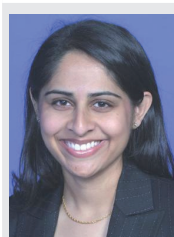


Symptom-adjusted therapy in asthma: it is time to listen to our patients

Expert Rev. Clin. Immunol. 7(3), 259–261 (2011)



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“...asthma continues to be treated suboptimally, probably because managing asthma according to the guidelines can be both complicated and cumbersome.”

Asthma is a complex disease and is often difficult to treat owing to its heterogeneity. Guidelines for asthma have been established [1,101], providing a standard management approach in order to offer higher quality treatment. Current guidelines primarily rely on inhaled corticosteroids (ICSs), which are known to be effective in controlling symptoms, improving lung function and preventing mortality. However, asthma continues to be treated suboptimally [2], probably because managing asthma according to the guidelines can be both complicated and cumbersome. Thus, there is a constant search for simpler methods to achieve asthma control.

Therapy tailored to each specific patient would be an ideal solution and several approaches have potential. Adjusting asthma treatments based on genetic polymorphisms is a promising research topic, but will probably require additional validation prior to broad utility in the clinical arena [3]. The use of biomarkers from sputum or exhaled breath condensates may add biologic information, but such techniques are labor intensive and difficult to implement in clinical practice. While exhaled nitric oxide (eNO) measurements may be easier to obtain in an office setting, the benefits of adjusting ICS dose by measuring eNO have not been robust or reproducible [4,5]. Furthermore, biomarkers may represent a moment in time, a ‘snapshot’, as opposed to asthma control over a period of months. Conversely, guideline-based therapy adjustment is hampered by the practical difficulty of incorporating all symptoms over a time interval. Furthermore, patients may be

reluctant to use, and physicians to prescribe, increased ICSs if currently asymptomatic, despite historical evidence of poor control. Improving adherence to medications is difficult, especially during asymptomatic periods. Hence, an attractive alternative option is to empower carefully selected patients to self-adjust ICS therapy to their acute needs. Over the last decade, several studies suggest that this option is viable with outcomes equivalent to daily ICS therapy.

“In carefully selected patients, temporal personalization of inhaled corticosteroid therapy provides control equivalent to standard guidelines, at a lower cost and with fewer side effects.”

The Improving Asthma Control (IMPACT) trial was a seminal evaluation of intermittent ICS use. In this three-group study, mildly asthmatic subjects were treated with a daily ICS, zafirlukast or placebo, plus intermittent ICS according to a symptom-based action plan [6]. Comparing daily ICS versus the intermittent ICS group revealed no significant difference in morning peak flow, frequency of exacerbations, quality of life or pulmonary function decline over 1 year among the groups. This study strongly suggested that well-selected mild asthmatics could be treated with ‘as-needed’ ICS when symptoms worsen, without undue concern that such patients may be undertreated.

Symptom-driven ICS adjustment in mild asthmatics was also examined in a randomized controlled trial by the BEST study group [7]. In this trial, the use of a single

rescue inhaler containing both ICS and a short-acting β_2 agonist (SABA) was compared with the standard therapy of daily ICS with rescue SABA. The primary outcomes, morning peak flow and exacerbations, were not significantly different to standard therapy. However, cumulative dose of ICS in the intermittent-use group was significantly less than in subjects allocated daily administration of ICS. The study concluded that the symptom-based use of this combination inhaler in mild asthmatics can be as effective as standard therapy, with a lower cumulative dose of ICS.

Several studies have demonstrated that, when added to a daily ICS or an ICS plus long-acting β_2 agonist (LABA) inhaler, use of combination ICS/LABA as rescue in moderate-to-severe asthmatics reduces frequency of asthma exacerbations in both children and adults [8–10]. The additional rescue ICS probably plays a significant role in these findings. This view is supported by other studies that suggest a short-term increase in ICS dose at the beginning of worsened symptoms is beneficial in preventing asthma exacerbations and improving long-term asthma control [11,12]. Of importance, the use of ICSs as rescue medications does not align with current US FDA policy.

The recently published TREXA study evaluated the use of ICSs with rescue in a randomized, double-blind, placebo-controlled trial in the pediatric population [13]. In mild asthmatic children who used placebo twice daily, the use of an ICS plus SABA as rescue therapy had a decreased frequency of exacerbation and treatment failure compared with those who used only a rescue SABA. Although the daily ICS group did lower exacerbation risk to a greater degree than the rescue ICS group, this effect was not significant. Cumulative ICS dose in the intermittent group was approximately 15–25% that of the children who used the daily ICS, and these patients lacked the 1.1-cm growth impairment noted in the daily ICS groups. Given these findings, the study concluded that use of an ICS coupled to a SABA as rescue therapy might be a practical step-down option for children with well-controlled mild asthma.

The most convincing evidence for symptom-based adjustment comes from the BASALT study, recently completed by the US Asthma Clinical Research Network and presented in abstract form, consisting of a 9-month double-blinded three-arm trial [14]. Adjustments of ICSs in mild-to-moderate adult asthmatics was based on current guidelines, biomarkers (including eNO) or patient symptoms. The novel findings in this study illustrated that there was

no difference in the primary outcome, treatment failure, among the three treatment groups, nor were exacerbations different. There was no difference among the three groups in symptom scores, quality-of-life measures or pulmonary function. Furthermore, number of days missed from work/school were fewer in the symptom-based adjustment group compared with those adjusted as per the guidelines, suggesting that for some important outcomes, symptom-based adjustment of ICS therapy may be superior.

Based on these studies, it seems worthwhile to suggest intermittent use of ICSs in appropriate patients, with usage initiated by the occurrence of symptoms sufficient to warrant rescue use of a SABA. This strategy would probably improve compliance since daily adjustments can be made by the patient depending on their current state. The previously discussed studies suggest that symptom-initiated ICS use produce similar asthma outcomes to those treated with daily ICS maintenance dosing. This strategy benefits healthcare providers by reducing severe exacerbations and thus, healthcare costs. Furthermore, symptom-based adjustment of ICSs results in a decreased overall ICS dose thereby reducing risks and costs of therapy.

Ideally, a combination inhaler with ICSs plus a SABA would be a convenient solution. However, current US regulatory guidelines do not support the symptom-based ICS use, so such a combination medication is unlikely to be approved for rescue; however, concomitant utilization of two approved medications does align with FDA policy and could also be implemented in Europe. This strategy of symptom-initiated use of ICSs provides temporal personalization of the asthma control regimen and appears to have a number of advantages to long-term healthcare, the physician and the patient. In carefully selected patients, temporal personalization of ICS therapy provides control equivalent to standard guidelines, at a lower cost and with fewer side effects. It is time to move towards this new model of asthma care.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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