Combination of ICSs and LABAs should be used in the management of patients with COPD – The pro argument

Don D Sin MD

THE EFFECTS OF INHALED CORTICOSTEROID MONOTHERAPY

Airway inflammation is a prominent feature of chronic obstructive pulmonary disease (COPD), even among ex-smokers (1), and its intensity is directly related to the severity of the underlying COPD (2). The inflammatory burden increases during periods of clinical exacerbation (3-5). Predictably, use of systemic corticosteroids during these episodes accelerates clinical recovery and improves health outcomes over several months of follow-up (6). Unfortunately, long term use of systemic corticosteroids is generally precluded by their toxic side effects. Inhaled corticosteroids, on the other hand, share much of the anti-inflammatory properties of the systemic formulations without the side effects (7). However, their effectiveness has been questioned and is a matter of heated debate among members of the scientific community (8,9).

Some have argued that the inflammatory process in the COPD airways may be resistant to corticosteroids for various reasons. First, cells within COPD airways have reduced histone deacetylase activity (10). Histone deacetylase is an important cofactor that assists corticosteroids in deactivating various inflammatory genes; its deficiency may, therefore, make the inflammatory process more resistant to the effects of corticosteroids (10). Second, corticosteroids have minimal effects on neutrophils, which are found in abundance in the airway lumen of COPD patients and are thought to have some (if not a predominant) role in COPD pathogenesis (10). Indeed, in some cases, corticosteroids may delay neutrophil apoptosis, which, paradoxically, could promote airway neutrophilia.

Notwithstanding these theoretical concerns, clinical studies have demonstrated that inhaled corticosteroids can down-regulate certain components of the inflammatory process within COPD airways. Patel and coworkers (11), for example, showed a marked attenuation of interleukin (IL)-6 and IL-8 production by bronchial epithelial cells from COPD patients taking inhaled corticosteroids compared with COPD patients not taking inhaled corticosteroids. In another experiment, six weeks of inhaled beclomethasone (1.5 mg/day) reduced IL-8 levels by 68% in the bronchial lavage fluid of patients with mild to moderate COPD (12). IL-8 is important in neutrophil recruitment and chemotaxis. This may explain why, although corticosteroids have minimal direct effects on neutrophils, Confalonieri and coworkers (13) demonstrated a marked reduction in the number of neutrophils in the sputum of

COPD patients after eight weeks of treatment with inhaled beclomethasone (1.5 mg/day).

Inhaled corticosteroids have other anti-inflammatory properties. They reduce the expression of soluble intercellular adhesion molecules, which are important molecules in effecting transmigration of proinflammatory cells across the endothelial surface into deeper tissues (11). They also repress mast cell expression in the stromal layers of bronchial epithelium. For example, three months of inhaled fluticasone therapy reduce the subepithelial mast cell concentration by 24% (14). Furthermore, four weeks of inhaled beclomethasone can reduce sputum eosinophil numbers by 47% (from baseline) (12). They also reduce inducible nitric oxide synthase-positive and nitrotyrosine-positive cells by 40% and 39%, respectively, from baseline levels, suggesting that, in addition to their anti-inflammatory effects, inhaled corticosteroids may attenuate oxidative stress within COPD airways (15).

Not surprisingly, given these biological effects of inhaled corticosteroids on the inflammatory and oxidative processes in the airways of COPD, large, randomized, controlled trials have demonstrated that inhaled corticosteroids have salutary effects on clinically relevant health outcomes. A meta-analysis of data from large, randomized studies showed that inhaled corticosteroids reduce clinical exacerbation rates by approximately 25% relative to placebo among COPD patients (relative risk [RR] 0.76; 95% CI 0.72 to 0.80) (16,17). The magnitude of the risk reduction was similar between short (less than one-year) and long (four-year) trials, suggesting that the symptomatic benefit of inhaled corticosteroids extends to at least three to four years of follow-up (16). The beneficial effects were more pronounced among those with severe underlying disease (forced expiratory volume in 1 s [FEV₁] less than 50% predicted). They were not particularly beneficial among those with an FEV₁ greater than 2.0 L (17). Inhaled corticosteroids also reduced the rate of decline in health status in COPD. For the Symptoms component of the St George's Respiratory Questionnaire, inhaled corticosteroids decelerated the rate of deterioration by over 50% (18). In other areas of the St George's Respiratory Questionnaire (Activity and Impacts score), the rate of deterioration was attenuated by approximately one-third compared with placebo, which represented clinically relevant changes (18). Discontinuation of inhaled corticosteroids, on the other hand, resulted in an increase in patient symptoms and an elevated risk of exacerbations. Van der Valk and colleagues (19) demonstrated among 244 COPD patients (with a mean FEV₁ of approximately 1.7 L)

James Hogg iCapture Centre for Cardiovascular and Pulmonary Research; Department of Medicine, Pulmonary Division, University of British Columbia, Vancouver, British Columbia; Institute of Health Economics, Edmonton, Alberta

Correspondence: Dr Don D Sin, James Hogg iCAPTURE Center for Cardiovascular and Pulmonary Research, St Paul's Hospital, Room 368A, 1081 Burrard Street, Vancouver, British Columbia V5Z 1Y7. Telephone 604-806-8395, fax 604-806-9274, e-mail dsin@mrl.ubc.ca

that withdrawal of inhaled corticosteroids after at least four months of therapy led to a 1.5-fold increase in clinical exacerbations (RR 1.5; 95% CI 1.05 to 2.1) compared with those who continued on with steroid therapy. Predictably, health-related quality of life deteriorated at a much faster rate when patients were taken off of inhaled corticosteroids compared with those who remained on these drugs. These beneficial clinical effects were observed in the absence of discernible changes in the rate of descent in FEV₁. This suggests that accelerated declines in lung function may be controlled by factors other than airway inflammation. Irrespective of the mechanisms involved, there is compelling evidence to indicate that monotherapy with inhaled corticosteroids improves clinical outcomes in COPD.

THE EFFECTS OF LONG-ACTING BETA₂-AGONISTS AND INHALED CORTICOSTEROIDS

Because airflow obstruction is a prominent feature of COPD, long-acting beta₂-agonists (LABAs) were introduced with the aim of maximizing bronchodilation in these patients. LABAs are potent bronchodilators. They act by stimulating the adenylylate cyclase pathways, which, in turn, increase intracellular concentrations of cyclic adenosine monophosphate (20). Although LABAs by themselves have weak anti-inflammatory effects, *in vitro* studies suggest that they can materially amplify the effects of corticosteroids when given as combination therapy, making it possible to achieve large anti-inflammatory effects even with relatively low doses of corticosteroids (20). For instance, the addition of LABAs to inhaled corticosteroids accelerates translocation of glucocorticoid receptors from the cytoplasm into the nucleus, where they can modify the actions of transcription cofactors, nuclear factor kappa-B and activated protein-1 (21). LABAs also appear to increase the effectiveness of corticosteroids in suppressing expression of adhesion molecules such as intercellular adhesion molecule-1 (20). The bronchodilatory effect of LABAs may also facilitate corticosteroid deposition into areas of the lung, wherein active inflammation is present and prominent. Finally, corticosteroids can potentiate beta₂ activity by upregulating expression of beta₂ receptors and by preventing receptor uncoupling in response to an inflammatory stimulus (22). Combined with an inhaled corticosteroid, LABAs may, therefore, have additive or even synergistic effects on airway inflammation.

Although there are fewer clinical studies of LABA and inhaled corticosteroid combination therapy than there are for monotherapy with inhaled corticosteroids, the data for combination therapy are, indeed, very impressive. Several high quality, randomized, controlled trials have shown that combination therapy leads to better health-related quality of life over short and long term follow-up periods than inhaled corticosteroids alone (23-26). Overall, patients who received combination therapy with inhaled corticosteroids and LABAs experienced 30%, 20% and 10% fewer clinical exacerbations (requiring oral corticosteroids) than those who received placebo, LABA or inhaled corticosteroid monotherapy, respectively (17). Combination therapy improved patients' FEV₁ values by over 100 mL compared with placebo within the first year of therapy. It was more powerful than inhaled corticosteroid or LABA monotherapy in improving trough FEV₁ (increase of

50 mL/year, 95% CI 26 mL/year to 74 mL/year compared with inhaled corticosteroid monotherapy; increase of 34 mL/year, 95% CI 11 mL/year to 57 mL/year compared with LABA monotherapy) (17). The beneficial effects of inhaled corticosteroids and LABAs, therefore, appeared to be additive, not synergistic. Although the effect of combination therapy on mortality remains uncertain (pending publication of larger studies powered specifically on mortality), there is a strong suggestion toward decreased mortality with combination products (RR versus placebo 0.52; 95% CI 0.20 to 1.34). These data are supported by an observational study by Soriano and co-workers (27). In this carefully performed epidemiological study using the United Kingdom General Practice Research Database, an automated database of primary care covering approximately 3.4 million people, the investigators found that COPD patients who received a prescription for an inhaled corticosteroid plus a LABA within 90 days of hospital discharge were 41% less likely to experience a combined end point of repeat hospitalization for COPD or all-cause mortality. This effect size was larger than that observed with each individual drug alone. Similar data have been reported by the Lovelace Group (28) and by Dutch investigators (28) using a similar experimental design.

CONCLUSIONS

The totality of evidence strongly indicates that combination therapy with inhaled corticosteroids and LABAs produces beneficial health outcomes in COPD. Combination therapy reduces the rate of exacerbations by nearly one-third and improves trough FEV₁ by over 100 mL compared with placebo within the first year of therapy. There are now emerging data to suggest that combination therapy may have salutary effects on survival. Overall, there is compelling evidence and scientific rationale for using combination therapy in the management of moderate to severe COPD (29).

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