Executive Summary/

Disease burdens of allergic rhinitis and asthma have recently been on the rise and Korea is not an exception. Lifetime prevalence of rhinitis reaches 39.0% and the medical expense for this disease has been significantly increased from KRW 113.7 billion(3.58 million patients) in 2006 to KRW 203.1 billion(5.96million patients) in 2010. Asthma is showing an increasing burden of disease as well. Of particular note, asthma in children is emerging as a social issue.

Among many different therapies for allergic rhinitis and asthma, immunotherapy is currently being used for the treatment of the two diseases in Korea and is gradually being used more widely as this is expected to change the natural pathway of allergic diseases and contribute to lower burden of disease by increasing the probability of cure. A problem with this immunotherapy though is that it is relatively more costly than other conventional therapies.

However, the evidence of effectiveness and safety of immunotherapy for the treatment of allergic rhinitis and asthma has not been sufficiently researched yet. Although there have been Cochrane Reviews on effectiveness and safety of subcutaneous and/or sublingual immunotherapy in allergic rhinitis and asthma, these reviews had been performed based on placebo controlled studies and therefore had limitations in reviewing the evidence of immunotherapy.

With this situation taken into account, this study was aimed to review the effectiveness and safety of immunotherapy for the treatment of allergic rhinitis and asthma, and review efficient therapeutic options with economic aspects also taken into account. Specific study objectives are as follows: Thus, this study was performed based on systematic review, retrospective study.

1. Systematic Review

First, the systemic review was aimed to verify effectiveness and safety of sublingual and/or subcutaneous immunotherapy in allergic rhinitis and asthma. Major search engines in Korea (Koreamed, KISS, KMbase, and KiSTi) as well as Core database (Cochrane library, Ovid-MEDLINE, and Ovid-EMBASE) were utilized for this purpose. Furthermore, Korean clinical academic journals related to allergic rhinitis and asthma were hand-searched. We asked pharmaceutical companies to submit clinical trial reports and included them in the review. In total, 1,937 and 4,028 articles were retrieved from Korean and international literature, respectively. Of these, 167 articles were finally selected for this study through inclusion/exclusion procedures; 115 pertained to studies comparing sublingual immunotherapy(SLIT) versus 45 placebo, were regarding subcutaneous immunotherapy(SCIT) versus placebo, and 9 were comparative literature of sublingual versus subcutaneous immunotherapy. Two reviewers independently assessed the quality of included articles using the Cochrane Risk of Bias tool for RCTs. Data were extracted independently by two reviewers independently using a standardized data extraction table.

For Direct comparison between SLIT and SCIT, 9 studies were included, with 337 patients in 6 RCTs suitable for meta-analysis. Compared with SCIT, SLIT significantly reductions in symptom medication score requirements(SMD -0.87; 95%CI, -0.58, -0.16) and lung function(PEFR) (SMD -0.79; 95%CI, -1.44, -0.15). SLIT were associated with no detectable differences in symptom score(SMD 0.34; 95%CI, -0.43, 1.12), systemic adverse reactions(RR 0.77; 95%CI, 0.54, 1.09), local adverse reactions(RR 0.23; 95%CI, 0.03, 1.99), total adverse reactions(RR 0.17; 95%CI, 0.01, 3.23), lung function(FEV1)(SMD -0.04; 95%CI, -0.53, 0.45), and QoL(SMD -1.91; 95%CI, -14.64, 18.46) compared with SCIT.

For comparing SLIT and SCIT, the evidence for SLIT and SCIT was

not sufficient. Therefore in this study indirect comparison between SLIT and SCIT was conducted. We used the Bucher et al., method in an indirect comparison of two immunotherapy, SLIT and SCIT, for allergic rhinitis sensitized by grass pollen. For the outcome symptom medication score, symptom score, and medication score, we determined that there was not a significant difference between the two immunotherapy. The results of indirect comparison were not consistent with direct comparison for symptom medication score. However the patient characteristics including allergen, age et al. in direct comparison and indirect comparison were different, therefore, it is difficult to compare the results of direct and indirect comparison. In this study, we could not conclude that two immunotherapy are different in subject to allergic rhinitis and asthma.

2. Retrospective study

The retrospective study was designed to find out the real cost of immunotherapy in Korea and its side effects in patients with allergic rhinitis and/or asthma. This was carried out in patients with allergic rhinitis and/or asthma who started immunotherapy for these diseases at hospital "A" located in metropolitan in Korea during the period between January and December 2007 and who did not receive any other immunotherapy within the recent 3 years. Medical records of a total of 161 patients were collected. Of these, 115 patients were adults and 46 patients were children and/or adolescents. As for disease distributions, there were 74 patients with rhinitis alone, 3 patients with asthma alone, and 84 patients with both rhinitis and asthma. For the purpose of analysis, these patients were reclassified into patients with rhinitis with or without asthma or patients with asthma with or without rhinitis. In the retrospective study, the patients' socio-demographic information, severity of the relevant diseases, seasons with worsened symptoms, types of antigens, methods of immunotherapy(subcutaneous or sublingual), and side

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effects and adverse events during the treatment with immunotherapy were examined.

As a results, total cost of SCIT for 3 years of allergic rhinitis was KRW 6,492,401(Sensitivity analysis KRW estimated results: 5,686,744~6,252,827) in adults and KRW 5,090,494(Sensitivity analysis results: KRW 4,672,231~4,833,776) in children. SLIT for allergic rhinitis was estimated KRW 7,926,433(Sensitivity analysis results: KRW 7,120,776~7,686,859) KRW in adults and 7,302,680(Sensitivity analysis KRW 6,884,417~7,045,962) in children.

Total cost of asthma was higher than for allergic rhinitis. For SCIT, the estimated cost was KRW 7,701,629(Sensitivity analysis results: KRW 6,734,589~7,470,562) in adults and KRW 6,105,060(Sensitivity analysis results: KRW 5,415,597~5,820,426) in children. The SLIT cost for asthma was estimated KRW 8,915,343(Sensitivity analysis results: KRW 7,948,303~8,684,277) in adults and KRW 8,077,023(Sensitivity analysis results: KRW 7,387,560~7,792,390) in children. In Korea, if patients of allergic rhinitis are treated with SLIT instead of SCIT, the total cost for 3 years would be 1.2-1.4 times higher than SCIT and in case of asthma, the estimates would be similar.