REVIEW

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Add-on Therapy for Symptomatic Asthma despite Long-Acting Beta-Agonists/Inhaled Corticosteroid

Michael Dreher, M.D. and Tobias Müller, M.D.
Division of Pneumology, University Hospital RWTH Aachen, Aachen, Germany

Asthma, remains symptomatic despite ongoing treatment with high doses of inhaled corticosteroids (ICS) in conjunction with long-acting beta-agonists (LABA), is classified as "severe" asthma. In the course of caring for those patients diagnosed with severe asthma, stepping up from ICS/LABA to more aggressive therapeutic measures would be justified, though several aspects have to be checked in advance (including inhaler technique, adherence to therapy, and possible associated comorbidities). That accomplished, it would be advisable to step up care in accordance with the Global Initiative for Asthma (GINA) recommendations. Possible strategies include the addition of a leukotriene receptor antagonist or tiotropium (to the treatment regimen). The latter has been shown to be effective in the management of several subgroups of asthma. Oral corticosteroids have commonly been used for the treatment of patients with severe asthma in the past; however, the use of oral corticosteroids is commonly associated with corticosteroid-related adverse events and comorbidities. Therefore, according to GINA 2017 these patients should be referred to experts who specialize in the treatment of severe asthma to check further therapeutic options including biologics before starting treatment with oral corticosteroids.

Keywords: Asthma; Biological Products; Interleukin-5; Immunoglobulin E

Introduction

Regarding Global Initiative for Asthma (GINA) 2017 the definition of asthma is as follows: "Asthma is a heterogeneous disease, usually characterized by chronic airflow inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation"[1].

Despite adequate treatment some patients still have symptoms such as wheeze, chest tightness, shortness of breath and cough. In these patients a step up therapy is indicated to achieve asthma control. Asthma control has two domains: symptom control and minimize future risk of adverse outcomes like exacerbations, fixed airflow limitation or treatment side effects[1].

This article provides an overview of diagnostic and treatment strategies for patients still having symptoms despite treatment with an inhaled corticosteroid (ICS) in combination with long-acting beta-agonists (LABA). According to the European Respiratory Society/American Thoracic Society definition these patients fulfill the criteria for severe asthma[2]. However, before considering stepping up from ICS/LABA several aspects have to be checked including inhaler technique, adherence to therapy, and comorbidities as all these factors can be responsible for persistent symptoms.

Address for correspondence: Michael Dreher, M.D.
Division of Pneumology, University Hospital RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany
Phone: 49-241-8088763, **Fax:** 49-241-8082153
E-mail: mdreher@ukaachen.de
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Before Step-up Treatment in Symptomatic Patients

1. Check inhalation technique and improve inhaler technique

In patients on ICS/LABA who are still symptomatic the diagnosis of asthma should be reviewed as a misdiagnosis of asthma is common especially in primary care[3,4]. If the diagnosis of asthma is correct adherence to therapy should be addressed as this is an underestimated problem[5]. Incorrect inhaler technique has been identified as a major risk factor for poor asthma control and exacerbations[6]. However, incorrect inhaler technique is very common in clinical practice and has not improved over the past 40 years[7,8]. Of note a large proportion of health care professionals are unable to adequately demonstrate the correct use of inhalators to patients[9]. Therefore, new approaches for patient education are urgently needed and here, freely available web-based videos might be a successful tool to improve inhalation technique as these videos were easy to understand and effectively improved inhalation technique[10].

2. Assess for comorbidities

Modifiable risk factors and comorbidities should be addressed before stepping up asthma treatment[1]. Comorbidities may contribute to respiratory symptoms and impaired quality of life, and hence to poor asthma control. Therefore, detecting comorbidities which might impact on symptoms or even cause the latter is very important and should be reassessed every time an intensification of therapy is considered. Typical asthma related comorbidities are listed in Table 1. Those comorbidities should be treated appropriately in order to determine their respective influence on asthma and improve both, asthma symptoms and control[11].

Table 1. Example for (treatable) asthma-related comorbidities[11]

Comorbidity
Rhinitis/sinusitis/rhinosinusitis
Gastro-oesophageal reflux disease
Obesity
Obstructive sleep apnoea
Bronchiectasis
Allergic bronchopulmonary aspergillosis
Chronic obstructive pulmonary disease
Smoking/nicotine dependence
Psychopathologies
Vocal cord dysfunction
Nasal polypoids

3. Assess for sublingual allergen immunotherapy in patients sensitized to house dust mite

For adult patients with allergic rhinitis and a sensitization to house dust mite adding sublingual allergen immunotherapy (SLIT) might be an option to reduce exacerbation frequency. To date, it is not clear if symptoms can be improved as well. A recent study has shown that among adults with house dust mite allergy related asthma SLIT improved time to first moderate or severe asthma exacerbation during ICS reduction whereas there were no significant changes in asthma control questionnaire or asthma related quality-of-life questionnaire[12]. However, the only controller used in this trial was budesonide whereas ICS/LABA combinations were not allowed.

Step-up Treatment in Patients with ICS/LABA

Possible step up therapies in patients with ICS/LABA still having symptoms are: increasing the dose of ICS, add an leukotriene receptor antagonist (LTRA), add tiotropium, add low dose of oral corticosteroids, and assess eligibility for biologicals like omalizumab, mepolizumab, reslizumab, or other antibodies which might be available soon.

1. Increase ICS dose

Increasing the dose of ICS is an option in symptomatic patients already using ICS/LABA, though the benefit is often limited and this is associated with an increased risk for side effects[1,13]. In contrast, a recent study demonstrated improved pulmonary function and reduced need for systemic steroids in patients with oral steroid dependent asthma when high dose budesonide administered via a novel inhalation device was added to ICS/LABA[14].

2. Leukotriene receptor antagonists

LTRAs are less effective than ICS and, therefore should only be used for initial controller treatment for patients who are unwilling or unable to use ICS[1,15]. However, adding LTRA resulted in better asthma control and improved lung function in patients with inadequately controlled asthma despite ICS or ICS/LABA[16].

3. Tiotropium

In patients with poorly controlled asthma despite a standard combination therapy with ICS/LABA, tiotropium administered via Respimat significantly increased the time to first exacerbation and was associated with less symptoms and

improved lung function compared to placebo[17]. Therefore, tiotropium can be used as add-on therapy in patients with symptomatic asthma despite ICS/LABA and a history of exacerbations[1]. Of note the beneficial effects of tiotropium were independent of baseline characteristics such as age, degree of airway obstruction, or allergic status[18].

4. Biologicals versus oral corticosteroids

According to GINA 2017 the preferred option in step 5 should be the referral to a specialized center taking care of patients with severe asthma to check other treatment options including biologicals[1].

Adding low-dose oral corticosteroids is no more the preferred controller choice once a patient has persistent symptoms or exacerbations despite correct inhalation technique and good adherence to step 4 treatments due to the fact that oral corticosteroid-related adverse events are common in patients with severe asthma[19-21]. In a recent study, 93% of patients with severe asthma suffered from at least one oral corticosteroid related comorbidity[19]. Therefore, new treatments like biologicals which are able to reduce the use of oral corticosteroids are not only effective in improving lung function or reducing exacerbation frequency in severe asthma patients but might also be able to reduce oral corticosteroid related comorbidities.

1) Omalizumab

Omalizumab is a monoclonal antibody that binds and inhibits free serum IgE. Omalizumab is effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to inhaled steroids and during steroid tapering phases of clinical trials[22]. Omalizumab represents the first targeted therapy for patients with severe uncontrolled asthma; a decade of its use in clinical practice has shown that omalizumab is a safe and very effective therapy for patients with severe IgE-mediated allergic asthma[23]. Furthermore, increasing data are available for the use of omalizumab in severe non-atopic asthma though its use in non-atopic asthma is not recommended so far[24].

2) Mepolizumab

Mepolizumab is a humanized monoclonal antibody that binds to and inactivates interleukin (IL)-5, a cytokine which is the major maturation and differentiation factor for eosinophils. It is administered subcutaneously every 4 weeks and has been shown to reduce asthma exacerbations in patients with severe eosinophilic asthma and has a significant glucocorticoid-sparing effect. Furthermore, it improved control of asthma symptoms[25-27]. Therefore, it is recommended in patients with severe eosinophilic asthma that is uncontrolled on step 4 treatment[1].

3) Reslizumab

Reslizumab is another humanized anti–IL-5 monoclonal antibody. It disrupts eosinophil maturation and promotes programmed cell death. Reslizumab is administered intravenously every 4 weeks. In patients with severe eosinophilic asthma who are inadequately controlled reslizumab can significantly reduce the frequency of asthma exacerbations[28].

4) Benralizumab

Benralizumab is a monoclonal antibody directed against the alpha subunit of the IL-5 receptor leading to the depletion of eosinophils via antibody-dependent cell-mediated cytotoxicity[29]. Benralizumab has been shown to significantly reduce the incidence of asthma exacerbations in patients with severe asthma associated with eosinophilia. Furthermore, benralizumab administered subcutaneously either every 4 weeks or every 8 weeks has been shown to significantly reduce oral corticosteroid use while reducing exacerbation frequency[30,31].

5) Dupilumab

Dupilumab is a fully human monoclonal antibody that blocks to the alpha subunit of the IL-4 receptor thereby inbiting the biologic effects of the Th2 cytokines IL-4 and IL-13 and has been investigated in patients with asthma and blood eosinophilia. Dupilumab received its first global approval in March 2017 in the United States for the treatment of adults with moderate-to-severe atopic dermatitis[32]. Furthermore, dupilumab is under phase III development for the treatment of asthma and nasal polyposis as well as for atopic dermatitis in pediatric patients[32]. Dupilumab has been assessed in patients with uncontrolled persistent asthma irrespective of baseline eosinophil count; treatment with dupilumab was associated with improved lung function and a reduction in the number of severe exacerbations[33].

5. When to start/when to stop antibody treatment?

In the recent years, considerable progress has been made in the development of personalized medicine for patients with severe asthma, especially in those patients with eosinophilia. Various targeted biologicals have been investigated and some of them are clinically available in the meantime[34]. However, as these biologicals cannot cure asthma there is an urgent need for guidance when to start, when to switch between different biologicals and when to stop treatment. Recently, an expert task force has published a roadmap to consensus in severe eosinophilic asthma advising to firstly decide about (dis-) continuation of anti-eosinophilic treatment after 4 months. They advised to (1). continue treatment in super-responders; (2) to continue treatment for a year to assess response, or consider switching if response is low in intermediate responders; or (3) stop treatment in non-responders[34].

Conclusion

Before stepping up the treatment in asthma patients with symptoms despite ICS/LABA it is advisable to step back, and think about treatable but so far undetected comorbidities. Furthermore, it is absolutely mandatory to check treatment adherence as well as inhaler technique. This is suggested to be the mandatory standard work up in patients with symptomatic asthma despite ICS/LABA treatment.

If this standard work up has not identified treatable risk factors it is advisable to step up following the GINA recommendation. Here, adding tiotropium and/or a LTRA seems to be a reasonable first step as there are limited side effects. Furthermore, tiotropium has been shown to be effective in all investigated subgroups.

Since the administration of oral corticosteroids is commonly associated with corticosteroid-related adverse events and comorbidities, assessing for biologic add-on treatment is advised to be done before starting treatment with oral corticosteroids.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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