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Editorial

Risk of Pneumonia Associated With the Use of Inhaled Corticosteroids in Asthma

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Corticosteroids are widely used in the treatment of various diseases because of their potent anti-inflammatory effects. Systemic corticosteroids are still considered a mainstay of treatment for many inflammatory conditions such as rheumatic disease, inflammatory bowel disease, and allergic disease. Asthma is characterized by chronic airway inflammation dependent on diverse pathophysiological pathways. Since their introduction in the management of asthma,[1] systemic corticosteroids have played a major role in the management of uncontrolled severe asthma as well as its acute exacerbations. However, it has become very apparent that the long-term use of systemic corticosteroids is associated with serious effects such as osteoporosis, hypertension, diabetes, adrenal suppression, and cataracts,[2] that is the background against what we seek a safer way of using corticosteroids and promoting the use of inhaled corticosteroids (ICS) in the chronic management of asthma.[3]

In addition to its clinical efficacy, the strikingly lower risk of adverse reactions associated with ICS vs oral corticosteroids (OCS) makes ICS the current mainstay of pharmacotherapy of chronic asthma. However, there is a large body of data suggesting that long-term use of ICS can also induce systemic adverse effects, including adrenal insufficiency, osteoporosis, cataract, and immunity, in a dose-dependent manner.[4] The possibility of a risk of pneumonia associated with ICS use was first raised in chronic obstructive pulmonary disease (COPD) patients.[5] This led to concerns about pneumonia risk in asthmatic patients who have to use ICS as the treatment of choice for long-term control. The incidence of pneumonia seems relatively low in asthmatic patients compared with COPD patients who are older and have more comorbidities. In a retrospective analysis of double-blind clinical trials using budesonide, there was no increased risk of pneumonia in asthmatic patients using ICS.[6] There was also no dose-dependency for the development of pneumonia with use of budesonide, or any difference in risks between budesonide and fluticasone. In a recent meta-analysis of randomized trials on the use of ICS and the risk of pneumonia in asthmatic patients, ICSs were associated with a decreased risk of pneumonia.[7] In contrast, observational studies revealed an increased risk of pneumonia with ICS use in asthmatic patients. These conflicting findings show that real-world data (RWD) can yield different results than clinical trials.[8]

In the current issue of *Allergy, Asthma & Immunology Research*, Kim *et al.*[9] analyzed nationwide Korean health insurance claims data to examine the risk of pneumonia with ICS use in asthmatic patients aged over 15 years.[9] Using multivariate logistic regression analysis

adjusting for age, sex, comorbidities and history of hospitalizations, they find that ICS use is significantly associated with the development of pneumonia. Evidently asthmatic patients, as well as COPD patients, are at the risk of incident pneumonia with the use of ICS. However, since there were no data on the use of chronic or multiple bursts of OCS in their study subjects, it is not clear whether the association of ICS with pneumonia might have been affected by the use of systemic corticosteroids. Indeed, it is very likely that the risk of pneumonia is more influenced by the duration and dose of administered OCS than by the ICS themselves. In addition, there was no detail data to analyze of the dose-dependency of ICS based on the numbers of ICS canisters dispensed. Also, it would also be useful to compare pneumonia risks between different ICS.

Given the possible adverse effects of ICS such as pneumonia, what is the best pharmacological treatment strategy in asthma? Just informing a possible risk of pneumonia associated with ICS for our patients is not enough. The relative risks and benefits of ICS indicate that they should be recommended as the treatment of choice to achieve and maintain controls in patients with moderate to severe asthma. Studies in COPD have shown that higher doses of ICS and longer durations of their use increase the risk of pneumonia, though there have been contrary results.[10] Therefore, it would be reasonable to step down from high dose-ICS to low dose as soon as possible, once asthma is in well controlled. In cases of mild asthma, recent clinical trials showed that as-needed use of low dose- ICS/formoterol was as effective as regular use of ICS in reducing exacerbations even at quite low daily ICS doses.[11,12] Since the prescription rate of ICS remains low in the real world, their use in asthma should not be discouraged because of the possible risk of pneumonia.

What if a patient with asthma experiences pneumonia? Should we reduce the dose of ICS and add other controllers? Or would it be better to switch to other ICS drugs? In COPD, intra-class differences in the risk of pneumonia associated with different ICS have been suggested, and fluticasone was found to have a higher risk of pneumonia than budesonide due to the prolonged duration of its action in the airways.[13] However, in asthma, no intra-class differences in the risk of pneumonia associated with ICS have been reported so far.[6] Since changing devices can affect the manifestations of asthma, such as exacerbations,[14] the question whether switching of device type could reduce the occurrence of adverse reactions including pneumonia remains to be answered. Should routine pneumococcal vaccination be recommended for asthmatic patients considering the possible risk of pneumonia associated with ICS use?—more evidence is needed, from clinical trials as well as RWD.

RWD is being used more and more to answer questions regarding drug safety. While randomized controlled trials have strengths in generating high-quality information regarding efficacy and safety in limited numbers of enrolled subjects, large-volume routinely collected population health data can provide insight into safety in a population with diverse characteristics and phenotypes.[15] To answer many questions about the safety of ICS, including the pneumonia risk associated with asthma, one can analyze various kinds of RWD, such as health insurance claims data at a national level, and electronic health records. Common data models such as the Observational Health Data Sciences and Informatics have been adopted for pharmacovigilance and drug safety analysis. ICS remains the most potent controller, with proven efficacy in reducing asthma mortality and risk of exacerbations. More evidence of ICS safety is needed to allow us to use ICS wisely and safely in our asthma patients.

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REFERENCES

1. CONTROLLED trial of effects of cortisone acetate in status asthmaticus; report to the Medical Research Council by the subcommittee on clinical trials in asthma. Lancet 1956;271:803-6.
PUBMED
2. Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. J Allergy Clin Immunol 2018;141:110-116.e7.
PUBMED | CROSSREF
3. Crompton G. A brief history of inhaled asthma therapy over the last fifty years. Prim Care Respir J 2006;15:326-31.
PUBMED | CROSSREF
4. Pandya D, Puttanna A, Balagopal V. Systemic effects of inhaled corticosteroids: an overview. Open Respir Med J 2014;8:59-65.
PUBMED | CROSSREF
5. Restrepo MI, Sibila O, Anzueto A. Pneumonia in patients with chronic obstructive pulmonary disease. Tuberc Respir Dis 2018;81:187-97.
PUBMED | CROSSREF
6. O'Byrne PM, Pedersen S, Carlsson LG, Radner F, Thorén A, Peterson S, et al. Risks of pneumonia in patients with asthma taking inhaled corticosteroids. Am J Respir Crit Care Med 2011;183:589-95.
PUBMED | CROSSREF
7. Bansal V, Mangi MA, Johnson MM, Festic E. Inhaled corticosteroids and incident pneumonia in patients with asthma: systematic review and meta-analysis. Acta Med Acad 2015;44:135-58.
PUBMED | CROSSREF
8. Singh G, Schulthess D, Hughes N, Vannieuwenhuyse B, Kalra D. Real world big data for clinical research and drug development. Drug Discov Today 2018;23:652-60.
PUBMED | CROSSREF
9. Kim MH, Rhee CK, Shim JS, Park SY, Yoo KH, Kim BY, et al. Inhaled corticosteroids in asthma and the risk of pneumonia. Allergy Asthma Immunol Res 2019;11:795-805.
10. Iannella H, Luna C, Waterer G. Inhaled corticosteroids and the increased risk of pneumonia: what's new? A 2015 updated review. Ther Adv Respir Dis 2016;10:235-55.
PUBMED | CROSSREF
11. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018;378:1877-87.
PUBMED | CROSSREF
12. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med 2018;378:1865-76.
PUBMED | CROSSREF
13. Janson C, Larsson K, Lisspers KH, Ställberg B, Stratelis G, Goike H, et al. Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting β_2 agonist: observational matched cohort study (PATHOS). BMJ 2013;346:f3306.
PUBMED | CROSSREF
14. Park HS, Yoon D, Lee HY, Ban GY, Wan Yau Ming S, Jie JL, et al. Real-life effectiveness of inhaler device switch from dry powder inhalers to pressurized metred-dose inhalers in patients with asthma treated with ICS/LABA. Respirology. Forthcoming 2019.
PUBMED | CROSSREF
15. Harpaz R, DuMochel W, Shah NH. Big data and adverse drug reaction detection. Clin Pharmacol Ther 2016;99:268-70.
PUBMED | CROSSREF