Economic issues with new rheumatologic therapeutics

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Abbreviations

FCA: friction cost approach; HAQ: Health Assessment Questionnaire; HCA: human capital approach; NSAID: non-steroidal anti-inflammatory drug; PsA: psoriatic arthritis; QALY: quality-adjusted life year; RA: rheumatoid arthritis; TNF: tumor necrosis factor.

Introduction

As a result of numerous research studies conducted by investigators across the globe over the past few decades, data supporting the basis for pharmacoeconomic studies in rheumatic diseases have been well established. This is particularly true in the case of rheumatoid arthritis (RA). It has been clearly established that RA is a chronic progressive autoimmune disease that has a tremendous impact on affected patients. The joint destruction and attendant functional disability characteristic of RA are associated with substantial morbidity and even accelerated mortality. The severe sequelae of untreated or inadequately treated RA result directly in sizable economic costs, not only to RA patients and their families, but to society as well. While the costs of RA have been clearly delineated through rigorous observational studies and in-depth analyses, only recently have the implications of these costs gained significant attention. This increasing interest has been driven primarily by the introduction of newer therapeutic agents.
Progress in understanding the immunopathogenesis of RA, combined with advances in biotechnology, has allowed the development of novel therapeutic agents that target specific components of the dysregulated immune system. These so-called ‘biologic agents’, particularly the inhibitors of the key pro-inflammatory cytokine TNF-α, have proven highly effective, not only in improving the signs and symptoms of disease, but also in inhibiting the progression of joint damage, improving patient’s quality of life, and preserving their functional status. The introduction of tumor necrosis factor (TNF) inhibitors has resulted in dramatic changes in the therapeutic approach and treatment paradigms for patients with RA [1]. The ability to improve clinical outcomes in such a meaningful way has resulted in the goals of treatment being enlarged. Thus, remission is now considered not only highly desirable, but also an achievable goal for treating RA patients. In addition to their efficacy in RA, biologic agents have been shown to have impressive utility in various other systemic inflammatory diseases, including psoriatic arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease. They are under study for a number of other autoimmune conditions.

A key concern that has affected the ability of clinicians to use these newer biologic agents is their relatively high acquisition costs. In the US, the average wholesale price (AWP) for 1 year of therapy with standard RA dosages of either etanercept or adalimumab in 2006 was approximately $16 000. The exact cost of the TNF inhibitor infliximab is harder to determine because it is given intravenously, and therefore its costs are charged through the hospital pharmacy, and the dosing is weight-based; however, its cost is comparable with that of the other TNF inhibitors. Although costs slightly lower than the AWP may be available for the TNF inhibitors through negotiated discounts and other means, the costs of the three currently available agents still far exceed those of older therapeutic agents. For example, the AWP for 1 year of treatment with generic methotrexate at a dose of 17.5 mg/week is approximately $500. While methotrexate is certainly cheaper, however, recent trials employing all anti-TNFs have shown that combinations of methotrexate and anti-TNFs are clearly more effective than methotrexate alone in terms of improving signs and symptoms, optimizing quality of life, and perhaps most notably, slowing or preventing the progressive joint destruction characteristic of severe RA. The extent to which the greater clinical outcomes achievable with the use of newer medications are ‘worth’ their higher costs is perhaps the most pressing economic debate in current rheumatology.

With healthcare costs rising globally, and with newer therapeutics consuming a greater portion of healthcare budgets, there has been increased attention on pharmacoeconomic analyses as a means to justify therapy with newer, more expensive agents. This has certainly been the case in rheumatology [2]. Over the past year, important studies concerning three key facets of pharmacoeconomics relevant to rheumatic diseases have been published: first, studies defining the costs of rheumatic disease, which help provide the basis for assessing the value of their treatment; secondly, consideration of methodologic issues and other factors relevant to pharmacoeconomic evaluations; and thirdly, actual cost-effectiveness studies.

Costs of rheumatic diseases

A wealth of literature attests to the severity of RA, specifically in terms of progressive functional impairment and work disability, and hence costs. While there is heterogeneity among the studies, there are several consistent themes. Total yearly costs typically average approximately $10 000 (US dollars), and indirect costs typically exceed direct costs, not infrequently by a factor of two or more. The costs of disease are not uniformly distributed among the RA population; such skewing reflects the substantially higher costs incurred by the subset of patients with the worst RA. Relevant to pharmacoeconomic assessments of novel biologic agents such as the TNF inhibitors, patients with the most severe disease have been also the type of RA patient for whom these agents have been most commonly utilized in the clinic. The strongest predictor of cost, across numerous studies, was functional disability, typically measured with the Health Assessment Questionnaire (HAQ). Germane to pharmacoeconomic analysis, worsening in HAQ score over time resulted in higher costs whereas improvements resulted in lower costs of disease. The implication of this is that therapeutic agents capable of achieving significant improvements in functional status would be expected to lower the costs of disease. Improvements in functional status correlate with, and can also be used to quantify, improvements in quality of life, a key metric for cost assessments.

Researchers from Finland have applied pharmacoeconomic evaluations to a cohort of patients initially enrolled in the FIN-RACo trial [3••]. This original study compared several treatment strategies using traditional disease-modifying antirheumatic drugs in patients with early RA. This follow-on analysis assessed work status for a subset of 162 patients from the original cohort who were employed or employable at study entry, and followed them for 5 years. A strength of the study is its length, which is particularly relevant for a chronic progressive condition such as RA, where important outcomes may take some years to become evident. As a result of the length of the study and because of the completeness of the work productivity data collected, which was facilitated by the social system in the country, the investigators are able to use actual costs rather than modeling. Over the course of the study, 75% of patients lost work days. This finding is in keeping with the documented impact of RA on work ability. The range of costs due to lost productivity was large, up to nearly [€uro sign]200 000 over 5 years, with a mean of [€uro sign]7217 per patient year. In the initial study, the goal of
treatment was remission, and indeed, overall, many patients did achieve low levels of disease activity. Nevertheless, the investigators were able to establish a clear relationship between response to therapy and costs of disease in terms of lost productivity. For example, patients achieving full function, with a HAQ score of zero, incurred mean annual productivity losses of approximately [Euro sign]2500, compared with [Euro sign]13 000 for persons who had some functional disability. Interestingly, using work productivity as the sole measure of indirect cost of disease raises an ethical conundrum not addressed by the authors: are persons with higher-paid occupations, whose work productivity losses would be greater, potentially more ‘worthwhile’ candidates for expensive therapies? Certainly few, if any, would agree with such a proposition, but it does highlight the tenuous basis of relying on work productivity exclusively to assess value in pharmacoeconomic studies.

Nevertheless, work disability is commonly used as the key determinant of the indirect costs of disease in pharmacoeconomic evaluations. There are distinct methods to accrue such data. The ‘human capital approach’ (HCA) considers the loss of productivity in work due to disease-related disability and absenteeism from employment from a patient standpoint; thus, economic losses continue until the disease subsides and employment can be regained, or until social benefits replace income lost if the disease continues to prevent employment. The ‘friction cost approach’ (FCA) considers the same factors but from the employer’s viewpoint, with losses occurring only until a replacement worker is able to perform the duties of the afflicted worker. In both types of evaluation, the time missed from work due to the disease, multiplied by the affected person’s salary, gives the indirect cost of the disease. Clearly, these different methods can yield discrepant results. This was highlighted nicely in a publication from Germany [4••]. In this study, investigators from 24 centers across Germany collected direct and indirect cost data for patients with RA, and also patients with ankylosing spondylitis, psoriatic arthritis (PsA) and systemic lupus erythematosus (SLE). As might be expected, costs using the HCA were much greater than those using the FCA. In RA patients, annual direct costs of disease were [Euro sign]4737; annual indirect costs were [Euro sign]10 900 using the HCA, compared with [Euro sign]3162 using the FCA. Determining if the HCA or the FCA is the ‘right’ method would require extended philosophical discussion, and would likely not be resolved satisfactorily for all. Nevertheless, clinicians need to be familiar with the implications of the different methods used as they review pharmacoeconomic literature. This study also confirmed the previously established association between functional disability and cost in RA. A major strength of this study was that it also included other rheumatic diseases. While many pharmacoeconomic evaluations focus on RA, there has been increasing interest in performing similar assessments for other rheumatic conditions [4••,5,6]. This has been particularly the case as newer and more expensive therapeutic agents are being brought to the clinic for various rheumatic conditions. Costs for RA, PsA, ankylosing spondylitis, and systemic lupus erythematosus from the German study are shown in Table 1. Further studies assessing the economic impact of these and other rheumatic conditions and their treatment can be expected.

Table 1

<table>
<thead>
<tr>
<th>Disease</th>
<th>Direct costs (€)</th>
<th>Total costs (€) using HCA (€)</th>
<th>Total costs (€) using FCA (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>4737</td>
<td>15 837</td>
<td>78</td>
</tr>
<tr>
<td>AS</td>
<td>3676</td>
<td>13 513</td>
<td>72</td>
</tr>
<tr>
<td>PsA</td>
<td>3162</td>
<td>11 075</td>
<td>55</td>
</tr>
<tr>
<td>SLE</td>
<td>3111</td>
<td>14 411</td>
<td>65</td>
</tr>
</tbody>
</table>
RA affects women more than men, and has a peak incidence in the fifth and sixth decades. Therefore, economic assessments focusing exclusively on work productivity are biased against a large group of affected patients who do not work outside the home. Interestingly, one study has suggested that loss of household productivity may actually exceed that of work productivity [7]. This study also highlights that discrepant results can be achieved using different accounting methods, with the HCA generating higher cost estimates than the FCA. Consistent with other studies, this study also clearly demonstrated that worse functional disability was associated with higher costs.

'Failure costs', those costs related to therapies that a patient is currently taking that could be avoided if a new effective treatment was added, are seldom included in economic evaluations. In RA, the use of the TNF inhibitors has been shown to allow reduction in the need to use other arthritis treatments, such as glucocorticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). Although the acquisition costs of these medications are relatively low, the treatment of adverse effects related to their use can be costly, and should therefore be included in an overall assessment of the costs of therapy. For NSAIDs, this could include any costs related to the diagnosis, treatment, and prevention of NSAID-induced gastrointestinal symptoms or bleeding, as well as other NSAID-related adverse effects. For corticosteroids, this would include glucocorticosteroid-induced osteoporosis and accelerated atherosclerosis, and potentially myriad other side effects. This issue was recently addressed [8]. Using data from published literature, direct costs of several common complications related to steroid use were estimated. Overall, steroid-related adverse effects cost approximately (2001 US dollars) $215 annually per person. Where appropriate, these costs and failure costs for other treatment modalities ought to be accounted for in economic analyses of newer therapies. For example, if newer therapies are proven capable of obviating the need for orthopedic surgical intervention, this could be an important contributor to the overall assessment of their value.

Methodology and other issues in pharmacoeconomics

The increasing importance of pharmacoeconomics can be attested to by the numbers of reviews and editorials addressing this subject, with great interest in biologic agents in rheumatology and other disciplines [2,9–11]. While sometimes considered esoteric, pharmacoeconomic issues are quite relevant to individual clinicians, as well as affected patients. Responses to a survey sent to physicians in California demonstrated that physicians consider cost issues primarily at the patient level, focusing on patient out-of-pocket expenses in choosing drugs [12]. In the case of biologic agents, individual patient payments have been shown to have an important effect on choice of a specific agent. Thus, patients with public insurance were 30% more likely to receive the intravenous TNF-inhibitor infliximab because it was covered by Medicare [13]. Several studies have also shown that medication costs affect patient compliance, which in turn can impact disease outcome. In a study focusing on Medicare enrollees, 12.6% of elderly persons and 29.4% of disabled persons reported medication noncompliance related to cost [14•]. Notably, those with greater numbers of comorbid medical conditions had increased levels of noncompliance, possibly related to multiplicity of medications used. Similarly, the poorer the patient’s self-reported health status, the greater the prevalence of noncompliance. Thus, patients most at risk for poor outcomes were affected to the greatest extent by cost. The relationship between drug copayment and medication compliance has also been clearly shown in other populations. From a database that included several hundred thousand patients using lipid-lowering medications, the probability of noncompliance varied directly with increasing copayment for medication, with a greater effect among new users of the medications [15]. Another study assessed the effect of copayment in a health plan that offered three tiers of pharmacy benefit based on price [16]. As might have been expected, adherence to therapy across a range of therapeutic areas was greater when the copayment costs were lowest, for example, for generic drugs. These studies highlight the importance and relevance of pharmacoeconomic concerns for individual patients.

Cost-effectiveness studies in rheumatic diseases

In RA, there is a growing body of data, including several comprehensive reviews, addressing the potential cost-effectiveness of TNF inhibitors [17,18]. As a result of their remarkable clinical efficacy, it appears that TNF inhibitors may have an incremental cost efficacy in RA within the range of generally accepted medical interventions. Much of the data upon which this is based come from follow up of patients participating in clinical trials of these agents over the past decade. In general, changes in health states, such as the HAQ score, were modeled over time using data from the studies.
Simulations are performed using sensitivity analysis to account for reasonable variations in relevant outcomes. Either directly or indirectly, for example, by transforming functional status, utilities were created for the various transition states that then define the level of response to treatment in terms of quality-adjusted life years (QALYs) gained. Cost-effectiveness estimates thus generated showed the cost of treatment to be approximately $30,000 per discounted QALY gained (Table 2).

Table 2  
Cost-effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost per QALY (US)</th>
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<tbody>
<tr>
<td>Infliximab</td>
<td>30,600</td>
</tr>
<tr>
<td>Etanercept</td>
<td>34,320</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>29,390</td>
</tr>
<tr>
<td>QALY, quality-adjusted life year. Reproduced from [17].</td>
<td></td>
</tr>
</tbody>
</table>

Over the past year, additional studies have addressed the cost-efficacy of TNF inhibitors in RA [19]. Some [20], but not all [21•], studies have shown improvements in work status with treatment, highlighting the need to carefully assess the populations of patients treated in each study. Such studies have confirmed that treatment of RA with TNF inhibitors had an incremental cost-effectiveness within the range of what is often considered acceptable [19,22].

Perhaps one of the most exciting developments related to pharmacoeconomics evaluations of new rheumatologic therapies has been data emerging in conditions other than RA. In an analysis of patients with PsA, investigators used data from clinical trials and obtained utilities from clinic patients to assess the cost-effectiveness of treatment with a TNF inhibitor [23••]. In this carefully performed analysis, as compared with combination disease-modifying antirheumatic drugs therapy, TNF inhibitor therapy cost approximately £30,000 per QALY gained. Other studies have begun to explore the effect of TNF inhibitor treatment on employability; in one study, such treatment significantly improved employability and reduced days missed from work [24].

Another condition that has witnessed great interest from a pharmacoeconomic standpoint is ankylosing spondylitis. Over the past year, several analyses have begun to define the requisite groundwork and conducted economic assessments [5,25–28]. Whereas PsA, because it can be characterized by polyarticular peripheral arthritis, may be more directly extrapolable to RA as regards economic assessments, ankylosing spondylitis is distinct. Thus, studies defining the economic impact of disease, the relationship between specific outcomes and economic sequelae, and the impacts of therapy are all key to defining the value of novel therapies.

**Conclusion**

The relatively higher acquisition costs of novel biologic agents has brought pharmacoeconomic considerations to the forefront in rheumatology. Beginning with RA, and now expanding to other conditions, there is a growing body of data confirming the substantial cost implications of autoimmune rheumatic diseases. For the TNF inhibitors, the notable clinical efficacy observed needs to be factored into a comprehensive assessment of their value. While there is still active discussion concerning such analyses [29], results from a number of studies have begun to make a compelling case that these agents may indeed be cost-effective, particularly in patients with severe disease.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:  

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 315–316).


3 Puolakka K, Kautiainen H, Pekurinen M, et al. Monetary value of lost productivity over a five year followup in early rheumatoid arthritis estimated on the basis of official register data on patients' sickness absence and gross income: experience from the FIN-RACo trial. Ann Rheum Dis 2006; 65:899–904. Bibliographic Links This is a well done pharmacoeconomic evaluation that assesses patients participating in the previously published FIN-RACo study. Using 5 year followup data, the authors are able to assess the impact of RA on work productivity. This study confirms earlier observations on the relationship between functional status and work ability. [Context Link]

4 Huscher D, Merkesdal S, Thiele K, et al. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. Ann Rheum Dis 2006; 65:1175–1183. Bibliographic Links This study from Germany uses data from a registry to assess costs of illness for several rheumatic conditions. Importantly, the authors calculate indirect costs using both the human capital approach as well as the friction cost method. Strengths of this study include its completeness as well as its assessment of diseases other than RA. [Context Link]


18 Doan QV, Chiuo C-F, Dubois RW. Review of eight pharmacoeconomic studies of the value of biologic DMARDs in the management of rheumatoid arthritis. J Manag Care Pharm 2006; 12:555–569. Bibliographic Links [Context Link]


21• Laas K, Peltomaa R, Kautiainen H, et al. Pharmacoeconomic study of patients with chronic inflammatory joint disease before and during infliximab treatment. Ann Rheum Dis 2006; 65:924–928. Bibliographic Links This study followed patients with inflammatory arthritis at a Finnish clinic, and looked at disease measures as well as costs, and correlated these with treatment. [Context Link]


23•• Bansback NJ, Ara R, Barkham N, et al. Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis. Rheumatology 2006; 45:1029–1038. Bibliographic Links This is a carefully performed analysis assessing the cost effectiveness of treatment of psoriatic arthritis patients with a TNF inhibitor as compared to combination DMARD therapy. [Context Link]


Keywords: biologic agents; cost-effectiveness; pharmacoeconomics; rheumatoid arthritis

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