Considerations and Preliminary Proposals for Defining a Reference Case for Economic Evaluations in Ankylosing Spondylitis

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ABSTRACT. Since healthcare resources are scarce, choices have to be made on how they will be allocated. The use of economic evaluations using cost-effectiveness analyses has increased rapidly as policymakers have realized their value in maximizing the population's benefits (in terms of length of life and health status) within a given budget. Following efforts by OMERACT to create reference case definitions for the conduct of economic evaluation in rheumatoid arthritis, osteoporosis, and osteoarthritis, we review various methodological areas and research decisions that could benefit from a consensus between researchers, clinicians, and drug developers in terms of an ankylosing spondylitis (AS) reference case. Ten methodological issues are presented that will be important for future development of evaluations. Tentative proposals to define the issues in a reference case for AS are made, along with recommendations for further research. (J Rheumatol 2007;34:1178–83)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS ECONOMICS COST EFFECTIVENESS

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that can have a progressive disabling course, resulting in impaired physical functioning, work disability, and reduced health related quality of life[1-4]. The recent increase in attention to AS has come from findings that the disease is nearly as prevalent and equally disabling as rheumatoid arthritis (RA)[5,6], and the discovery that anti-tumor necrosis factor (TNF) therapy is highly effective in improving the manifestations of the disease[7].

Through improvements in patient function, therapy has the potential to enhance health related quality of life and reduce concomitant employment of healthcare resources[8,9]. Consequently, a number of economic evaluations have estimated whether the additional cost of spa therapy[10], cyclooxygenase-2 (COX-2) selective inhibitors[11], or TNF antagonists[12-17] in patients with predominantly axial AS represent worthwhile use of health resources. Such analyses are important for government agencies and managed care groups when deciding to allocate resources to new health technologies. Of particular importance are decisions around expensive technologies like TNF antagonists, where use could result in a significant increase in drug budgets. Given that economic evaluations exist to inform decisions about resource allocation, analyses should reflect what happens in the real world so trial-based analyses or models based on a single randomized controlled trial (RCT) usually represent only a partial and limited form of analysis[18]. Decision-analytic models can be used to combine multiple sources of evidence through systematic review and metaanalysis, and can extrapolate evidence to time horizons more useful for decision-making. However, such models can be difficult to develop and, since they are based on numerous methodological choices and assumptions, are open to inaccuracy and bias[19].

As a consequence, several guidelines are available for those developing and performing economic evaluations[20]. These provide direction on many generic issues in the conduct of economic evaluations, and reflect the consensus within the research community[21]. However, these guidelines are not spe-

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Supported by the OMERACT 8 Special Interest Group. N.J. Bansback is the recipient of an OMERACT fellowship.

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cific for particular health conditions or interventions. The Outcome Measures in Rheumatology (OMERACT) initiative has played a significant role in supporting the recommendation of disease-specific reference case definitions for the conduct of economic evaluation in RA, osteoporosis, and osteoarthritis[22,23]. A reference case as defined by the US Public Health Service Panel on Cost-Effectiveness is "a standard set of methodological practices that an analyst would seek to follow in a cost-effectiveness study."[24] OMERACT is considering expanding these efforts to include AS, and this article describes the achievements in this direction to date.

Process

Many assumptions and choices have to be made when developing an economic evaluation. Our objective was to identify topics for which a number of alternative options exist for analysts developing economic evaluations of all current and potential technologies, which could benefit from a consensus between researchers, clinicians, and drug developers. A list of candidate issues was based on issues raised by previous OMERACT initiatives for other rheumatological conditions[21-23]. The list was complemented with items from the wider economic evaluation literature, which has seen advances in methodology over the past few years. A systematic review of economic evaluations in AS was performed to identify discrepancies between published analyses. These articles and 4 abstracts were appraised and helped to focus the issues that would benefit most through consensus[25]. Next, a Web-based questionnaire was developed containing each candidate issue with possible consensus options, along with an open question to allow additional issues to be included. Over 30 invited experts returned a completed questionnaire. Finally, these issues and their possible definitions were the focus of a discussion between rheumatologists, economists, and other interested parties at the OMERACT 8 meeting in 2006. We present the 10 issues identified from this process. Each is described with its relevance in AS. Preliminary recommendations are given and areas for further research are identified (Table 1).

Methodological issues

1. Time horizon/Duration of followup. An important starting point for all analyses is the time within which the benefits and costs associated with an intervention are evaluated. Some payers prefer a short time horizon, since they have interest in only the short-term influence of interventions as a result of the frequent changes in health plans experienced by many employees. In contrast, many guidelines for economic evaluations state that the time horizon should be long enough to identify all longterm effects and costs[20]. For example, in AS, if it is plausible that TNF antagonists can modify disease progression, then the effect of treatment could last for the duration of a patient's life and consequently only a lifetime perspective would indicate future cost savings and improved quality of life. If TNF antagonists only relieve symptoms temporarily, and after withdrawal patients return quickly to their previous disease state, as is the case in many physiotherapies or spa therapies, then a lifetime perspective would not be necessary. The relevance of the time horizon for anti-TNF in AS is shown in the publication of Kobelt, *et al*[12] in which the cost-utility ratio decreased by more than 50% when the 2-year result was extrapolated to 30 years. Selecting the appropriate time horizon is relatively simple, but finding evidence to populate such horizons is usually very difficult. The selection and approaches to estimating these inputs are discussed below.

2. Duration of treatment. The duration that a treatment is administered in a clinical trial usually does not reflect the duration in real life. In a trial setting, the protocol will normally require a patient to continue treatment until the end of the study. However, for some treatments, like TNF antagonist therapy, real-life guidelines suggest that the patient must achieve an initial response to be eligible to continue therapy[26-28]. From an economic perspective, this approach avoids the continued accrual of costs of expensive agents when patients are showing little evidence of efficacy. After an initial response, patients can withdraw from treatment in the real-life setting for several reasons, e.g., insufficient effect, noncompliance, side effects, death. Including withdrawal in the models has implications for the model structure and for populating the model with appropriate sources of evidence that can provide estimates for withdrawal. The 2 published analyses of TNF antagonists in AS give different estimates for the length of time patients will remain on treatment. Boonen, *et al* assume that patients remain on treatment only if they initially respond to treatment, or until they relapse or have major toxicity over the duration of the model[14]. Response, defined as reaching a state of < 4 on the Bath AS Disease Activity Index (BASDAI), is populated initially through data from the clinical trials, then later from observational data. In contrast, Kobelt, *et al* in their basecase analysis assume all patients withdraw from TNF antagonists after 12 weeks, but then they model the longer-term effect of that period of therapy[12]. These different approaches have a large effect on the predicted costs associated with treatment.

3. Extrapolation of effects beyond treatment and/or trial duration. When extrapolation of effects beyond the duration of the treatment and beyond the duration of clinical trials is deemed appropriate, careful consideration of the disease in question, knowledge of its natural course, and some longterm evidence on the treatment effects are required. Different assumptions about longterm benefits based on short-term evidence can give widely varying results. In the base-case analyses, Kobelt, *et al* assumed that after the initial 12 weeks of treatment, the Bath AS Functional Index (BASFI) would progress at 0.07 points per year under usual care as well as in the active treatment group[12]. Boonen, *et al* assumed that there would be no change in the BASDAI in the usual-care group after the first year, whereas relapse to high disease activity was possible

Table 1. Proposals and areas of further research for each issue identified.

Tentative Proposal	Areas for Further Research
1. Time horizon/duration of followup	
• The time horizon of an evaluation should be linked with the length of the trial evidence that provides the primary source of effectiveness • Taking into account comparability with the RA reference case, results should be reported at 1 year (DMARD and SMARD), 5 years, and lifetime (DMARD only)	• Along with further evidence on the longterm effectiveness of treatments, in particular radiographic studies, understanding of the epidemiology of other factors such as mortality and toxicity
2. Duration of treatment	
• Decision models should include an option for initial nonresponders for whom therapy will be discontinued at a specified timepoint	• The exact criteria used for assessing initial response require acknowledgement of economic as well as clinical consequences • Registries should examine reasons and rates of withdrawal and mortality and follow the sequence of treatments given to patients
3. Extrapolation of effects beyond treatment and/or trial duration	
• Unless there is overwhelming evidence of the longterm benefits of treatment, a sensitivity analysis should always be presented that assumes that there is no longterm effect	• Registries and observational datasets should incorporate economic endpoints (HRQOL and costs)
4. Choice of comparator and synthesis of comparisons and treatment strategies where clinical trials do not exist	
• New economic models should always include the comparator "usual care" • The absence of head-to-head studies should not restrict comparisons, although appropriate methods and sensitivity analysis should be used when making indirect comparisons	• Methods for making indirect comparisons, particularly when there is heterogeneity in patient characteristics
5. Outcome measures	
• Measures of both disease functioning and disease activity should be modeled	• The components of clinical trials that best measure (1) clinical response, (2) health improvements when on treatment, (3) progression of disease, and (4) cost of illness if no treatment
6. Valuation of health in terms of quality of life or health utilities	
• A generic health utility (health state preference) measure should be included in clinical trials and registries	• How to perform various (direct and generic) health utility instruments in AS • The relationship between changes in the clinical measures and changes in health utilities in AS
7. Resource utilization and costing	
• Estimates of the changes in productivity costs associated with an intervention should not be included in the base-case result, but reported separately as an alternative central result	• How productivity costs should be measured in AS and are there any additional challenges posed in this disease?
8. Population risk stratification—subgroups	
• Different subgroups of patients should be analyzed in economic models to explore which groups are most cost-effective, but limitations in the evidence should be clearly disseminated	• How subgroups of patients that are candidates for new interventions in AS should be defined
9. Uncertainty analysis	
• Extensive one-way sensitivity analysis should always be performed • Probabilistic sensitivity analysis should be used where the description of parameter uncertainty is possible, and the method is feasible	• How methods such as expected value of information can be used to direct further research in AS most efficiently?
10. Model development and reporting	
• All parameters associated with the model can be reported so the analysis is transparent and reproducible. All assumptions should be reported explicitly. Where space does not allow in journal format, online appendices should be used • All potential conflicts of interest should be reported and specific roles of each author disseminated	• How reproducible and therefore reliable are existing economic evaluations?

throughout the 5 years in the active treatment group[14]. Assumptions are not restricted only to the efficacy of the intervention, but also to what would happen once the patient has withdrawn, and what the natural course of disease is for the comparator arm. An example from the literature is the "rebound" after withdrawal from treatment with TNF antagonists. Brandt, *et al*[29] found that nearly all patients experienced a relapse 24 weeks after stopping etanercept. If this relapse is not correctly incorporated into the analysis, the extrapolation could unfairly assume the intervention has longterm sustained benefit, but without additional treatment costs[30]. Both Kobelt and Boonen assumed patients under treatment would return to the initial health state within 12 weeks. In line with this issue, once patients are withdrawn from a particular treatment, increasingly they move to another treatment, and sequences of treatments might increasingly become clinical practice. Jansen, *et al* describe the only study to look at this issue, where nonresponders to COX-2 selective inhibitors are assumed to move on to TNF antagonist treatment[11].

4. Choice of comparator and synthesis of comparisons and treatment strategies where clinical trials do not exist. The question posed in most RCT where the active agent is com-

pared to placebo is that of efficacy, or "does the intervention work?". Economic evaluations have a different perspective, that of effectiveness, or "how well does the intervention work in comparison to the best conventional care?". Currently, conventional care in AS comprises nonsteroidal antiinflammatory drugs (NSAID) and physical exercise. However, a proportion of AS patients may not receive even this, having stopped seeing their physician, as until recently no disease modifying treatments were available. Since primary RCT are unlikely to compare new active compounds with existing active treatments, data from secondary direct head-to-head studies would be necessary to populate economic evaluations. Such trials are unlikely to happen in the future since there is little incentive for manufacturers to risk their market share, and the cost would be too high for most public agencies.

Singh, *et al*[15,17], Duff, *et al*[16], and Boonen, *et al*[14] use simple methods to compare the outcomes of the TNF antagonists etanercept and infliximab either directly or indirectly by comparing to usual care, using results from separate clinical trials. All methods follow an assumption regarding the comparability of patient populations and some adjustment for the placebo effect. New statistical methods have been developed to compare multiple treatments that combine direct and indirect evidence in a single analysis and to include Bayesian methods to reduce uncertainty[31,32].

3. Outcome measures. Essential for developing economic evaluations is the choice of the disease related specific health or disease states that represent, clinically and economically, important events in the disease process that is to be modeled. In AS, several patient-reported outcomes are available. Among these, the BASDAI[33] and BASFI[34] are most frequently used. However, there is insufficient evidence on which (combination of) measures reflect clinical and economic outcomes most adequately. Further, response criteria for short-term treatment and biologics have been defined by the ASsessment in AS (ASAS) study group. In economic evaluations, absolute outcome measures are much preferred to relative response criteria, especially in longterm studies. Boonen, *et al* used 2 levels of the BASDAI to describe the clinical health state, and included toxicity as a separate state[14]. However, having just 2 states limits the discriminative ability of an analysis to reveal changes in disease over time. Since the BASDAI does not measure domains of physical functioning, Kobelt, *et al* used combined states of BASDAI with the BASFI[12].

6. Valuation of health in terms of quality of life or health utilities. Among all study types, cost-utility analyses, whereby health benefits are quantified in terms of quality-adjusted life-years (QALY), are recommended in the great majority of health economics guidelines as the method of choice for allowing economic comparison between diseases[24]. Preference-weighted measures are preferred using societal tariffs, and can be collected using a variety of generic indirect utility instruments, such as the Health Utilities Index, EQ-5D, or SF-6D.

In AS, the effect on quality of life (the quality adjustment) is more notable than length of life (life-years)[35,36]. While it is already difficult to identify all these effects of the disease in a disease-specific QOL instrument, it is unlikely these are adequately identified in the generic QOL instruments and indirect utility instruments.

Importantly, instruments to calculate the indirect utilities are not all comparable. The "floor effect" in the SF-6D has shown that the instrument is not discriminative or responsive in differences between severe states[37]. While the EQ-5D does not suffer from such a floor effect, its sensitivity is more limited. In the published analyses, both Kobelt, *et al*[12] and Boonen, *et al*[14] mapped the clinical outcomes onto EQ-5D utilities.

7. Resource utilization and costing. AS carries a significant economic burden, driven by productivity loss, ambulatory care, and formal (and informal) care[8,12,38]. The societal perspective, which is widely considered to be the most appropriate from an economic point of view, requires all components of costs to be included in the economic evaluation, regardless of who bears these costs. While previous work on the development of standardized cost domains was mostly for patients with RA, it should also be appropriate for patients with AS[39]. Since AS affects many people of working age, a large proportion of the costs attributable to AS is from work disability[40,41]. The inclusion or exclusion of productivity costs and the choice of method to calculate productivity costs (friction costs or human capital approach) can influence the cost-utility ratios in economic evaluations importantly. One study shows that when indirect costs were included (using the human capital approach), the cost-effectiveness ratio decreased by over 50%[12]. Even if it is feasible to measure all direct and indirect costs directly during a (short) clinical trial, these costs can be subject to the selection bias of patients recruited into most clinical studies. An alternative is to use an observational study that collects resource utilization data to populate the health states in the model. An example of this is the work by Kobelt, *et al*, which found disease activity measured using the BASDAI had a strong influence on costs at non-severe levels, while the BASFI caused costs to increase as the disease worsened[12].

8. Population risk stratification — subgroups. Interventions may have differential effects within the AS population, depending on the disease characteristics of the group. Within the population of patients with predominantly axial AS, for which this reference case is aimed, subgroup analysis can be used to identify populations in whom the target intervention benefits the most. However, it is necessary to ensure that the choice of subsample is justified where there is *a priori* a sound biological rationale for doing so and where there is evidence that clinical effectiveness or cost-effectiveness may vary between groups, and that it was not chosen after "data dredging" to try to identify the subsample that yielded the most favorable results in terms of the cost-effectiveness. The credibility of a subgroup analysis can be improved if confined to the primary outcome and to a few predefined subgroups on the

basis of biologically plausible hypotheses. In AS, potentially relevant subsamples would be based on the disease duration, level of disease activity, amount of radiographic damage, number of prior therapies, and other recognized prognostic factors for poor outcomes for axial disease such as uveitis or hip arthritis[42,43]. In the review, we found that no subgroup analyses have been performed in published analyses.

In addition, some interventions may have a benefit beyond that of AS. In the case of TNF antagonists, it has been suggested that patients with comorbidities such as presence of inflammatory bowel disease, uveitis, psoriasis, and peripheral arthritis might also receive benefit. By contrast, while NSAID may also prevent radiological damage, they may increase the risk of cardiovascular and gastrointestinal disease[44].

9. Uncertainty analysis. It is not generally considered appropriate to truncate economic evaluations just because we are not certain about specific parameters[45]; for example, if the analyses on TNF antagonists in AS were restricted to using just the short-term evidence. The current analyses suggest that TNF antagonists would not be considered cost-effective interventions. However, by using reasonable synthesis of data from external sources, the longterm benefits of treatments can be considered, and the cost-effectiveness appears more promising. However, sensitivity analysis shows that if specific parameters are changed to other reasonable scenarios or values, the cost-effectiveness can change dramatically. Therefore uncertainty in the extrapolations leads to uncertainty in the results.

The past decade has seen the development of more comprehensive methods to understand the implications of uncertainty. By assigning a probability distribution to each parameter to describe its range of plausible values and by using techniques such as Monte Carlo simulation, the results can be presented as the probability that an intervention is cost-effective[46]. As an example, if the benefit of treatment is extrapolated beyond the available clinical evidence, the full range of what future benefits might be (say, from no prolonged effect to continued constant effect) can be built into the analysis and therefore into the decision. Of even more value is the ability to quantify whether, for each parameter, it would be more financially prudent to fund further research to reduce the uncertainty in that parameter or to risk the financial impact of making the wrong decision[47]. In published analyses, univariate but not multivariate sensitivity analyses have been performed, nor have any analyses used more sophisticated techniques to analyze the uncertainty or prioritize future research.

10. Model development and reporting. The last issue considers how investigators develop and disseminate their analysis. The need for transparency by detailing every parameter and assumption, either in the journal article or as an appendix, is universally accepted, but rarely adhered to[48]. Since most evaluations focus on a specific country, this becomes even more important for the generalizability of results to other healthcare settings. Our review found the published articles on the whole were disappointing in this respect.

Conclusion

The economic implications of AS, in particular since the advent of TNF antagonists, have caused much interest[49]. Interventions for AS will compete for funding with other interventions in other diseases and so the role of cost-effectiveness analyses to evaluate the efficiency of treatments will become even more important. Economic evaluations will only be useful to inform decision-making and help guide further research if they are of good quality.

A number of important issues are raised in this article. We make tentative proposals on each issue (Table 1), and define areas of further research that would improve economic evaluations and their development in the future. It is likely that future clinical research will have to pay more attention to the economic considerations of interventions, through more pragmatic trials and collecting new endpoints. The hope is that future economic evaluations in AS will be of better quality, more transparent, and comparable. With further discussion and deliberation, we hope to develop a consensus-based reference case for future economic evaluations. The issues raised here are by no means exhaustive, but are what we consider the 10 most important. Further work on the reference case will be required to provide a definitive tool for use in AS.

ACKNOWLEDGMENT

To persons that completed the questionnaire, those that participated in the group discussion at OMERACT, and the members of the ASAS group for their invaluable contributions.

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