Critical analysis of economic tools and economic measurement applied to rheumatoid arthritis

M. Her¹, A. Kavanaugh²

¹Division of Rheumatology, Pusan Paik Hospital, Inje University, Busan, South Korea;
²Division of Rheumatology, Allergy, and Immunology, the University of California, San Diego, CA, USA.

Minyoung Her, MD
Arthur Kavanaugh, MD

Please address correspondence to: Arthur Kavanaugh, Director, Center for Innovative Therapy, Division of Rheumatology, Allergy, and Immunology, University of California, San Diego, 9500 Gilman Drive, mail code 0943, La Jolla, CA 92037, USA.
E-mail: akavanaugh@ucsd.edu

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ABSTRACT
Rheumatoid arthritis (RA) is chronic, progressive systemic inflammatory disease that if uncontrolled may lead to significant joint damage, dysfunction, work disability and other sequelae that result in large economic losses. A rich literature estimating the economic burden of RA, has been intensified recently, driven by costly biologic agents that have had a notable effect improving the outcomes of patients with RA. In order to optimally assess the value of therapies, it is best to take a comprehensive approach, considering all related costs of illness. This includes direct costs (e.g. the costs of the medications themselves and the monitoring required), indirect costs (e.g. loss of productivity, such as employment due to uncontrolled disease) and intangible cost (e.g. effects on pain and quality of life). Indirect costs constitute a substantial part of total cost in the patient with RA. In order to help assess the impact of RA on productivity, various tools for measuring productive loss like absenteeism and presenteeism have been introduced. No single tool reflects the entire spectrum of the productive loss clearly, as other factors such as use of a human capital approach or friction cost approach affect the valuation of productive loss monetarily. Although favourable outcomes are achieved with the use of biologic agents, their higher acquisition costs, as compared to traditional disease-modifying anti-rheumatic drugs (DMARDs) remain a barrier to their use. Assessments of the cost effectiveness of novel therapies are critically important, but published results have been contradictory, in some measure due to the heterogeneity of instruments utilised. While the various instruments appear to be valid and reliable, correlations between instruments has been modest, driven by factors such as differences in recall times, attribution and other confounders.

Introduction
Rheumatoid arthritis (RA) is chronic, progressive systemic inflammatory disease that when uncontrolled leads to joint damage. Patients usually experience functional disability, which results in reduced capacity to perform activities of daily living, including work. Work disability represents a substantial economic loss to patients, their families and society. Previous studies showed that more than half of employed patients with RA experienced work loss due to RA during the course of their disease (1). Since the introduction of novel therapies, particularly biologic agents, outcomes for patients with RA have improved. Biologic agents suppress disease activity, retard progression of joint destruction and improve joint function and quality of life. However, the higher cost of biologic agents as compared to traditional disease-modifying anti-rheumatic drugs (DMARDs) presents important challenges. A large body of literature addresses the economic burden of RA, and impact of biologic agents on health care budgets. Given their higher costs but more favourable outcomes in appropriate patients, the value of biologic agents has been addressed in a number of cost effectiveness studies. In this paper, we undertook a review of the literature to identify the pharmacoeconomic instruments that have been used in RA.

Cost related to illness
Generally, the costs related to illness may be classified in 3 categories: 1) direct costs include the costs directly attributed to health care, including the acquisition costs of the medication fees, as well as inpatient and outpatient clinic costs related to treatment 2) indirect costs reflect productivity costs, usually monetarily measured as regards paid work outside the home by either the human capital approach and

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friction cost approach, and 3) intangible costs related to the costs of suffering like pain and disability (2).

In a paper that systematically reviewed 26 cost-of-illness or cost effectiveness studies, overall mean total cost of RA was approximate €14,906 per year and indirect productivity costs constituted the largest part of the total cost (3). Another analysis showed that the total costs of RA to society in 2006 were estimated at €45.3 billion in Europe and €41.6 billion in the US (4). The mean annual cost per patient was estimated at around €13,500 in Europe. The mean annual cost per RA patient in the United States has been suggested to be higher (€21,000) than that of the Europe (4). Using the claim data of 2005, the societal cost of RA in the US was $19.3 billion and $39.2 billion without and with intangible costs, respectively. Direct societal cost was estimated at $8.4 billion (44%) and indirect cost was $10.9 billion (56%) (5).

The introduction of biologic agents resulted in substantial changes in the cost of RA, mostly regarding direct costs (2), as reported in several studies (6, 7). One study was conducted before the introduction of biologic agents, but in another study 27% of patients were treated biologic agents. The annual direct cost in the former study were on average €4,003 per patient year and the proportion of that related to medication costs was 13% of total direct cost (6, 7). In the latter study, the annual direct costs per patient were €11,757; medication costs of €4,406, represented approximately 37% of total direct costs (6, 7).

Indirect productivity costs

Indirect costs relate mostly productivity loss and constitute a substantial part of the total cost of RA. Productivity costs refer to the value of the time lost from productive work at paid employment or at home, related to the impact of the disease. It can be subdivided into discrete measures such as (1) absenteeism: absent workdays due to health reason (2) presenteeism : reduced or impaired performance at work due to health reason (3) inability to participate in leisure activity (4) loss of productivity in unpaid work activity such as household work, shopping and childcare and (5) loss of time and wages by spouse and caregiver (8).

Many studies have focused on work disability related job loss and absenteeism rather than the other components like presenteeism and occupational change because of the greater difficulty quantifying the latter (8). In a systematic review of arthritis studies on work productivity, 36%~ 84% of employed RA patients missed work or took short term disability within the previous year. The median duration of work loss was 39 days (1). A longitudinal study showed that work disability rate increased over time in RA patients (9). Of note, the introduction of biologic agents coincided with a decrease in disability pension in Sweden related to RA over the past twenty years. These trends also may reflect earlier, more aggressive treatment with conventional use of DMARDs and escalation of treatment of DMARDs in various combination (10).

Presenteeism is less frequently measured in the studies; although the number of studies on absenteeism outweighed that of presenteeism, reduced performance during working rather than the absenteeism might be the more important cause of productivity losses and indirect costs (11, 12). In one study of the indirect cost of patient with arthritis, presenteeism accounted for 41% loss of productivity compared to 12% due to absenteeism (11).

Depending on the health status, workers could move between absenteeism and presenteeism. In order to provide a complete view of the impact of arthritis on work, both absenteeism and presenteeism should be measured concurrently. Since both of these components are part of a continuum, Outcome Measures in Rheumatology (OMERACT) has called for a single unifying outcome that would combine assessments of absenteeism and presenteeism (13).

A recent paper systematically reviewed effects of biological agents on participation in paid work among patients with RA (14). Nineteen studies, including randomised controlled trials, as well as controlled and uncontrolled cohort studies, in which patients were treated with biologic agents were included, having met the quality standard used by the authors. Employment status improved in four out of the 14 studies in which it was measured. Absenteeism was the outcome that most frequently showed a favourable effect. Among ten studies quantifying effects of biological agent on absenteeism, all showed the reduction in absence from the work. Presenteeism was improved in seven out of nine studies in which it was measured. Beneficial effects of biological agents on both absenteeism and presenteeism may offer an opportunity to offset the higher acquisition costs by accruing savings in indirect costs (14).

Such achievement of very low levels of disease activity may be required to demonstrate this, particularly in the shorter term. In a study assessing the combination of methotrexate and etanercept in patients with early RA, achievement of clinical remission or major improvement might be necessary to significantly impact work outcomes (15). In a 5-year prospective study of patients with early and clinical active RA, remission during first year was good indicator of maintenance of work capacity. None of the 44 patients in remission at either 6 months or 12 months experienced RA permanent disability work (16).

The results of studies evaluating the impact of biologic agents on employment included important differences that can affect their results, including differences in the study population (e.g. early vs. established), study duration, and importantly, differences in the measurement tool used (17). Various instruments differ as regards perspective, recall period, attribution, and confounding. Although the instruments have been shown to be valid and reliable, the differences are seen when various instruments are applied in clinical research; further work may provide consensus in the future.

Quantification of productivity loss

Many instruments have been developed to measure productivity. Table I shows various tools that measure presenteeism and/or absenteeism (18). The instruments are different in concept and some measure different domains. Some instruments directly calculate time loss (e.g. Health and Labor Questionnaire...
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(HLQ); others estimate the percent of time loss (e.g. Quantity and Quality (QQ) questionnaire, Work Productivity and Activity Impairment Questionnaire (WPAI), Osterhaus method). Some are multidimensional questionnaires (e.g. the Work Limitations Questionnaire (WLQ)). To date there is no single instrument that is clearly superior in measuring the entire spectrum of productive loss; Thus further assessment, more experience and careful interpretation will be needed (18).

When various tools applied to same patient with RA, the correlation between the instruments has not been consistent. Some tools like QQ questionnaire and Work Productivity and Activity Impairment Questionnaire General Health (WPAI-GH) modestly correlated with each other, the HLQ correlated poorly with the other instruments (19).

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Table I. Instrument for measuring productivity loss.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Concept</th>
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<tbody>
<tr>
<td>EWPS (31)</td>
<td>Endicott Work Productivity scale</td>
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<tr>
<td>HLQ (32)</td>
<td>Health and Labor Questionnaire</td>
</tr>
<tr>
<td>HRPQ-D (33)</td>
<td>Health related Productivity Questionnaire Diary</td>
</tr>
<tr>
<td>HWQ (34)</td>
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<td>LFQ (35)</td>
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<td>OST (36)</td>
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<td>ORQ (37)</td>
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<td>QQ (38)</td>
<td>Quantity and Quality method</td>
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<tr>
<td>RA WIS (39)</td>
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<tr>
<td>RA-WPS (40)</td>
<td>RA specific Work Productivity Survey</td>
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<td>SPS 13(41)</td>
<td>Stanford Presenteeism Scale</td>
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<td>WALS (42)</td>
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<td>WHI (43)</td>
<td>Work and Health Interview</td>
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<td>WHO-HPQ (44)</td>
<td>Health and Work Performance Questionnaire</td>
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<tr>
<td>WIS (39)</td>
<td>Work Instability Scale</td>
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<tr>
<td>WLQ 25 (45)</td>
<td>Work Limitation questionnaire</td>
</tr>
<tr>
<td>WPAI-GH (46)</td>
<td>Work Productivity and Activity impairment-General Health</td>
</tr>
<tr>
<td>WPSI (47)</td>
<td>Work Productivity Short Inventory</td>
</tr>
<tr>
<td>WRF/WL26 (48)</td>
<td>Work Role functioning</td>
</tr>
</tbody>
</table>

A: absenteeism; P: presenteeism.

Beaton et al. tested 5 different tools like Workplace Activity Limitations Scale (WALS), 6-item Stanford Presenteeism Scale (SPS-6), Endicott Work Productivity Scale (EWPS), RA Work Instability Scale (WIS), and WLQ for the patients with RA and Osteoarthritis. Although this study showed WALS and RA WIS as superior instruments for measuring at-work productivity loss in workers with arthritis, it is not apparent that one specific tools is clearly superior to others (20). Because different instruments using different scales were applied to across many studies, it is difficult to compare and interpret productive loss precisely between the different studies.

The OMERACT group identified measurements that were designed to assess and combine absenteeism and presenteeism; HLQ, WHO Health and Work Performance Questionnaire (WHO-HPQ), Health related Productivity Questionnaire Diary (HRPQ-D), Osterhaus method, SPS 13, Work and Health review (WHI), WPAI-GH, Work Productivity Short Inventory (WPSI) and RA specific Work Productivity Survey (RA-WPS) (21). Among various tools described in Table I, six measurements met the OMERACT filter based on evidence: these include WALS, WIS, WLQ-25, WPAI, RA-WPS and Health Productivity Questionnaire (HPQ) (21).

The value of productivity

There are two main monetary valuation methods for productivity loss among the employed (22, 23). The human capital method takes the patient’s perspective. It counts any hour not worked as an hour lost and calculates produc-
Cost effectiveness studies

Since a substantial burden of biologics could be the financial burden of RA care, cost effectiveness studies of biologics agent versus traditional DMARDs have been performed. The patients’ health benefits are qualified using quality adjusted life years (QALY). USA dollars $50,000–$100,000 per QALY has been regarded the threshold in the medical literature to decide whether or not an intervention may be cost effective. It has been suggested that costs are definitely acceptable below $20,000 per QALY, are acceptable up to $50,000 per QALY, and are possibly acceptable up to $100,000 per QALY (25, 26). The incremental cost effectiveness ratio (iCER) weighs the difference in costs between the new drugs versus traditional drugs, against the difference in effects (2). The effects in treatment can be quantified with QALYs, based on the ability of a therapy to improve patients’ quality of life. When two treatment options are compared, one is preferred, or ‘dominates’ in pharmacoeconomic parlance, if it has lower costs per QALY than another option. The decision models employed to estimate the costs and benefits of one agent over other therapies have used modelling that has included simple decision tree, Markov models, and individual sampling models (27).

A systematic review derived from eighteen cost effectiveness studies showed that biologic agents were not cost effective compared to DMARDs at a cost effectiveness threshold of $50,000 per QALY (28). In patients who had failed methotrexate monotherapy, biologic combination therapy was cost effective at a willingness to pay threshold $100,000 per QALY for the payer and societal perspective (28). In a model to estimate cost-effectiveness for US Medicare patients with of RA, use of etanercept or adalimumab in place of infliximab as first-line biologic agent was considered cost effective (29).

In Behandel-Strategieen treatment strategies’ (BeSt) trials for early RA, initial combination therapy with infliximab resulted in significantly better quality of life than other strategies (30). Using the friction cost method, costs of initial combination therapy with infliximab were generally considered too high, and initial combination therapy with prednisone would be more cost effective. However, under the human capital method, the value of productivity after initial infliximab combination therapy resulted in only €22,000 per QALY which is an acceptable cost effectiveness ratio. In early RA, the productivity costs could compensate for the cost of biologic agent depending on the method used to calculate the productivity losses.

Conclusion

Recently, there has been a marked increase in studies attempting to estimate the economic burden of patients with RA, and the value of various treatment strategies. Although biologic agents had greater impact on improving the signs and symptoms as well as the progression of RA, their high acquisition costs have affected their use. Indirect costs, related to productivity loss, constitute a substantial part of total costs in the patient with RA. Various tools for measuring productivity loss have been introduced, but there is no single ‘best’ instrument. The validation of these tools and the consistency between tools needs to be further evaluated. Results of the cost effectiveness studies with the biologic agent have been somewhat contradictory, but as has been shown in systematic reviews, the use of biologic agent appears to be pharmacoeconomically favourable in certain patients.

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