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Editorial

# Risk of Pneumonia with Use of Inhaled Corticosteroids in Patients with Chronic Obstructive Pulmonary Disease

Inhaled corticosteroids (ICS) are widely used in patients of chronic obstructive pulmonary disease (COPD). Though the use of ICS in COPD patients fails to prevent reduction in lung function, yet it has been shown to reduce the frequency of exacerbations.[1] In these patients the relative risk of exacerbation is reduced by 33% with regular use of ICS.[2] Patients with severe COPD with a history of recurrent exacerbations requiring frequent antibiotics and steroids have been found to benefit the most.[3] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has also recommended the use of ICS in patients with severe COPD having frequent exacerbations.[4] Reduction in the frequency of exacerbations not only reduces mortality, but also reduces the use of oral steroids and antibiotics causing less adverse effects and thereby improves the quality of life (QOL).[5,6] Beneficial effects have been substantiated in several studies including the TORCH study.[7-10] Therefore, the present evidence favours the use of ICS in patients with severe COPD, in combination with long-acting beta-agonists (LABAs).[4] Along with beneficial effects, the use of ICS in patients with COPD is also associated with some adverse effects. Candidiasis in throat and esophagus, dyspnoea and cough are some of the adverse effects reported with the use of ICS. Such local adverse effects can usually be prevented/reduced by using a spacer with meter dose inhaler, rinsing mouth after its use, reducing the dosing frequency of ICS and taking ICS before food. In contrast to the local adverse effects, systemic adverse effects of ICS are less frequent but are also more serious. Osteoporosis, glucoma and cataract are some of the systemic effects observed in patients with COPD on high dose of long-term ICS.[11-18] The attributable risk is difficult to quantify, however, as these diseases are also age-related and seen frequently in the same age group as COPD, osteoporosis and its consequences resulting into increased risk of vertebral and hip bone fractures has been observed in many studies.[11-13] Cataract has been more frequently observed in elderly patients on high doses of ICS.[14-16] Glucoma has also been reported in patients using ICS.[17,18]

In addition to these adverse effects in the TORCH study,[10] pneumonia was recently reported as being more frequently in patients with COPD treated with fluticasone. The risk factors for pneumonia were age greater than 55 years, forced expiratory volume in one second less than 50% of the predicted, COPD exacerbations in the year prior to the study, poor dyspnoea scores and body mass index less than 25kg/$m^{-2}$.[19] In another study,[20] use of salmeterol and fluticasone was associated with an increased risk of pneumonia (8%) as compared to tiotropium bromide (4%) over a two years period and appeared to be related to fluticasone component.[20] These observations were further substantiated in a study by Ernest *et al*.[21] They found a relation between increased use of ICS and the risk of hospitalisation for pneumonia. They also observed increased mortality in elderly COPD patients with pneumonia. These studies have raised a serious concern about the safety of ICS in patients with COPD. A recent meta analysis[22] published last year tried to resolve this by including all randomised controlled trials in patients with COPD, where ICS were used atleast for 24 weeks follow-up. Many of these studies compared ICS with placebo while others compared ICS used in combination with LABA *versus* LABA alone. In the 18 trials that fulfilled the inclusion criteria, data of 16,996 patients with COPD were evaluated. Out of these 8635 received ICS while 8361 received control therapy. Occurrence of pneumonia, serious pneumonia and mortality were measured. The ICS therapy in COPD was associated with an approximately 60% increased risk of pneumonia and 70% increased risk of serious pneumonia. However, mortality due to pneumonia and overall mortality was similar in the two treatment classes. The increased risk of pneumonia was causally attributed to ICS as the risk of pneumonia was higher in patients receiving ICS plus LABA in comparison to those on LABA alone. The basis of the ICS-related increased risk of pneumonia is not known. It has been proposed that ICS may achieve high concentration in the lung that may increase the risk of pneumonia due to an immunosuppressive effect.[23]

These studies suggest that long-term use of ICS may cause increased risk of pneumonia. On the other hand, it was not associated with increased risk of mortality. The current recommendations favour the use of ICS in severe and very severe patients of COPD having repeated episodes of exacerbations.[4] However, in light of the above evidence, clinicians should observe these patients for occurrence of pneumonia. As the symptoms of early pneumonia and an acute exacerbation are similar, hence, pneumonia may go undiagnosed in patients with severe COPD. Close observation and imaging including repeated plain chest radiographs and computed tomography should enable a differentiation and appropriate management.

**Virendra Singh**
*Member, Editorial Board and Professor and Head*
and
**Prabhat Kanvaria**
*Assistant Professor*
*Pulmonary and Allergy Division*
*SMS Medical College, Jaipur (Rajasthan)*
*E-mail: drvirendrasingh@yahoo.com*

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