Cost-effectiveness of Early Use of Etanercept in the Treatment of Rheumatoid Arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic illness of unknown etiology characterized by symmetric, erosive joint inflammation throughout the body\(^1\). Treatment involves nonsteroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs)\(^2\). The extent of joint erosion in early disease has resulted in the early initiation of DMARDs being a mainstay of the management of patients with RA\(^3-5\) with methotrexate (MTX) being the gold standard. However, remission is uncommon with these treatments and the long-term outcomes can be poor, with many patients switching medication due to lack of efficacy or adverse effects. Consequently, a sequential treatment strategy involving DMARDs that varies with disease progression is a common intervention.

Recently, the introduction of new DMARDs such as leflunomide (LEF) and tumor necrosis factor (TNF) antagonists (infliximab, etanercept [ETN], and adalimumab) has transformed the management of RA\(^6-9\). In particular, TNF antagonists have emerged as important therapies for RA because of their ability to reduce the signs and symptoms of disease, slow the rate of radiographic progression, and improve functional capacity. ETN was approved for use in Korea in 2003. The potential greater efficacy of ETN is associated with a much higher drug cost, making this a natural candidate for cost-effectiveness analysis, and several studies have provided evidence of its cost-effectiveness in patients with active RA who were resistant to traditional DMARDs therapy\(^10,11\).

Whilst clinical guidelines currently recommend the use of ETN as a step therapy after a nonresponse to traditional DMARDs\(^2\), in early and established RA the combined use of ETN and MTX (the most widely used DMARD) is known to be more effective than monotherapy with either MTX or ETN alone\(^9,12\). Moreover, there have been several reports that the induction of remission with early use of ETN+MTX regimen significantly improves functional status and quality of life (QoL)\(^13-15\). These observations implicate for the optimal use of expensive biologic therapy, and hence another economic analysis is required for the new treatment strategy.

Therefore, in this study we compared the long-term cost-effectiveness of a sequential treatment strategy involving the early use of ETN with that for the conventional late use of ETN in Korean RA patients.

MATERIALS AND METHODS

1. Model Framework

The model compared two hypothetical treatment sequences based on the societal perspective. The first sequence was the
conventional late use of ETN, in which the patients who failed MTX were treated with LEF+MTX followed by ETN+MTX for unresponsive cases, with the treatment finishing with MTX as a maintenance therapy. The second sequence was of early use, in which patients started directly on combination therapy of ETN and MTX. Discussion with clinical experts in Korea confirmed that these sequences were reasonable.

The decision tree of the clinical pathways for RA treatment is shown in Figure 1. Decision analysis and Markov cohort simulation were used based on a previously published model\textsuperscript{[10,16]}. Outcomes were quantified as the quality-adjusted life years (QALYs). The model focused on the progression of the Health Assessment Questionnaire (HAQ) disability score, which ranges from 0 (best function) to 3 (worse function). The 6-monthly trends in HAQ score over time were simulated for 1000 patients using Microsoft Excel, and the regression of HAQ/EuroQol (EQ-5D) utility yielded the gain in QALYs.

The model cycle was 6 months. After the first 6-month cycle, a patient could be either an initial responder and remain on treatment, or a nonresponder and be switched to the next treatment in the sequence. The mean HAQ improvement for responders was quantified using published data\textsuperscript{[10,17]}. Initial responders remained on treatment for multiple
Table 1. Parameter values used in model estimation

<table>
<thead>
<tr>
<th>Variable</th>
<th>ETN+MTX Early use [Ref.]</th>
<th>ETN+MTX Late use [Ref.]</th>
<th>MTX Early use [Ref.]</th>
<th>MTX Late use [Ref.]</th>
<th>LEF+MTX [Ref.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>◆ Effectiveness variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response (ACR20) at 6 months (%)</td>
<td>82</td>
<td>71</td>
<td>64</td>
<td>24</td>
<td>46</td>
</tr>
<tr>
<td>Withdrawals at each 6-month period (%)</td>
<td>6.5</td>
<td>3.4</td>
<td>10.4</td>
<td>14.7</td>
<td>19.2</td>
</tr>
<tr>
<td>Initial HAQ improvement from baseline</td>
<td>-1.0</td>
<td>-0.7</td>
<td>-0.45</td>
<td>-0.22</td>
<td>-0.4</td>
</tr>
<tr>
<td>HAQ improvement of ACR20 responders at 6 months</td>
<td>-1.11</td>
<td>-0.83</td>
<td>-0.58</td>
<td>-0.38</td>
<td>-0.57</td>
</tr>
<tr>
<td>6-monthly HAQ progression of ACR20 responders</td>
<td>0.0051</td>
<td>0.0051</td>
<td>0.017</td>
<td>0.017</td>
<td>0.017</td>
</tr>
<tr>
<td>6-monthly HAQ progression of ACR20 nonresponders</td>
<td>0.0055</td>
<td>0.0055</td>
<td>0.005</td>
<td>0.005</td>
<td>0.0055</td>
</tr>
<tr>
<td>◆ Cost variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug costs at each 6-month period (thousand won)</td>
<td>7,467</td>
<td>7,467</td>
<td>1,020</td>
<td>1,020</td>
<td>1,504</td>
</tr>
<tr>
<td>Monitoring costs at 6(thousand won)</td>
<td>191</td>
<td>191</td>
<td>190</td>
<td>190</td>
<td>225</td>
</tr>
<tr>
<td>6-monthly monitoring costs from second period (thousand won)</td>
<td>87</td>
<td>87</td>
<td>87</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Prescription and injection costs at each 6-month period (thousand won)</td>
<td>46</td>
<td>46</td>
<td>45</td>
<td>45</td>
<td>45</td>
</tr>
</tbody>
</table>

HAQ, Health Assessment Questionnaire; ACR20, American College of Rheumatology-20.

6-month cycles until subsequent long-term withdrawal owing to lack of efficacy or an adverse event. At the point of long-term withdrawal, the patient was assumed to exhibit a worsening HAQ score and was switched to the next treatment in the sequence. The modeling time horizon for the base case was 5 years, and the death of patient was considered to be the termination of treatment.

The population in this model was assumed to comprise adult patients who had active RA, a mean age of 50 years, and a baseline HAQ score of 1.7 based on a published ETN trial18. As disease duration significantly affects the response to treatment, the patient characteristics from similar studies were compared. A systematic MEDLINE literature search from 1996 to 2005 identified English-language articles concerning the drugs used in the two sequences. The parameter values for the modeling were extracted, and a meta-analysis was performed.
2. Modeling the Long-term Response to Treatment

Since switching to the next treatment was triggered by a lack of response or withdrawal, American College of Rheumatology-20 (ACR20) data and the withdrawal rates that were extracted from the finally selected clinical literature were used as transition probabilities.

Table 1 lists the initial improvements in HAQ scores for the ACR20 responders. In cases where only the mean HAQ changes for both ACR20 responders and nonresponders were published, the HAQ score for ACR20 responders were estimated based on the formula of Brennan et al.

Subsequent long-term withdrawal occurred due to failure of treatment effect or adverse events. In cases where the ongoing drug therapy was withdrawn, it was assumed that the HAQ score increased again to the level of the first HAQ improvement after the administration of the corresponding drug.

Since one of the clinical pathways was death, the probability of death was included. Considering that the mortality risk is higher for patients diagnosed with RA than for a normal population, a relative risk (RR) for mortality of 1.32 was applied and adjusted to the mortality of a normal population cohort obtained from the data of the Korea National Statistical Office.

The model assumed a slight long-term progression of disability over time even when patients were responding to treatment based on Brennan et al. Regarding the HAQ progression level of ACR20 responders per cycle, the estimated value of 0.0051 was used for ETN+MTX, whereas 0.017 was used for MTX and MTX+LEF treatments as the long-term response to therapy. For the ACR20 nonresponders, the 6-month HAQ progression level of all drug therapy groups was estimated to be 0.005.

Regarding the calculation of QALY from HAQ, we assumed that HAQ was linearly related to EuroQol (EQ-5D) in accordance with previous studies. In our study, the HAQ score was converted into QALYs based on the formula of Brennan et al.: utility change = 0.86 - 0.20(HAQ score change).

3. Costs of Treatment Strategies

The cost of RA treatment included drug and monitoring costs, and was calculated by multiplying the health insurance payment with the frequency of drug administration and the frequency of monitoring (Table 1). The frequencies of drug administration and monitoring were calculated based on existing clinical practices in Korea as obtained by consulting rheumatologists and from the ACR guideline.

Data on direct costs such as drug purchases and injection and dispensing fees were obtained from the pharmaceutical
Table 2. Indirect costs for 6 months by HAQ score (unit: thousand won)

<table>
<thead>
<tr>
<th>State</th>
<th>HAQ score</th>
<th>Work capacity</th>
<th>Indirect costs by age groups (years)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 - 54</td>
</tr>
<tr>
<td>1</td>
<td>&lt;0.5</td>
<td>0.5000 [23]</td>
<td>8,214</td>
</tr>
<tr>
<td>2</td>
<td>0.5&lt;1.1</td>
<td>0.3770 [23]</td>
<td>10,235</td>
</tr>
<tr>
<td>3</td>
<td>1.1&lt;1.6</td>
<td>0.2345 [23]</td>
<td>12,576</td>
</tr>
<tr>
<td>4</td>
<td>1.6&lt;2.1</td>
<td>0.0547 [23]</td>
<td>15,530</td>
</tr>
<tr>
<td>5</td>
<td>2.1&lt;2.6</td>
<td>0.0476 [23]</td>
<td>15,646</td>
</tr>
<tr>
<td>6</td>
<td>&gt;2.6</td>
<td>0.0000 [23]</td>
<td>16,428</td>
</tr>
</tbody>
</table>


benefits pricing file, health insurance fees of the Health Insurance Review Agency, and the National Health Insurance Statistics Yearbook. Monitoring costs included physician visits and test costs. During the initial 6 after drug administration, monitoring was performed at 0, 2, 8, 16, and 24 weeks. However, from the second cycle the monitoring interval was every 2.

For the purpose of sensitivity analysis the costs of lost productivity were also calculated based on the severity of RA disease, which was categorized into six stages according to the HAQ score. The costs of lost productivity were estimated based on work capacity. We applied the research results of Kobelt et al. [23], who calculated work capacity according to the HAQ score: scores of 1.0, 0.5, and 0.0 were assigned to full-time employment, part-time employment, and unemployment, respectively.

The monthly labor costs and the annual special payments from the 2008 Statistics Survey Report on Wage Structure [24] were used as the data source for the monthly average incomes of laborers. The costs of lost productivity were calculated by multiplying the 6-monthly income by work capacity (Table 2). Also, it was considered that participation in financial activity occurred up to an age of 65 years on average, with retirement thereafter. Thus, the indirect costs were included only up to the age of 65.

4. Analyses

Both strategies were simulated for 1000 patients using Excel. Estimated population mean costs and QALYs were calculated, and the incremental cost-effectiveness ratio (ICER) was determined from the mean differences in costs and QALYs. According to Korean guidelines for pharmacoeconomic evaluation [25], this article took societal
The sensitivity analysis was performed to major parameters to consider the inherent uncertainty of the economic evaluation model of RA treatment. The following five key parameters were analyzed: (i) the effect of alternative scenarios on HAQ/QALY conversion based on the literature, (ii) mortality estimation, (iii) discount rate (3% and 7.5%), (iv) indirect costs, and (v) model time horizon (10, 15, and 30 years). Regarding indirect costs, as it is no clear if the indirect preference-based measures adequately capture utility losses due to decreased levels of income and productivity, indirect costs need be reported separately.

RESULTS

1. Base case analysis

The direct costs were estimated to be 26,879 thousand won higher in the second sequence (early use of ETN) than in the first sequence (late use of ETN). The second sequence was also estimated as providing an extra 0.34 QALYs over a 5-year time horizon. The incremental cost per QALY gained for the second sequence was 78,101 thousand won (Table 3).

2. Sensitivity analyse

Table 4 indicates that for the majority of parameters varied, the cost per QALY gained was above 20,000 thousand won, which is the implicit threshold for reimbursement in Korea. The sensitivity analysis of the coefficient representing the linear relationship between HAQ and QALY revealed that ICERs ranged from 47,768 thousand won per QALY to 92,977 thousand won per QALY gained.

Estimating the mortality of RA patients in Korea is difficult due to a lack of data. We therefore also used the estimates of mortality of the normal population (i.e., without allowing for the RR for RA patients) in the literature, which only changed the ICER by 82 thousand won per QALY, from 78,101 thousand won per QALY to 78,019 thousand won.
Korean pharmacoeconomic guidelines suggest that sensitivity analyses should be conducted for discount rates of 3% and 7.5%. Changing the discount rates had little impact on the ICER: it was 76,232 thousand won per QALY and 80,412 thousand won per QALY for discount rates of 3% and 7.5%, respectively.

The estimated cost per QALY gained can be improved by including the indirect costs of lost productivity and extending the model time horizon. The inclusion of indirect costs decreased the ICER from 78,101 thousand won per QALY to 36,508 thousand won per QALY. Also extending the time horizon from 5 years to 10, 15, and 30 years resulted in estimated costs per QALY gained of 30,012 thousand won, 6,620 thousand won, and -10,054 thousand won, respectively.

**DISCUSSION**

The aim of this study was to elucidate the cost-effectiveness of a sequential treatment strategy with early use of ETN comparing with the conventional late use of ETN in RA patients in Korea. Our study shows that the ICER for the strategy involving the early use of ETN with MTX relative to the strategy involving the late use of ETN was 78,101 thousand won per QALY gained. Willingness-to-pay (WTP) can be changed with the differences on the economic level of the nation, disease severity, burden of disease,
and budget impact of the alternatives. Although no definitive willingness-to-pay threshold has been established in Korea, it undoubtedly exceeds those in the UK (£20,000–£40,000/QALY)\(^{27}\) and US ($50,000/QALY)\(^{28}\). This implies that adopting a sequential treatment strategy with the early use of ETN in RA may not be a cost-effective alternative to the conventional treatment strategy in Korea. However, our ICER reduced from 78,101 thousand won to 30,012 thousand won and 6,620 thousand won per QALY gained when the treatment period was extended from 5 years to 10 and 15 years, respectively. Moreover, on a lifetime analysis, the early use of ETN was dominant compared with the late use of ETN, and hence the former strategy can be more cost-effective in the long term. In the US, 6-month to 3-year analyses seem to be preferred by managed care and health maintenance organizations while National Institute for Clinical Excellence (NICE), in the UK, assessment of TNF antagonists, a lifetime approach was requested. Although we understand that the benefits of modifying the course of the disease by early aggressive treatment will be evident only in the long term, we used a time horizon of 5 years in base case analysis because extrapolating to 5 years based on clinical trials may be too uncertain to be clinically acceptable.

Treating RA involves not one therapeutic agent but rather a sequence of therapies that are applied over a long time period. Thus, modeling therapeutic sequences is of particular importance to long-term economic evaluations of DMARDS\(^{29}\). We chose the therapeutic sequence strategies based on the expert opinions of rheumatologists, because there has been no nationwide survey of RA treatment in Korea. In Korea, ETN is reimbursed by national health insurance when it is prescribed to patients with moderate to severe RA who have failed to respond to at least two DMARDs for 6 (longer than 3 each), one of which is MTX. Accordingly, doctors have been persuaded to implement step-up therapy from MTX to ETN+MTX in the clinical setting. On the other hand, many recent reports have suggested the advantage of starting ETN early in RA\(^{13–15}\). Thus, our treatment sequences were modeled to examine the cost-effectiveness of a new potential sequential treatment strategy compared to the strategy currently employed in most clinical settings.

The choice of sequence used in this study was also constrained by technical considerations imposed by the Markov modeling assumptions, and the limited availability of information in the literature. For example, the combination of MTX and hydroxychloroquine (HCQ) is more frequently used than MTX monotherapy as either a first line or maintenance therapy, but the combination therapy could not be modeled because there is no report on ACR20 response rates for this
이의경 외: 류마티스관절염 치료에 있어 Etanercept의 조기사용전략에 대한 비용효과분석

There has been a randomized controlled trial of a combination therapy with MTX, sulfasalazine, and HCQ for MTX-naïve patients, but we could not include this triple therapy in the sequence of step therapies for MTX-resistant patients.

Our analysis is likely to be conservative because we did not consider the savings in indirect costs from the early use of ETN in the base case analysis. The indirect costs from disability associated with RA are substantial, including an increasing unemployment rate with increasing disease duration, and decreased productivity. In our sensitivity analysis that included the indirect costs, the ICER unsurprisingly reduced from 78,101 thousand won to 36,568 thousand won per QALY gained.

This study was subject to several limitations. Its main limitations relate to data availability. The relative efficacy estimates were generated from separate controlled trials, which may not have been directly comparable. That is, most of the parameters in our model, such as the ACR20 achievement rate, the background HAQ score change, improvements in HAQ scores with therapy, and the equation used to calculate the utility from the HAQ score change were derived from clinical trials and economic studies conducted in Western countries.

Our analytic model was based on the Trial of Etanercept and Methotrexate with Radiographic and Patients Outcomes because only one open-label study for ETN and few well-designed cohort studies for RA patients have been reported in Korea.

Secondly, we were unable to include any costs for adverse drug reactions in the analyses. Often it is unclear whether events are directly related to the treatment, and frequently no data are available on the clinical management of such events. This issue is particularly difficult for small samples of patients with severe and sometimes long-standing disease, and the results of the analysis could be heavily influenced by comorbidity in the sample. Tuberculosis has been observed in patients receiving TNF-blocking agents. In this regard physicians should monitor patients receiving etanercept for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection. Patients who develop an infection should be evaluated for appropriate antimicrobial treatment. Both the monitoring and treatment cost need to be added as the cost for adverse drug reaction. However, in this study, we assumed that the frequency of severe adverse events did not differ between the sequential treatment strategies, due to all the treatment options in our sequences including both MTX and etanercept.

Thirdly, many clinical trials have shown that the progression of radiographic scores varies with the regimen. However, radiographic score change was not incorporated as...
a separate measure into our model owing to a lack of adequate data sets. We therefore conservatively assumed that the effect is included in the HAQ scores while patients are receiving treatment. Background HAQ scores and their percentage reductions were taken from Brennan et al.\textsuperscript{10}, and they may not accurately represent how the treatment effects of these drugs progress, especially in Koreans. Moreover, we used data sets of established RA in this analysis, and future studies should be performed based on the data of aggressive treatment with biological agents in early-RA patients. The clinical benefits of lower physical impairment will increase when any future benefit from radiographic stabilization of structural joint damage due to ETN and MTX is included, especially in early-RA patients. Thus, this is likely to increase the actual cost-effectiveness of a new strategy.

CONCLUSIONS

Our study suggests that the strategy of using combined ETN and MTX as an early treatment in RA should not be considered a cost-effective alternative to the conventional late use of ETN over a time horizon of 5 years. However, scenario analyses showed that the inclusion of indirect costs and long-term use might improve the cost-effectiveness outcomes for the early use of ETN.

ABSTRACT

Objective: To compare the long-term cost-effectiveness of a sequential treatment strategy involving the early use of etanercept (ETN) with that for the conventional late use of ETN in Korean RA patients.

Methods: A cost-effectiveness analysis was performed to compare two treatment sequences using etanercept with methotrexate: early versus late start to the rheumatoid arthritis (RA) patients in Korea. Decision analysis and Markov cohort simulation were used to extrapolate short-term clinical trial results to a long-term time horizon. The outcome was quantified as the quality-adjusted life years (QALYs). The 6-monthly trends in Health Assessment Questionnaire disability scores were simulated for 1,000 patients for 5 and converted into QALYs. Direct medical costs including drugs and monitoring were estimated based on the Korean National Health Insurance reimbursement schedule.

Results: The incremental cost-effectiveness ratio for the early versus late use strategy was 78,101 thousand won per QALY gained, but this reduced to 30,012 thousand won, 6,620 thousand won, and -10,054 per QALY gained when the treatment period was changed to 10, 15, and 30 years, respectively.

Conclusions: These results show that a sequential treatment strategy with early use of ETN in RA may not represent a
cost–effective alternative to the conventional late use of ETN over a 5-year time horizon. However, scenario analyses showed that both the inclusion of indirect costs and long-term use might further improve the cost–effectiveness outcomes for the early use of ETN.

Key words: cost–benefit analysis, arthritis, rheumatoid, quality–adjusted life years.

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