Executive Summary

1. Study objective

This study was aimed to promptly review the literature regarding clinical usefulness of anti-CCP antibody tests in patients with rheumatoid arthritis to provide the basis of decision makings in the relevant policies.

2. Methodology

In this study, data from the Fourth Korea National Health and Nutrition Examination Survey (KNHANES Ⅳ, 2007-2009) were analyzed to verify the prevalence of Korean patients with rheumatoid arthritis, and the previous basis was confirmed based on the review of overseas medical technology assessment reports and guidelines. Next, the existing systematic reviews were reviewed by using a frame suggested by the US AHRQ(Figure 1), additional basis was combined with the existing systematic reviews in Korean population, and eventually the latest basis was suggested.

□ Overview of systematic review analyses

Previously published systemic reviews were retrieved from Pubmed and Cochrane Library. After the procedures of inclusion/exclusion of studies, a total of 9 reviews were selected for which quality assessment was performed by using AMSTAR, a quality assessment tool preferred by the WHO, AHRQ, and COMPUS. Results of these systematic reviews were extracted and assorted by using the pre-defined standardized form.

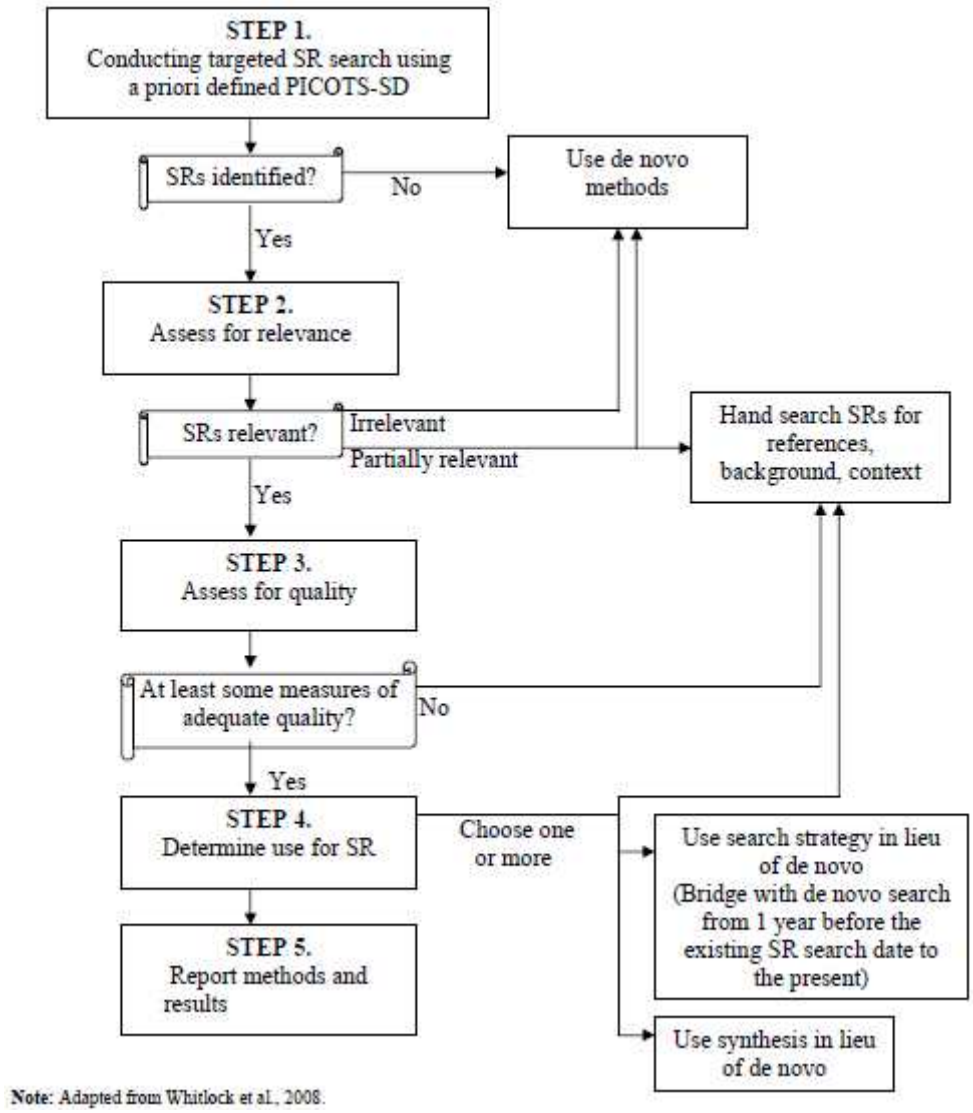

Figure 1. Systematic process for identifying, assessing, and using existing systematic reviews (AHRQ, 2009)

□ Systematic reviews in Korean population

To evaluate clinical effects regarding the diagnostic accuracy of anti-CCP antibody tests in Korean population, using existing systematic reviews were carried out by using the primary systematic review studies. In this study, the primary studies that have been published since 2006, one year before the search was initiated in the systematic review by Lee et al.(published in 2008), and that met the

inclusion/exclusion criteria of this study were retrieved from the MEDLINE, KoreaMed, and the Journal of the Korean Rheumatism Association. A total of 9 primary studies selected through the study inclusion/exclusion procedures were assessed for quality through QUADAS II, a quality assessment tool for diagnostic accuracy studies, results from each of the systematic reviews were extracted by using the pre-determined standardized form, and meta analysis was performed for diagnostic accuracy.

3. Study results

□ Status of patients with rheumatoid arthritis in Korea

To understand the status of patients with rheumatoid arthritis in Korea, data from the Fourth Korea National Health and Nutrition Examination Survey (KNHANES Ⅳ, 2007-2009) were analyzed. The results indicated that the prevalence of patients with rheumatoid arthritis in Korea was 2.2% based on lifetime prevalence (a proportion of patients who have had rheumatoid arthritis at any time to date) or 1.9% based on the physician's diagnosis (a proportion of patients who have been diagnosed with rheumatoid arthritis by a physician at any time in their life). In addition, mean quality of life (EQ-5D index) in patients with rheumatoid arthritis based on the physician's diagnosis was 0.803, lower than the mean quality of life index of 0.933 in general population, and also lower than that of patients with hypertension (0.865), diabetes mellitus (0.852), asthma (0.842), and angina pectoris(0.811).

□ HTA report and guidelines

A number of international clinical guidelines and international reports have been presented for diagnosis of rheumatoid arthritis. Although there may be some differences among countries and

institutions, these documents consistently support that it is necessary to perform anti-CCP antibody tests for diagnosis of rheumatoid arthritis.

Argentina's IECS (Augustovski F, 2007) notes that the anti-CCP antibody test can be used as a diagnostic criterion in people suspected to have rheumatoid arthritis although their rheumatoid factor is tested negative and that it is appropriate to use this test as a prognostic factor for the progress of rheumatoid arthritis. In France (HAS, 2007), anti-CCP antibody test is deemed appropriate for diagnosis and prognostic assessment of rheumatoid arthritis. It was suggested that the expenses of anti-CCP antibody tests should be reimbursed by the French NHI. In Brazil (da Mota, 2011), too, significance of the anti-CCP antibody test as a diagnostic marker was highly emphasized due to its high specificity as well as its sensitivity similar to that of rheumatoid factor. In addition, the AHRQ's CER report (Wong, 2012) mentioned that this test could possibly be used clinically to detect inflammatory arthritis in children complaining musculoskeletal pain or the presence of connective tissue diseases.

Although the recently announced 2010 ACR/EULAR classification criteria are yet to be verified, the most notable difference from the 1987 ACR classification criteria is addition of the anti-CCP antibody test to the classification criteria where it is noted that the anti-CCP antibody test will contribute to a higher diagnostic specificity in patients with early rheumatoid arthritis.

□ Overview of systematic review analyses

Results from the analysis of the existing 9 systematic reviews on anti-CCP antibody tests indicated that their search DB, duration of search, and study objectives varied and that there were also differences in terms of quality assessment for literature by AMSTAR. Nevertheless, there was no objection to the fact that sensitivity of

anti-CCP antibody is similar to or higher than that of the rheumatoid factor and anti-CCP antibody has a markedly high level of specificity in the diagnosis of rheumatoid arthritis. It was also confirmed that the second generation anti-CCP antibody has a higher sensitivity and specificity than the first generation. These reviews conclude that this test is relevant to early diagnosis of rheumatoid arthritis and can help predict the probability of further progress to rheumatoid arthritis.

Of particular note, the review by Whiting (2010) which received the highest scores in appropriateness and quality assessment combined 69 reports to compare rheumatoid factor and anti-CCP antibody. The results indicated that anti-CCP antibody had a 0.67 (95% confidence interval [CI] : 0.64-0.70) sensitivity and a 0.95 (95% CI : 0.94-0.96) specificity, with a positive likelihood ratio of 14.4 (95% CI : 11.6-18.0) and a negative likelihood ratio of 0.35 (95% CI : 0.32-0.38) which are also indicative of a high specificity. Fifteen cohort reports in patients with early rheumatoid arthritis were combined, from which the sensitivity and specificity of anti-CCP2 antibody were 0.57 (95% CI : 0.51-0.63) and 0.96 (95% CI : 0.93-0.97), respectively. The report by Nishimura (2007) that received the second best scores also showed similar results of anti-CCP2 antibody with a sensitivity of 0.67 (95% CI : 0.65-0.68), specificity of 0.95 (95% CI : 0.95-0.96), positive likelihood ratio of 12.46 (95% CI : 9.72-15.98), and negative likelihood ratio of 0.36 (95% CI : 0.31-0.42).

□ Systematic reviews in Korean population

Quality assessment was performed in the finally selected 9 primary studies on anti-CCP antibodies in Korean population, and the results indicated that bias risks in the patient selection area of QUADAS II were high or uncertain since the types of these studies were case control studies or cross-sectional studies. Except for this patient

selection part, the studies were evaluated to have high quality in most of the other points. That is, all of the finally selected 9 primary studies had low levels of overall biases and application concerns, making these studies applicable.

Results from the meta analysis of overall control groups indicated that the pooled sensitivity was 0.76 (95% CI : 0.73-0.79), pooled specificity was 0.96 (95% CI : 0.93-0.97), and positive (the probability where a person with a disease may show an abnormality relative to the probability where a person without a disease may show an abnormality) and negative (the probability where a person with a disease may not show any abnormality relative to the probability where a person without a disease may not show any abnormality) likelihood ratios calculated from the pooled sensitivity and specificity were 18.04 (95% CI : 11.80-27.57) and 0.25 (95% CI : 0.23-0.28), respectively. Results from the meta analysis of disease control groups indicated that the pooled sensitivity was 0.79 (95% CI : 0.73-0.83), pooled specificity was 0.92 (95% CI : 0.88-0.94), and positive and negative likelihood ratios calculated from the pooled sensitivity and specificity were 9.43 (95% CI : 7.00-12.71) and 0.23 (95% CI : 0.19-0.29), respectively.

4. Conclusions

Results from the systematic review of HTA report and guidelines, existing systematic reviews, and systematic reviews of reports in Korean population support the consistent conclusion that the anti-CCP antibody test is both necessary and useful in the diagnosis of rheumatoid arthritis, and suggest that this test is expected to contribute to early treatment of patients with this disease by enhancing specificity in the diagnosis of rheumatoid arthritis, especially when the disease is in its early stage.