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Abstract

Asthma is a chronic inflammatory disease of the airways characterized by varying and recurrent symptoms, reversible airway obstruction, and bronchospasm. In this paper, clinical important studies on asthma published between March 2021 and February 2022 were reviewed. A study on the relationship between asthma and chronic rhinosinusitis, bronchiectasis, and hormone replacement therapy was published. A journal on the usefulness of fractional exhaled nitric oxide for the prediction of severe acute exacerbation was also introduced. Studies on the effect of inhaler, one of the most important treatments for asthma, were published. Studies on the control of severe asthma continued. Phase 2 and 3 studies of new biologics were also published. As the coronavirus disease 2019 (COVID-19) pandemic has been prolonged, many studies have explored the prevalence and mortality of COVID-19 infection in asthma patients.

Keywords: Asthma; Fractional Exhaled Nitric Oxide; COVID-19; Inhaler Therapy; Biologics

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Asthma Epidemiology and Diagnosis

1. Bronchiectasis in patients with overlapping asthma and chronic rhinosinusitis[1]

The term “united airways” refers to the coexistence of upper and lower respiratory tract diseases and their similar pathogenic mechanisms. A typical ‘united airways’ disease means asthma-chronic rhinosinusitis (CRS) overlap. Although there have been several studies on the association between bronchiectasis and asthma or chronic rhinosinusitis, the correlation between the presence of bronchiectasis and asthma-chronic sinusitis has not been fully explored. Therefore, the prevalence, inflammatory characteristics, and clinical significance of bronchiectasis were investigated in a prospective cohort of asthma-CRS patients. It was found that 40.9% of asthma-CRS patients in this cohort were co-diagnosed with bronchiectasis. Forced expiratory volume in 1 second (FEV_1) less than 71.40% of the predicted value, peripheral blood eosinophil counts greater than 0.6×10^9/L, the presence of nasal polyps, or at least one severe exacerbation within 12 months are criteria used to differentiate bronchiectasis in asthma-CRS patients. Therefore, patients with asthma-CRS together with nasal polyps, impaired lung function, eosinophilia, and acute asthma attacks need high-resolution computed tomography scans for early diagnosis and treatment of bronchiectasis.

2. Hormone replacement therapy and development of new asthma[2]

A large-scale observational study of the Danish registry has reported results of multivariate analysis performed on 34,533 women with asthma between ages of 40 and

65 years and on 345,116 women without asthma. Its results showed that active hormone replacement therapy (HRT) could lead to the development of asthma (hazard ratio [HR], 1.63). Termination of HRT also increased the likelihood of discontinuation of asthma treatment (HR, 2.12; 95% confidence interval [CI], 1.94–2.33; p<0.001). When subtypes of HRT were analyzed, progesterone was found to prevent the development of asthma. The relationship between menopause, asthma, and HRT is complicated. Results of that study could not reveal any causal relationship between HRT and asthma. Aggressive menopause was also a confounding factor in that study. Asthma is more likely to be triggered by unstable estrogen levels associated with menopause, rather than by levels of estrogen. These findings affect a vast number of women around the world. Thus, potential side effects should be considered when prescribing HRT. A prospective study examining the effectiveness of HRT in women who already have asthma along with mechanistic studies will help women requiring treatment for menopausal symptoms.

3. Baseline fractional exhaled nitric oxide as a prognostic biomarker for severe asthma exacerbation[3]

The presence of type 2 inflammation and the possibility of future exacerbation have been explored using biomarkers such as peripheral blood eosinophils and fractional exhaled nitric oxide (FeNO). However, apart from the contribution of peripheral blood eosinophils, data identifying FeNO as a predictor of future exacerbation remain insufficient. Results of a *post hoc* analysis of the 52-week LIVERTY ASTHMA QUEST study have revealed that the value of FeNO, baseline eosinophil count, and previous exacerbation history are independent prognostic factors for predicting the risk of asthma exacerbation. As a result, the rate of acute asthma exacerbation was 1.54 times higher in patients with a baseline FeNO of 50 ppb or more than in patients with a baseline FeNO of less than 25 ppb (relative risk [RR], 1.54 [95% CI, 1.11–2.14]; p=0.0097). Similarly, patients with FeNO values between 25 and 50 ppb had a 1.33 times higher risk of acute exacerbation than patients with FeNO less than 25 ppb. Furthermore, patients with baseline FeNO higher than 25 ppb, blood eosinophil counts higher than 150 cells/μL, and two or more acute exacerbations (n=157) had a 3.62 times higher exacerbation rate (RR, 3.62 [95% CI, 1.67–7.81]; p=0.0011) than those with FeNO less than 25 ppb, blood eosinophil count less than 150 cells/μL, and one acute exacerbation (n=116). However, further studies must be conducted to confirm the usefulness of FeNO value as an independent risk factor for asthma exacerbation. Recently, the American Thoracic Society has published new clinical practice guidelines of FeNO testing, which recommend testing of FeNO for patients with asthma considering treatment[4].

Asthma and Inhaler Therapy

1. Effect of a single day of increased as-needed budesonide-formoterol use in mild asthma[5]

As a result of the SYmbicort Given as needed in Mild Asthma (SYGMA) 1 study published in 2017[6], as-needed budesonide-formoterol is known to be better for controlling asthma in the prevention of the long-term risk of exacerbation than as-needed terbutaline-only in mild asthma. In the SYGMA study, although mild asthma patients used the reliever on less than a third of days during a 52-week study period, terbutaline-only was often associated with an increased use of the reliever. Even if there was only one day of increased terbutalin use, it was associated with an increased risk of severe exacerbation within a short-term period. A *post hoc* analysis of the SYGMA 1 study evaluated the relationship between the frequency of reliever use and the short-term risk of severe exacerbation for 21 days after 2, 4, 6, or 8 or more uses of reliever via inhalation within 24 hours. Increased use (two or more via inhalation as needed) of as-needed budesonide-formoterol in mild asthma was found to reduce the risk of acute exacerbation for a short-term period compared with as-needed short-acting β2-agonists. These results suggest that, in patients with mild asthma, using low-dose inhaled corticosteroids (ICS)–formoterol several times a day as needed for symptom relief can effectively prevent severe exacerbation as effectively as regular maintenance ICS. These findings also indicate that the greater the risk of severe exacerbation and the greater the frequency of use of the reliever, the greater the benefit of budesonide-formoterol as needed with high compliance.

2. Triple versus dual inhaler therapy for moderate to severe asthma outcomes[7]

Long-acting muscarinic antagonists (LAMAs) have a different bronchodilator mechanism from long-acting β2-agonists (LABAs), making them a beneficial add-on therapy for persistent and uncontrolled asthma. Tiotropium was approved for pediatric use by the Food and Drug Administration (FDA) in 2017. A number of clinical trials have been completed for triple therapy for asthma, including LAMAs other than tiotropium. A meta-analysis of 20 randomized controlled trials and

11,894 patients comparing triple therapy versus dual therapy has revealed that triple therapy can significantly reduce the frequency of acute exacerbations and improve asthma control compared to dual therapy (ICS plus LABA; HR, 0.83). However, there was no significant difference in the quality of life or mortality. Serious adverse events were not significantly different either. Thus, it is important to consider the patient's risk of underlying exacerbation when choosing triple or dual therapy. Patient selection and consideration of risk for future exacerbation can help identify patients who could benefit the most from triple therapy with the addition of LAMAs to ICS and LABAs.

Severe Asthma and Biologics

1. Sputum tumor necrosis factor markers and azithromycin treatment in severe asthma[8]

A previous study has shown that long-term, low-dose azithromycin treatment can reduce the exacerbation of poorly controlled asthma[9]. However, the mechanism remains unclear. One study has demonstrated the dysregulation of key tumor necrosis factor (TNF) pathway components in clinically important phenotypes of asthma, including neutrophilic and severe asthma. It is known that azithromycin can exert its anti-inflammatory effect by modulating the TNF pathway. Neutrophilic asthma is associated with significantly increased levels of sputum TNFR (TNF receptors 1 and 2), which are positively correlated with sputum neutrophils. The increase in TNFR, particularly sputum TNFR2, is significantly associated with a poor prognosis of asthma outcomes. Long-term, low-dose azithromycin treatment can inhibit TNFR2 and TNF ligand in the airways and TNFR2 in the serum. Thus, azithromycin is an important anti-inflammatory component that can regulate TNF-related signaling in neutrophilic asthma.

2. Tezepelumab for severe, uncontrolled asthma[10]

Recently, the FDA has approved tezepelumab as an additional maintenance treatment for patients with severe asthma over 12 years of age. Tezepelumab is a treatment for severe asthma that acts by blocking thymic stromal lymphopoietin (TSLP), thereby suppressing inflammation that causes asthma exacerbation. In the NAVIGATOR phase 3 trial, tezepelumab was found to significantly reduce the annual rate of asthma exacerbations compared to placebo in adults and adolescents with severe, uncontrolled asthma, including patients with low blood eosinophil counts. Currently available biologics have not been shown to consistently reduce exacerbations in patients with blood eosinophil counts of less than 150 cells/μL. Tezepelumab can simultaneously reduce FeNO and IgE levels and blood eosinophil counts, indicating its ability to inhibit various inflammatory pathways. Significant improvements in FEV_1 and scores on the Asthma Control Questionnaire (ACQ-6), Asthma Quality of Life Questionnaire (AQLQ), and Asthma Symptom Diary (ASD) were found in this trial. Moreover, a significant reduction in exacerbation leading to admission to emergency room or hospitalization was observed with tezepelumab compared to placebo. However, frequencies and types of adverse events did not differ significantly between tezepelumab and placebo groups.

3. Itepekimab in patients with moderate to severe asthma[11]

Biologic therapeutic agents targeting IgE, interleukin (IL)-4, IL-13, and IL-5 have been developed. They are being used in moderate to severe type 2 asthma. However, many patients continue to show worsening symptoms and reduced lung function despite receiving biological therapy. Itepekimab, whose phase 2 results have been published recently, is a novel, human IgG4P monoclonal antibody against IL-33 that can control inflammation contributing to asthma.

Broad inflammatory responses induced by cytokines, including IL-4, IL-5, and IL-13, are initiated by "alarmins" released from IL-33, IL-25, and TSLP as a result of response of airway epithelial cells. This leads to exacerbations such as eosinophilic inflammation, mucus production, and bronchospasm. The upstream of these epithelial cytokines was identified as a potential therapeutic target to improve lung function and prevent exacerbation in both type 2–high and type 2–low asthma[12]. Compared to placebo, itepekimab treatment reduced failure of asthma control in adults with moderate to severe asthma and improved lung function in this phase 2 trial. This is consistent with the role of IL-33 in the pathogenesis of asthma exacerbation and airflow restriction.

4. Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma[13]

The investigation of drugs targeting alarmin is underway. IL-33 is an epithelial-derived alarmin that is secreted in response to tissue damage. Inhalation of allergens as common causes of asthma exacerbation can strongly induce IL-33 synthesis and release.

Astegolimab, a monoclonal antibody, is a drug that blocks IL-33/ST2 signaling. It is being proposed as a treatment for severe asthma patients who do not respond to available biological agents. Astegolimab can

reduce the rate of asthma exacerbation by 43% compared with the placebo in a randomized control phase 2b trial. The efficacy of astegolimab in severe asthma patients with blood eosinophil counts below 300 cells/μL has been found to be similar to that in the overall group, supporting the hypothesis that IL-33 participates in asthma pathogenesis upstream of Th2 pathways.

5. Long-term safety and efficacy of dupilumab in patients with moderate to severe asthma[14]

Approximately 80% of asthma patients have type 2 inflammatory disease characterized by elevated levels of blood eosinophils, serum periostin, and FeNO. IL-4 and IL-13 are key drivers of type 2 inflammation. Upregulation of these cytokines is a crucial component of asthma. Dupilumab is a fully human monoclonal antibody against IL-4 receptor α that blocks IL-4 and IL-13 signaling. The 2018 LIBERTY ASTHMA QUEST study showed that lung function and asthma control were superior in the group of asthma patients with high eosinophilic levels who were administered with dupilumab. They showed significantly lower rates of severe asthma exacerbations compared to those who received placebo[15]. Accordingly, dupilumab has been approved by the FDA as a biological agent for moderate to severe asthma patients with the eosinophilic phenotype.

In the TRAVERS study of 2,282 adult and adolescent patients, the long-term safety and efficacy of dupilumab were evaluated when treatment was extended up to 148 weeks. Dupilumab showed a safety profile that was consistent with the previously known safety profile. The reported rate of adverse events was 76.3%–94.7%. The efficacy of dupilumab in the TRAVERS study was also consistent with previously reported efficacy of dupilumab. In non-oral-corticosteroid-dependent patients, acute exacerbation rates (AERs) remained low (0.277–0.327) and the improvement of FEV_1 persisted until the end of treatment at week 96. AER, asthma control, and quality of life were also improved. This study is the first one that evaluates the long-term safety and efficacy of dupilumab in patients with asthma. These results support the long-term safety of dupilumab in patients with uncontrolled moderate to severe asthma.

Asthma and Coronavirus Disease 2019

1. Asthma and risk of infection, hospitalization, intensive care unit admission, mortality from coronavirus disease 2019[16]

A systematic review has been conducted to assess the vulnerability of asthma patients during the coronavirus disease 2019 (COVID-19) pandemic. The prevalence of COVID-19 among asthma patients reported so far varied from study to study. According to this systematic review and meta-analysis, which included 57 studies, asthma patients accounted for 7.46% (95% CI, 6.25%–8.67%) of COVID-19 patients, which was similar to the global asthma prevalence. This study also showed that asthma patients had a 14% (RR, 0.86 [95% CI, 0.80–0.94]; p<0.0001) lower risk of acquiring COVID-19, which showed an absolute reduction of 50 cases per 1,000 people and 13% reduced chance of being hospitalized with COVID-19 (RR, 0.87 [95% CI, 0.77–0.99]; p=0.03) compared with those without asthma. The lower risk of COVID-19 infection in asthma patients can be attributed to several reasons. First, asthma patients with high T2 showed decreased levels of the angiotensin-converting enzyme-2 (ACE-2) receptor, which might reduce the risk of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection[17]. According to a severe asthma research program-3 study, ICS therapy, the most important treatment in asthma patients, is related to low expression of ACE-2, one of the binding sites of SARS-CoV-2[18]. It is possible that this has lowered the risk of COVID-19 infection in asthma patients and reduced the risk of progression to severe diseases. Additionally, the fact that asthma patients were more concerned about COVID-19 and were more careful about their behavior than healthy patients could also be the cause of the lower incidence of COVID-19 infection in asthma patients.

2. Risk of adverse outcomes with underlying respiratory conditions admitted to hospital with COVID-19[19]

The OpenSAFELY Study[20] did not confirm that regular use of ICS in patients with asthma or COPD could reduce COVID-19–related mortality. However, a retrospective study of 75,463 patients evaluated the relationship between underlying respiratory diseases (asthma and chronic pulmonary disease) and multiple in-hospital outcomes. Patients with asthma were significantly more likely to receive intensive care than patients without asthma (age 16–49 years: odds ratio [OR], 1.20 [95% CI, 1.05–1.37]; p=0.0080; age ≥50 years: OR, 1.17 [95% CI, 1.08–1.27]; p<0.0001). In age group of 16–49 years, the mortality rate in patients with severe asthma was higher than that in patients without asthma (HR, 1.96 [95% CI, 1.25–3.08]). In contrast to the OpenSAFELY study, another retrospective study showed that the use of ICS within two weeks of hospitalization was associated with a reduced mortality rate in patients with asthma without beneficial effect on mortality in patients with chronic pulmonary disease.

These two large observational cohort studies showed contrasting effects of ICS, although the timing of ICS might be different. These results imply that patients with respiratory diseases are vulnerable to SARS-CoV-2 infection. Thus, they should continue to take preventive measures.

3. Asthma phenotypes and COVID-19 risk[21]

A study of a large cohort of 434,348 asthma patients has investigated the relationship between asthma phenotype and COVID-19 risk. Asthma phenotypes and comorbidities are important factors when assessing the risk of SARS-CoV-2 infection and disease severity as findings suggest that Th2-high inflammation can reduce the risk of SARS-CoV-2 infection and disease severity in contrast to an increased risk observed for Th2-low asthma patients. Asthma with regular ICS use (HR, 1.27 [95% CI, 1.01–1.61]), intermittent ICS plus add-on asthma medication use (HR, 2.00 [95% CI, 1.43–2.79]), regular ICS plus add-on use (HR, 1.63 [95% CI, 1.37–1.94]), and frequent exacerbations (HR, 1.82 [95% CI, 1.34–2.47]) were significantly associated with hospitalization. Only patients with regular ICS plus add-on asthma therapy (HR, 1.70 [95% CI, 1.27–2.26]) or frequent exacerbations (HR, 1.66 [95% CI, 1.03–2.68]) had a significantly higher risk of intensive care unit admission or death. More severe asthma, but not type 2 inflammation, was associated with more severe COVID-19 outcomes. The use of ICS is safe for asthma patients with SARS-CoV-2 infection. However, when asthma patients are infected with SARS-CoV-2 while using systemic corticosteroids chronically or repeatedly, ICS therapy is a major risk factor for poor prognosis and increased mortality. Conversely, patients who have been using biologic therapy for severe allergic and eosinophilic asthma did not show an increased risk of higher rate or severity of COVID-19 infection.

Authors' Contributions

Conceptualization: Kim JY, Choi JS. Methodology: Lee JH, Kim JY, Choi JS. Investigation: Lee JH, Kim JY, Choi JS. Writing - original draft preparation: Lee JH. Writing - review and editing: Na JO. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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