Executive Summary

Comparative effectiveness of medication therapies in the rheumatoid arthritis patients

Hyun Ah Kim[1,2], Min Kyung Hyun[1], Miyoug Choi[1], Seongmi Choi[1], Ha jin Tchoe[1], Young Ok Jung[1,2], Kyeong Min Son[1,2], Sung Yeon Lee[1,2]

[1] National Evidence-based Healthcare Collaborating Agency

[2] Division of Rheumatology, Department of Internal Medicine, Hallym University College of Medicine

☐ Introduction

: Traditionally Disease modifying anti-rheumatic drugs (DMARDs) including non-steroidal anti-inflammatory drugs (NSAIDs), steroids and immunosuppressants have been used for rheumatoid arthritis. Recently, biological agents with a mechanism of action targeting the pathogenesis of rheumatoid arthritis have emerged as an important treatment. Especially, as anti-TNF (anti-tumor necrosis factor antagonist) drugs is effective for patients who do not respond to the existing drugs. Recent studies focus on this class of drugs. Therefore, there is a need for further study to generate data to compare the efficacy of biological agents with that of the traditional DMARDs.

The objective of this study was to identify the treatment patterns of rheumatoid arthritis and to compare the effectiveness of biological agents and disease modifying anti-rheumatic drugs (DMARDs). First, the study aimed to find out the grounds for drug treatment regimens containing DMRADs and anti-TNF through a systematic review of existing scientific literatures. Second, this study attempted to identify differences in efficacy between DMARDSs and anti-TNF by conducting a comparative effectiveness research (CER). And finally, this study aimed to analyze the current status of DMARDs and biological agents prescribed for patients with early rheumatoid arthritis by analyzing the claims data submitted to the National Health Insurance.

☐ Study Method

First, the comparative effectiveness review (CER) was conducted by using an analytic framework suggested by AHRQ (White et al., 2009, USA) for the systemic review. Subsequently, an updated systematic review was carried out on the recent randomized comparative clinical trials including the selected existing literatures. In the systemic review of existing scientific literature, the research questions were presented in a PICOTS-SD format via consultation with experts. In terms of the scope of drugs, this study focused on 4 DMARDs and 5 anti-TNF drugs. The literature selection and qualitative evaluation of selected papers to data extraction was conducted by more than two researchers, who independently performed the assessment and made decisions through a consensus.

In data analysis, this study synthesized data extracted from the selected research papers. The data were divided for qualitative analysis and quantitative synthesis, and as these were about comparative clinical trials with random assignment, the study was also possible to conduct a quantitative synthesis. However, the Mixed Treatment Comparison (MTC) was carried out by designing the control group as placebo and methotrexate (hereinafter 'MTX') used together due to lack of clinical trial researches for direct comparison.

To analyze the patterns of rheumatoid arthritis drug treatment regimens, the study reviewed the claims application data submitted to the National Health Insurance for the past 9 years from January 1, 2004 to December 31, 2012. To identify new rheumatoid arthritis patients who were first prescribed to RA drugs, the study checked the claims data from January 1, 2006 to December 31, 2010.

The exclusion criteria was those who had had medical history of RA within the past two years before the date of the first MTX prescription (index date), who were less than 20 or more than 100 years of age and those with no age specified. All statistical analysis was conducted using the SAS program version 9.2, and the statistical significance was set at 5%.

☐ Study Results

Ⅰ. Review of Existing Literature

The search was conducted with three databases; Ovid-MEDLINE, Ovid-EMBASE and The Cochrane Library to search for relevant studies. As a result, a total of 693 studies were found, and two studies were added from manual selection. After excluding overlapping literature, the study eliminated a total of 426 studies by reviewing the title and abstracts. After the study secured copies of the remaining 112 eligible studies and assessed them in a second review, a total of 52 studies were finally selected for the systematic review of research literatures. In addition, 4 papers were additionally evaluated for the systematic review of economic feasibility. The Assessment of Multiple Systematic Reviews (AMSTAR) was used as a qualitative assessment tool and was evaluated independently by each of the five reviewers, who made their decisions through consensus if there was a disagreement in their opinions.

For patients with early rheumatoid arthritis, MTX-refractory patients and DMARDs-refractory patients were predominant among patients of the existing researches. The indirect comparison method was used to carry out a comparative effectiveness research between anti-TNF agents, and most of the existing research papers concluded that there were no significant differences between them. However, some mixed treatment comparisons reported that there were some anti-TNF agents which showed significant clinical responses in patients who were refractory to the existing DMARDs. For the comparison between anti-TNF agents and DMARDs, the study carried out the comparative effectiveness assessment between the DMARDs monotherapy and the DMARDs combination therapy and between the anti-TNF agent combination and the DMARDS combination therapy. Although the effectiveness of combination regimens was enhanced compared to monotherapies, it was reported that they could also slightly increase toxicity. The lack of consistency in the results made it impossible to verify comparative advantages of the anti-TNR or DMARDs combination therapies.

According to the results of the systematic review of the four existing research literatures on economic feasibility, it was known that all of them dealt with the cost-effect aspects of all biological agents. Although they provided useful information on some drug agents, it was concluded that it was almost impossible to build a model for a treatment strategy, due to wide differences in the selection methods of study subjects, analysis perspectives and selection of alternatives for comparison as well as a wide deviation of the results of the cost-effectiveness comparison. Therefore, the study planned a systemic literature review system which reflected the results of the mixed treatment comparison between DMARDs and anti-TNF

agents, and carried out a new systematic research review method utilizing the current one.

||. Comparative Effectiveness Research between Anti-rheumatoid Agents (Using SR and MTC)

By using the final search equation for the systematic literature review, this study carried out the isearch in order to select the relevant studies which met the criteria and were published since 2008, which was one year before the previous search had been conducted. In case of domestic DBs, the search was done without any limitations to the year of publication. As a result, 84 research studies were finally selected, all of which were research papers on comparative clinical trials with random assignment. If we classify the finally selected existing papers depending on types of patients, 23 of them were on early RA patients, 26 were on active RA patients and 19 were on MTX-refractory patients.

The Cochrane 'Risk of bias' assessment tool was used to evaluate the quality of the selected studies. The results of the qualitative evaluation were displayed in a diagram with graphs using the RevMan 5.2 program. There were some studies which belonged to a large-scale clinical trial, which was assessed in accordance with the protocol based on the principle that the quality assessment should be individually done on each literature.

The results graphs of qualitative evaluation were created based on the patient group. Generally, in if the phrase "random assignment" was not present in the studies, and those where the specific methods of random number generation and assignment number concealing items was not stated in the paper or the protocol, were considered as 'uncertain.' There were many cases that the study was perceived as 'uncertain' in both items. However, there were a number of cases where the risk of bias assessment scores on inadequate result data or selective reports were evaluated as 'low.'

The patients were divided into the early rheumatoid arthritis patient group, MTX-refractory rheumatoid arthritis patient group, DMARDs-refractory rheumatoid arthritis patient group and active rheumatoid arthritis patient group. The mixed treatment comparison was done with a total of 6 outcome variables; DAS28-ESR, HAQ, DAS28-ESR<2.6 (remission) ratio, ACR20 responder rate, ACR 50 responder rate and ACR 70 responder rate.

<Evaluation of Drug Therapies in Early Rheumatoid Arthritis Patients (Early RA)>

The etanercept+MTX combination was the most effective treatment in reducing HAQ scores and offered the greatest benefit in helping patients perform their everyday lives.

If compared based on the results of ACR 20, the etanercept+MTX combination presented the greatest treatment benefits compared to MTX among drug combinations, whereas the results of ACR 20 showed that the infliximab+MTX combination displayed the greatest treatment effect compared to MTX among drug combinations.

In case of early RA patients, the etanercept+MTX combination showed the best results in the five categories of the outcomes, followed by the infliximab+MTX and the adalimumab+MTX. As the infliximab+MTX combination showed statistically significant results, it was reasonable to think that it was ranked second.

The molecular mass of etanercept which serves as a receptor was recorded at only one third of those of infliximab and adalimumab, which are antibodies. It was presumed that those with a small molecular mass could show more prompt clinical responses in the body system.

However, in case of etanercept and adalimumab, early RA patients have to receive a subcutaneous injection two times a week, while in case of infliximab they receive an intravenous injection only once every 8 weeks.

<Active Rheumatoid Arthritis (Active RA)>

The etanercept+MTX combination was also the most effective biological combination in patients with active Rheumatoid Arthritis. In addition, the leflunomide+MTX combination showed the most clinical benefit among DMARDs combinations.

<Patients who failed treatment with MTX >

For the MTX failure patients who discontinued MTX because of insufficient clinical responses, the certolizumab+MTX combination was more effective in lowering HAQ scores than MTX, which helped patients to perform their daily tasks easier.

If compared to the results of DAS28-ESR<2.6 (remission), the golimumab+MTX combination had the greatest treatment effect compared to MTX among the series of drug combinations. The ACR 70 results showed that the certolizumab+MTX combination offered the most treatment benefit.

||| Drug Treatment Patterns in Early Rheumatoid Arthritis

According to the results of the analysis on claims data submitted to the National Health Insurance, the number of RA patients who were prescribed MTX from January 1, 2006 to December 31, 2010 was 29,988 patients (including a total of 3,438 new patients). The majority of the female patients and patients, who were between 50 and 59 years of age, were MTX. Dividing the results by medical institution type, the clinics were ranked top with 38.98%, followed by general hospitals (28.82%). The outpatients who were prescribed MTX were approximately nine times more than inpatients. The comorbidities developed one year prior to and after the first diagnosis, osteoporosis was predominant (19.17%), followed by hypertension (27.43%). Out of all types of drugs excluding MTX, hydroxychloroquine (60.56%) was the most widely prescribed drug, followed by sulfasalazine (27.43%). The number of patients who were prescribed MTX at the time of the first diagnosis added up to 878 patients (25.54%).

In terms of the second drug prescribed after MTX, the MTX+HCQ combination was the most common combination (44.9%), followed by the MTX+LFN combination (22.0%). For patients who started their treatment with the MTX+HCQ combination, 44.4% were prescribed MTX as their second treatment, while 29.5% were prescribed the MTX+HCQ+SSZ combination. For patients who started their treatment with the MTX+HCQ+SSZ combination, 33.6% switched to the MTX+HCQ combination. For patients who started their treatment with the MTX+SSZ combination, 34.4% switched to the MTX+HCQ+SSZ combination. In terms of the period of time required for those patients who were first prescribed to MTX monotherapies to switch to their second treatment drugs, the MTX+HCQ combination took 92.1 ± 105.5 days, while the MTX+LFN combination required 154.5 ± 153.6 day.

☐ Conclusion & Policy Suggestion

The objective of this study was to assess the current status and identify the most effective treatment sequence of therapies for patients with rheumatoid arthritis, by utilizing a new systematic review. That adopted the mixed treatment comparison and the existing systematic literature review method and by using secondary information sources including the analysis of claims application data submitted to the National Health Insurance. However, there were

limitations to the study due to a lack of existing research data.

It the degrees of joint damage was difficult to assess in a quantitative manner using the joint count method or the standardized Sharp score method, as it required a lot of time and effort (to measure 28-68 joints) and to reflect those results in the treatment scores. In addition, most of the drug comparative effectiveness researches are currently being done mainly on second-line agents including biological agents.

Therefore the publication of a prospective clinical research in the future to compare the effectiveness between Rheumatoid arthritis drugs (for example between DMARDS and biological agents) will enable to provide guidelines for the prescription of cost-effective drug regimens in Rheumatoid Arthritis.

Key words: Rheumatoid arthritis(RA), disease modifying anti-rheumatic drugs(DMARDs), TNF-α inhibitor(TNFi), comparative effectiveness research(CER), Mixed Treatment Comparison (MTC)