalizations, rehabilitation services, ambulatory treatments and procedures, and durable medical equipment. Direct nonmedical costs refer to resources devoted to non-healthcare items necessary for the care of RA. These can include a variety of goods and services, such as childcare necessary when a parent is staying in the hospital, or homecare such as cooking and bathing[4]. Health may indirectly affect patients' productivity, the costs of which include lost wages because of disability or time spent seeking care for RA[5]. "Indirect costs" also occur when patients are unable to do chores or when a caregiver incurs productivity losses while caring for the patient.

Health benefits, on the other hand, can be expressed as either natural units or quality of life. Natural units are understandable to many decision-makers; examples in RA include: remission, defined as improvement of greater than 50% in American College of Rheumatology (ACR) composite criteria; achievement of full productivity by a patient; or a serious adverse event. Often, however, health benefits are aggregated into a single quality of life measure, to record both positive and negative events in one measure. A crucial advantage of this representation of health is the ability to describe a disease state in terms of its "full health" equivalent. For example, RA patients report that, for them, spending 10 years with RA

From the Division of Clinical Decision Making, the Department of Health Policy, Management, and Evaluation, University Health Network, University of Toronto, Toronto, Ontario, Canada.

Dr. Maetzel has received grant support from Schering Plough Canada Inc., Amgen Inc., Merck Frosst Canada Ltd., F. Hoffman-La Roche Ltd., and Aventis Canada Inc. in the preceding 5 years.

A. Maetzel, MD, MSc, PhD.

Address reprint requests to Dr. A. Maetzel, Division of Clinical Decision Making, University Health Network, 200 Elizabeth Street, EN6-232A, Toronto, Ontario M5G 2C4, Canada.
E-mail: maetzel@uhnresearch.ca

Table 1. Short listing of cost-effectiveness ratios reported for TNF-blocking agents in patients with RA refractory to methotrexate.

Reference	Duration/Order of Treatment	Duration of Model	Country	Cost per QALY† , US$
Infliximab				
Wong 14	1 year	Lifetime	US	$31K
Kobelt 15	1 year	10 years	UK/Sweden	$40K
Jobanputra 16	1st line	Lifetime	UK	$180K
Etanercept				
Brennan 17	1st line	Lifetime	UK	$26K
Jobanputra 16	3rd line	Lifetime	UK	$130K
Choi	1st line	6 months	US	$35K (ACR70W*)

* Weighted 20%, 50% and 70% response as per American College of Rheumatology response criteria.
† Direct costs only.

would be equivalent to spending 8 years in full health, i.e., 10 years with RA is worth about 8 quality-adjusted life-years (QALY)[6]. In other words, patients with RA, on average, would be willing to give up 2 years of a 10-year life expectancy to avoid living with RA. Gains in QALY are then generally used as the currency for benefits in economic evaluations.

Suppose a new intervention with an annual cost of $16,000 may lead to cost savings that offset the acquisition cost of the medication by $6,000, and an additional 25% of patients in remission with a gain of 0.1 QALY compared to standard therapy. Such a tenth of a QALY would amount to an extra 36.5 quality-adjusted life-days, or a bit more than a month of full-health equivalent. Thus, the "marginal" cost-effectiveness of the new intervention, for a one-year period and from the perspective of society, would be $10,000 divided by 0.25, or $40,000 per patient achieving remission. With health gains expressed in terms of QALY, the cost-effectiveness would be $10,000 divided by 0.1, that is $100,000 per QALY gained. Achieving a remission in one out of 4 patients, or a QALY gain of 0.1, would be considered clinically extremely relevant, and it is now up to the decision-maker to determine whether the new intervention is worth the extra costs and should be reimbursed.

Pharmacoeconomic considerations are likely to play an increasing role in the decision-making process when the clinical benefit is equivocal and the cost-effectiveness ratio exceeds $100,000 per QALY gained, which many consider to be at the margin of acceptability[7]. Reimbursing a new drug based on a higher cost-effectiveness ratio, for example $200,000 per QALY, may require proof of a very strong clinical benefit to persuade policymakers[8].

Results of economic evaluations performed for 2 tumor necrosis factor (TNF) blocking agents, infliximab and etanercept, in patients with RA refractory to methotrexate (MTX) are shown in Table 1. All cost-effectiveness estimates were converted from their original currency to US$ based on Organisation for Economic Co-operation and Development published estimates of gross domestic product based purchasing power parities, and rounded to the nearest 1000$[9]. As can be seen, the cost-effectiveness ratios vary in size, and differences are most likely attributable to model specifications chosen by the authors.

One obvious feature that may exert an influence on final cost-effectiveness ratios is the choice of the comparator. For example, only one evaluation used triple therapy with MTX, hydroxychloroquine, and sulfasalazine as a comparator[10], while evaluations of infliximab and etanercept were based on the original randomized controlled trials with placebo as the comparator drug in addition to MTX[11,12]. Health Assessment Questionnaire (HAQ) based disability measures were used to infer QALY estimates. Improvement in HAQ may not match clinical reality as closely as changes observed in supporting randomized controlled trials[13]. Further, projections of extended HAQ benefits may not be achieved in clinical reality, due to higher than expected withdrawal rates.

These observations notwithstanding, TNF blocking agents offer important treatment options to patients with RA and are essential for patients whose disease is refractory to MTX. Economic evaluations for TNF blocking agents will supplement this clinical information and may inform policymakers about the potential value for money associated with TNF blocking agents. Future longterm observational studies will provide additional information about the adverse event profile and economic attractiveness of TNF blocking agents in RA.

REFERENCES

1. Pausjenssen AM, Detsky AS. Guidelines for measuring the costs and consequences of adopting new pharmaceutical products: are they on track? Med Decis Making 1998;18 Suppl:S19-S22.
2. Hill SR, Mitchell AS, Henry DA. Problems with the interpretation of pharmacoeconomic analyses: a review of submissions to the Australian Pharmaceutical Benefits Scheme [see comments]. JAMA 2000;283:2116-21.

3. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effective ness in health and medicine. New York, Oxford: Oxford University Press; 1996.
4. Brouwer WB, Koopmanschap MA, Rutten FF. Patient and informal caregiver time in cost-effectiveness analysis. A response to the recommendations of the Washington Panel. Int J Technol Assess Health Care 1998;14:505-13.
5. Koopmanschap MA, van Ineveld BM. Towards a new approach for estimating indirect costs of disease. Soc Sci Med 1992;34:1005-10.
6. Maetzel A, Strand V, Tugwell P, Wells G, Bombardier C. Cost effectiveness of adding leflunomide to a 5-year strategy of conventional disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Arthritis Rheum 2002;47:655-61.
7. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ 1992;146:473-81.
8. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? Arch Intern Med 2003;163:1637-41.
9. Organisation for Economic Co-operation and Development. Purchasing power parities. Internet. Cited September 5, 2004. Available from: http://www.oecd.org/dataoecd/61/54/18598754.pdf
10. Choi HK, Seeger JD, Kuntz KM. A cost-effectiveness analysis of treatment options for patients with methotrexate-resistant rheumatoid arthritis. Arthritis Rheum 2000;43:2316-27.
11. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478-86.
12. Maini RN, St. Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.
13. Wolfe F, Michaud K, Pincus T. Do rheumatology cost-effectiveness analyses make sense? Rheumatology Oxford 2004;43:4-6.
14. Wong JB, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis. Am J Med 2002;113:400-8.
15. Kobelt G, Jonsson L, Young A, Eberhardt K. The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. Rheumatology 2003;42:326-35.
16. Jobanputra P, Barton P, Bryan S, Burls A. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess 2002;6:1-110.
17. Brennan A, Bansback N, Reynolds A, Conway P. Modelling the cost-effectiveness of etanercept in adults with rheumatoid arthritis in the UK [see comment]. Rheumatology Oxford 2004;43:62-72.