

Regular treatment for moderate asthma: guidelines hold true



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The present mainstay of asthma treatment is to prescribe maintenance daily inhaled corticosteroids in all patients with asthma who have more than intermittent symptoms, with the addition of maintenance longacting β_2 agonists in cases of insufficient asthma control.¹ On top of low-dose inhaled corticosteroids and longacting β_2 agonists, intermittent additional use of the combination treatment can be used (same maintenance and reliever therapy [SMART] principle).^{1,2} A few—mostly small—studies have challenged the aforementioned dogma of regular inhaled corticosteroid use in adults. These studies were undertaken in patients with mild asthma on low-dose inhaled corticosteroids only, all with a short-acting bronchodilator, and provided mixed results.³⁻⁷

The study by Alberto Papi and colleagues in *The Lancet Respiratory Medicine* is the first to investigate the efficacy of a symptom-driven approach in patients with moderate asthma, with use of an inhaled corticosteroid (budesonide) combined with a longacting β_2 agonist (formoterol) in a single inhaler.⁸ Recruited patients had stable moderate persistent asthma that was either uncontrolled on regular low-dose inhaled corticosteroids or controlled on regular inhaled corticosteroid and longacting β_2 agonist therapy (step 3 on the Global Initiative for Asthma scale). In this non-inferiority, double-blind, randomised controlled trial, Papi and colleagues compared as-needed 160 μ g budesonide and 4.5 μ g formoterol with regular twice-daily maintenance treatment with 160 μ g budesonide and 4.5 μ g formoterol plus as-needed 500 μ g terbutaline for 1 year.

As-needed budesonide and formoterol was less effective than was regular maintenance treatment with respect to the primary outcome of time to first treatment failure measured at 1 year—a composite event measure based on health care use, additional steroid or high rescue medication use, nocturnal awakenings, or withdrawal from the study by the doctor or because of patient dissatisfaction. Compared with regular treatment, as-needed treatment was associated with a lower probability of patients having no treatment failure at 1 year (Kaplan-Meier estimate 53.6% for as-needed treatment vs 64.0% for regular treatment; difference 10.3% [95% CI 3.2–17.4] at a predefined noninferiority limit of 9%). The difference in favour

of regular treatment was driven entirely by an almost 50% reduction in number of nocturnal awakenings (82 patients in the as-needed treatment group vs 44 in the regular group). The number of courses of systemic steroids was similar in both groups, which might have been affected by the significantly higher dropout rate in the as-needed group (34%) than in the regular group (26%), leaving less patient-exposure-years in which asthma exacerbations could occur.

Additionally, a large number of patients had missing data for many of the secondary endpoints. The fact that the study was investigator initiated (vs industry-initiated and sponsored trials) has perceived advantages regarding credibility, but this benefit needs to be balanced against the challenges of very strict monitoring, especially in multicentre trials.

A comprehensive and convincing list of secondary endpoints all favoured regular treatment over as-needed use. These endpoints included spirometry, peak expiratory flow, rescue medication use, symptom-free days, asthma control, and asthma quality of life scores. Not included in this study was a measure of inflammation, the hallmark characteristic of asthma. The continuous suppression of inflammation is the main argument in favour of corticosteroid administration in maintenance dosing. Two previous studies have reported that exhaled nitric oxide and sputum eosinophilia increase with intermittent compared with maintenance inhaled corticosteroid use.^{4,7}

Compliance to inhaled asthma medication is very low,⁹ and the actual pattern of use in individual patients is not well known. Actual use of intended regular therapy could be intermittent according to a similar algorithm as that used in Papi and colleagues' study, in which actual compliance and pattern of use were not well documented, as is the case in many trials. Suboptimum compliance, if present, would have reduced the difference between regular and as-needed therapy. More detailed studies of pattern of actual daily use, such as with computerised counting chips in devices,¹⁰ might help to identify patients in whom intermittent use of inhaled corticosteroids and longacting β_2 agonist is a good treatment option.

The use of inhaled corticosteroids is associated with side-effects and additional costs. These problems

could potentially be averted with intermittent use. Indeed, in this study, the estimated cumulative dose of inhaled corticosteroid use was substantially lower in the intermittent group (24.5 mg) than in the regular group (116.8 mg). Moreover, fewer patients in the as-needed group than in the regular group had nasopharyngitis and oropharyngeal pain. The costs were not measured, and should be assessed at a broader level than only the costs of the inhalers and also include health-care use. Side-effects and costs need to be weighed against the benefits in terms of asthma control and quality of life.

Some people will argue that the difference between as-needed and regular use on the primary composite endpoint in this trial is ambiguous since it was driven by nocturnal awakenings only. However, since all the secondary endpoints also significantly favoured regular use of the treatment, we believe the results clearly support the regular use of combined inhaled corticosteroids and longacting β_2 agonists in adult patients with moderate and higher severity asthma. This approach is in line with existing guidelines¹ but has now been substantiated.

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Vitamin D and COPD: who benefits from supplementation?



Much attention has been focused on the potential role of vitamin D deficiency on both the development and exacerbations of obstructive lung diseases. Vitamin D has immunomodulatory functions and anti-inflammatory properties, reduces oxidative stress, and acts as an epigenetic regulator of genes associated with lung disease.¹ Research into the link between vitamin D and asthma, including a large multicentre randomised trial, has been focused mainly on the potential for vitamin D supplementation to improve the effectiveness of inhaled corticosteroids by enhancing their anti-inflammatory effects and reversing steroid resistance.² By contrast, research into the link between vitamin D and chronic obstructive pulmonary disease (COPD) has been focused largely on the antimicrobial

and anti-inflammatory effects of vitamin D and its ability to stimulate the innate immune response and ward off upper respiratory infections, thereby reducing the frequency of COPD exacerbations.³

In *The Lancet Respiratory Medicine*, Adrian Martineau and colleagues present the results of a double-blind, multicentre placebo-controlled trial of the effect of vitamin D₃ (colecalciferol) supplementation on exacerbations and upper respiratory tract infections in adults with COPD in London, UK.⁴ 240 participants with COPD (aged ≥ 40 years) were followed up every 2 months, by telephone or in person, over 1 year. Individuals in the intervention group were given an oral bolus dose of 3 mg (120 000 IU) of vitamin D₃ every 2 months. Martineau and colleagues enrolled



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