Asthma Exacerbations: Pathogenesis, Prevention, and Treatment

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Guideline-based management of asthma focuses on disease severity and choosing the appropriate medical therapy to control symptoms and reduce the risk of exacerbations. However, irrespective of asthma severity and often despite optimal medical therapy, patients may experience acute exacerbations of symptoms and a loss of disease control. Asthma exacerbations are most commonly triggered by viral respiratory infections, particularly with human rhinovirus. Given the importance of these events to asthma morbidity and health care costs, we will review common inciting factors for asthma exacerbations and approaches to prevent and treat these events. **(J Allergy Clin Immunol Pract 2017;5:918-27)**

Key words: *Asthma; Asthma exacerbation; Viral infection; Allergy; Prevention; Treatment; Inhaled corticosteroids; Long-acting β2-agonists; Leukotriene antagonist; Anticholinergics; Anti-IgE; Anti-IL5; Systemic corticosteroids*

Despite optimal guideline-directed treatment, and irrespective of underlying disease severity, patients with asthma experience exacerbations, which are caused by an accentuation of existing inflammatory processes and a loss of disease control.

Asthma exacerbations are a major cause of disease morbidity, increases in health care costs, and, in some patients, a greater progressive loss of lung function.[1] The frequency of exacerbations can be reduced, but not always fully prevented, with adequate inhaled corticosteroid (ICS) treatment or combination ICS/long-acting β-agonists (LABA).[2] Because asthma exacerbations can break through standard treatment regimens, identifying at-risk patients and having a plan of management can improve disease control and patient well-being.

Asthma exacerbations remain a major reason for health care utilization and a significant financial burden to patients and society. Patients with asthma exacerbations have significantly higher total health care costs, $9223 versus $5011 (2007 dollars) per person per year, and asthma-specific costs, $1740 versus $847 per person per year, compared with matched patients without exacerbations.[3] In 2007, total expenditures for asthma were estimated to be $56 billion per year with productivity losses due to morbidity and mortality of $3.8 and $2.1 billion, respectively.[4] Moreover, patients requiring an emergency department (ED) visit or hospitalization for asthma are at significantly increased risk for future exacerbations independent of demographic and clinical factors, asthma severity, and asthma control,[5] collectively reflecting an ongoing need to develop better strategies to prevent and treat these events.

PATHOGENESIS

Viral respiratory infections

The most common triggers for an exacerbation are viral respiratory infections with human rhinovirus (RV), particularly subtypes A and C,[6,7] most frequent. In school-age children, hospital admission rates for asthma exacerbations correlate with the seasonal increase of RV infections in September through December and again in the spring.[8] Similar asthma hospitalization peaks are observed in adults.[9]

Other respiratory viruses also may cause exacerbations. During the 2009 H1N1 influenza A pandemic, mortality and admissions to the intensive care unit with H1N1 infections were frequently associated with asthma.[10-12] Respiratory syncytial virus, a frequent cause of wheezing in infants and young children, may also trigger acute asthma in adults, particularly, patients older than 65 years.[13] Coronaviruses, human metapneumoviruses, parainfluenza viruses, adenoviruses, and bocaviruses have all been detected in asthma exacerbations, but in low frequencies.[14]

Patient risk factors

There are a number of susceptibility, or risk, factors that help to determine whether a viral respiratory infection causes an exacerbation (Figure 1).

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Abbreviations used
ED- Emergency department
FEV_1- Forced expiratory volume in 1 second
ICS- Inhaled corticosteroids
LABA- Long-acting β-agonist
RV- Rhinovirus
SABA- Short-acting β_2-agonist

Allergy and defective anti-viral immunity

Allergic sensitization is a risk factor for wheezing with RV infection, particularly in children. Whether allergic inflammation often found with sensitization increases the susceptibility for viral infections or enhances their ability to provoke further inflammation is not entirely clear.[16] Type I interferons are important innate antiviral responses to respiratory viruses.[14,17] There is evidence that virus-induced interferon generation from peripheral blood mononuclear cells,[18-20] plasmacytoid dendritic cells,[21] and bronchial epithelial cells[22,23] is reduced in some patients with allergic asthma (Figure 2). It has been show that IgE occupancy of their membrane receptors inhibits antiviral generation of IFN-α from plasmacytoid dendritic cells and may increase susceptibility to RV-induced wheezing and asthma exacerbations (Figure 3). Deficient immune responses to viral infections may be present in type 2 inflammatory conditions with interferon production being inversely correlated with increasing airway eosinophilia, IL-4 levels, and total serum IgE.[23] Finally, the use of inhaled IFN-β at the time of an upper respiratory infection reduces the airway viral load and improves clinical symptoms in patients with asthma.[24]

Bacterial infections

Bacterial infections may impair mucociliary clearance and increase mucus production in the lung and may cause chronic lower airway inflammation. Evidence linking bacterial infections to acute asthma exacerbations has been limited.[25,26] However, respiratory viruses may impair the antibacterial defenses by human alveolar macrophages and thereby facilitate emergence of bacterial infections or change in the microbiome.[27] How these interrelationships contribute to exacerbations is not established, but they may be of potential therapeutic importance[28] to prevent acute asthma.

Allergen exposure

Environmental allergens can provoke asthma.[29] Furthermore, more than 80% of children with asthma are sensitized to environmental allergens, with indoor allergens being especially important to underlying asthma.[30,31] Mast cell activation by allergens releases[32,33] histamine, prostaglandin D2, and cysteinyl leukotriene generation to cause airway smooth muscle constriction, increased microvascular permeability, mucus secretion, and enhanced inflammation. Allergic sensitization is also associated with diminished innate immune responses and may be a susceptibility factor to viral-induced wheezing. This allergen associated inflammation also increases airway responsiveness to RV[34] to further enhance a loss of asthma control.

Mold sensitization and their seasonal increase parallel greater asthma severity and seasonal exacerbations. Patients sensitized to *Alternaria alternata* were approximately 5 times more likely to have asthma[35] and increased airway responsiveness, wheeze, and bronchodilator use.[36] Emergency visits for asthma exacerbations correlate with high airborne concentrations of mold.[37] Finally,

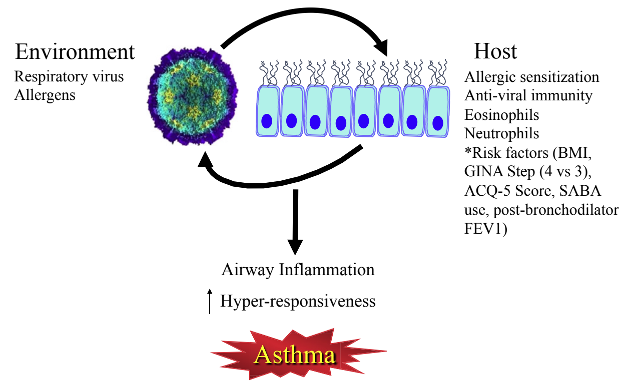


FIGURE 1. The interplay of the environment and host susceptibility factors in the pathogenesis of asthma exacerbations. Risk factors from Bateman et al.[15] *ACQ*, Asthma Control Questionnaire; *BMI*, body mass index; *FEV1*, forced expiratory volume in 1 second; *GINA*, Global Initiative for Asthma; *SABA*, short-acting β_2-agonist.

Alternaria sensitization was found to be associated with an approximate 200-fold increase in the risk of respiratory arrest in children and adults.[28,38]

Other contributing causes

Pollutants such as tobacco smoke, ozone, and particulate matter, along with occupational exposures, provoke asthma exacerbations. Tobacco smoke has also been implicated in the development of persistent wheezing[39] and greater asthma severity.[40] Hospitalizations and ED visits for asthma occur more frequently among cigarette smokers.[41]

Particulate matter, ozone, nitrogen dioxide, sulfur dioxide, and diesel exhaust can increase airway inflammation and airway responsiveness.[32,33,42] Airway pollutants, together with a viral infection, may act synergistically to cause asthma exacerbations. The severity of lower respiratory tract symptoms increased and peak expiratory flow measurements fell with rising exposure to nitrogen dioxide in the week before a respiratory infection.[33]

Prevention of exacerbations

Four essential components of asthma management include patient education, monitoring of symptoms and lung function, control of triggering factors and comorbid conditions, and pharmacologic therapy. Patient education on asthma decreases exacerbations and improves control.[43,44] However, because asthma severity varies and differs among individuals and age groups, it is essential to regularly monitor the effectiveness of asthma control to guide necessary treatment adjustments.

The Expert Panel Report 3 and Global Initiative for Asthma describe a stepwise treatment approach and strategy to reduce impairments and prevent future risks like asthma exacerbations.[45,46]

TREATMENTS

Inhaled corticosteroids

ICS improve disease control and reduce asthma exacerbations.[47-49] In new onset, untreated persistent, asthma, low-dose inhaled budesonide reduces asthma exacerbations by almost 50%.[50,51] In asthmatic patients already taking moderate doses of

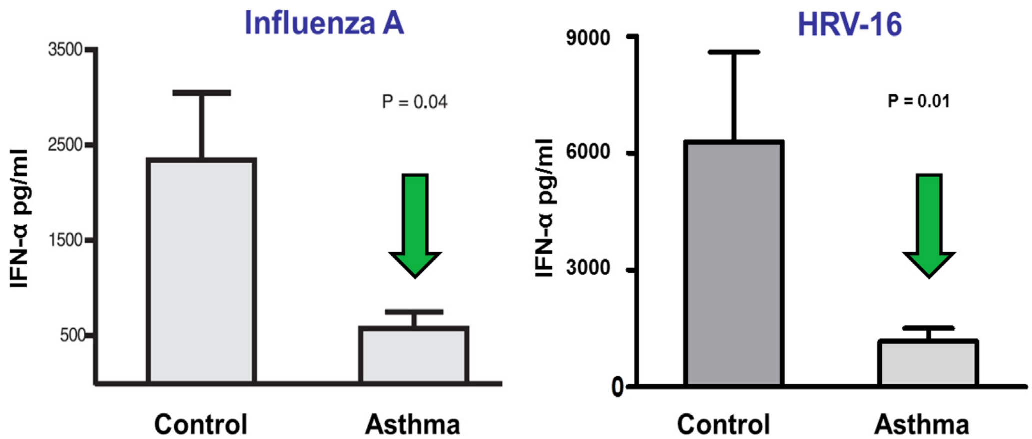


FIGURE 2. Impaired plasmacytoid dendritic cell (pDC) IFN-α response in patients with allergic asthma. pDCs from patients with physician-diagnosed asthma and allergic sensitization secreted less IFN-α on exposure to viruses compared with patients without asthma. Reproduced with permission from Gill et al.[21]

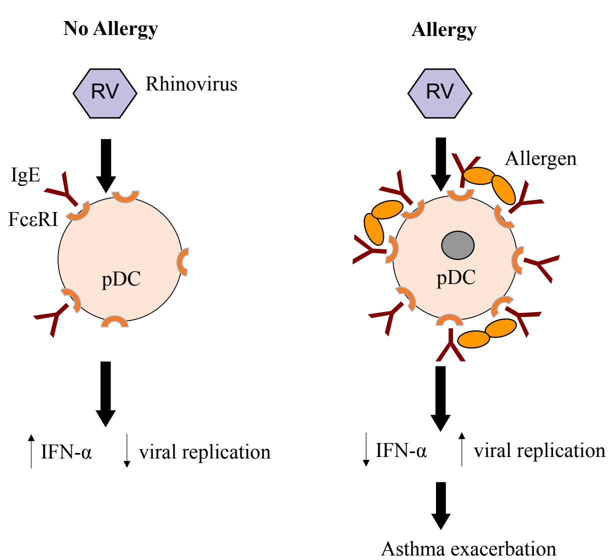


FIGURE 3. Effect of high-affinity IgE receptors (FcεRI) on plasmacytoid dendritic cells (pDCs) and antiviral immunity. In the absence of allergy, pDCs express low levels of cell surface FcεRI, some occupied by IgE. Rhinovirus (RV) infection induces secretion of interferon, thereby inhibiting viral replication. In the presence of allergen and allergic sensitization, FcεRI and IgE are increased, and cross-linking of IgE receptors by allergen can inhibit interferon secretion, resulting in increased viral replication, and an increased risk of asthma exacerbation.

ICS but under poor control,[50] Pauwels et al showed that high-dose budesonide further reduced severe asthma exacerbations, that is, need for systemic corticosteroids, by nearly 50% compared with treatment with low-dose ICS in adults.[50] However, as found by O'Byrne et al,[51] a doubling of the budesonide dose in patients poorly controlled on low-dose ICS also reduced exacerbation rates by 30%, but the degree of protection was less than those patients who recently started ICS. These findings indicate that dose-response benefits with ICS are relatively flat.[52] Overall, compared with placebo or a short-acting β_2-agonist, ICS reduce clinically relevant exacerbations by nearly 55%.[53] ICS also reduce exacerbations in children[54] and are superior to a leukotriene antagonist, montelukast.[55]

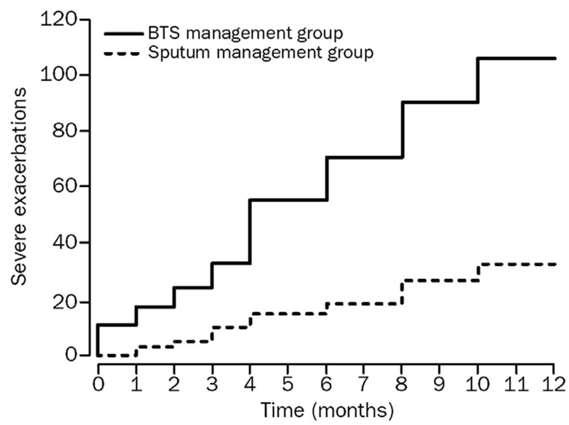
For patients with diminishing asthma control, quadrupling the recommended dose of ICS decreases the likelihood of an asthma exacerbation.[56] This protection does not occur with a doubling of the ICS maintenance.[57,58] However, the benefit of using an increase in ICS is time dependent to increased symptoms and need to be started early in the course of a cold. If higher doses of ICS are used pre-emptively at the onset of a respiratory tract infection and continued for 10 days, the need for oral corticosteroids is reduced.[59]

The mechanisms by which ICS prevent virus-induced exacerbations, beyond anti-inflammatory activity, are poorly understood. ICS can reduce the number of airway eosinophils that presumably reflect enhanced inflammation with a respiratory infection.[60,61] As approximately 50% of asthma exacerbations are associated with an increase in airway eosinophils, these cells are a reasonable target.[62] This concept is substantiated by studies showing that a reduction in airway eosinophils significantly diminishes exacerbations (Figure 4),[63,64] but this approach does not eliminate all exacerbations, particularly for patients with more severe asthma.[65,66] Furthermore, as airway neutrophils increase early in asthma exacerbations,[67] ICS treatment has no effect on these cells and alternative approaches will be needed.[68]

Inhaled corticosteroids and long-acting β-agonists

In patients with poorly controlled asthma and a history of prior asthma exacerbations, the combination of budesonide and formoterol significantly reduces asthma exacerbations compared with ICS alone.[50] ICS/LABA have consistently been shown to prevent exacerbations.[69-71] The benefit of ICS/LABA to prevent exacerbations versus ICS alone is primarily seen in patients requiring higher doses of ICS, thus suggesting that combination therapy to prevent exacerbations should be reserved for patients with more severe disease.

Asthma control can vary even in the face of ongoing ICS/LABA treatment. Consequently, the use of ICS/LABA combinations both for maintenance and symptom relief has been investigated and shown to reduce exacerbations.[72-74] These



Number of exacerbations

BTS group	0	12	19	26	35	59	75	93	109
Sputum group	0	1	4	7	12	17	21	30	35

FIGURE 4. Cumulative asthma exacerbations in the British Thoracic Society (BTS) asthma guidelines management group versus the sputum management group. There were significantly less asthma exacerbations in the sputum management group (35 vs 109; $P = .01$), where inhaled corticosteroid dose was titrated to normalize induced sputum eosinophil counts and reduce symptoms. Reproduced with permission from Green et al.[63]

benefits are also seen in children with a prior history of severe asthma exacerbations and poorly controlled moderate-to-severe persistent asthma despite the use of moderate doses of ICS.[75] The use of ICS/LABA as maintenance and reliever treatment should be restricted to formoterol because of its quick onset of action,[76] safety profile,[77] and dose-response effect.[78]

How the addition of LABA to ICS reduces asthma exacerbations remains unclear as LABA do not affect inflammation. ICS/LABA, however, attenuate allergen-induced airway eosinophilia and lung function changes to a greater extent than ICS alone.[79] Edwards et al[80] demonstrated that combination treatment synergistically suppressed induction of rhinovirus-generated chemokines in bronchial epithelial cells. Thus, the synergistic benefits of both ICS and LABA on airway eosinophilic inflammation might explain a greater reduction in exacerbations. Alternatively, an early use of ICS/LABA for relief of symptoms might simply deliver additional ICS to the airway early in the course of an emerging exacerbation.

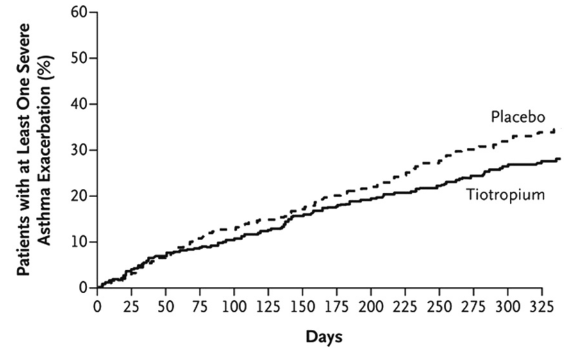
Leukotriene antagonists

Antileukotrienes reduce asthma exacerbations in children[72,81] and adults.[82,83] Montelukast reduced asthma exacerbations to RV infections that occurred on return to school in September.[81,84] In a systematic review and meta-analysis, compared with placebo, leukotriene modifiers/receptor antagonists lowered exacerbation rates by 41% but were inferior to ICS.[53]

Adding montelukast to inhaled budesonide was as effective as doubling the dose of inhaled budesonide, with no difference in exacerbation rates and asthma free days.[85]

Tiotropium

The anticholinergic tiotropium reduces the frequency of asthma exacerbations and is FDA-approved for long-term, maintenance treatment for patients 6 years of age and older with persistent asthma, that is uncontrolled with ICS plus one or



No. at Risk														
Placebo	454	435	412	338	379	367	356	339	332	319	303	290	282	272
Tiotropium	453	430	409	401	389	378	363	353	348	339	331	319	308	298

FIGURE 5. Cumulative number of severe exacerbations in patients with severe asthma on inhaled corticosteroid/long-acting β-agonist treated with the addition of tiotropium versus placebo. There was a 21% risk reduction in asthma exacerbations (hazard ratio, 0.79; $P = .03$ in pooled analysis) for the tiotropium group. Reproduced with permission from Kerstjens et al.[86]

more controllers. In 2 replicate trials with a total of 912 adult patients with severe asthma and using ICS/LABA, adding tiotropium, 5 mcg, increased the time to first exacerbation by 56 days over placebo, and reduced exacerbations by 21% (Figure 5).[86] In a systematic review of 13 randomized placebo-controlled trials,[87] tiotropium decreased rates of exacerbations and improved asthma control in patients with moderate symptomatic asthma already receiving medium-to-high doses of ICS or ICS/LABA. Studies in children aged 6 to 11 years demonstrate improvements in forced expiratory volume in 1 second (FEV_1) but not reductions in exacerbations, likely due to the short duration of the study.[88] However, given that decreases in the FEV_1/forced vital capacity ratio are associated with an increased risk of exacerbations,[89] improvements in FEV_1 with tiotropium may be associated with reduced exacerbations in children.

Environmental control

The benefit from environmental control measures to prevent exacerbations is limited. Perhaps, this is because environmental interventions usually focus on a single allergen, such as dust mites,[90] or environmental tobacco smoke,[91] and with this limited approach, no effect was seen on asthma morbidity. However, an Inner-City Asthma Study evaluated the effectiveness of a multifaceted, home-based, environmental intervention that used remediation of exposure to dust mites, passive smoking, cockroaches, pets, rodents, and mold[92] and was tailored to each child's skin-test sensitization profile and environmental exposures. The intervention group reported significantly fewer symptoms of asthma during both the intervention year and, interestingly, the follow-up year as well (Figure 6), with significantly fewer unscheduled asthma-related visits to the ED or clinic for the intervention group ($P = .04$). The correlation between the reduction in levels of cockroach allergen on the bedroom floor and asthma-related morbidity was particularly strong during the active intervention. Although it is difficult to generalize these results to all children with asthma, a reduction in continuous exposure to environmental allergens and irritants, like those present in the homes of inner-city patients with

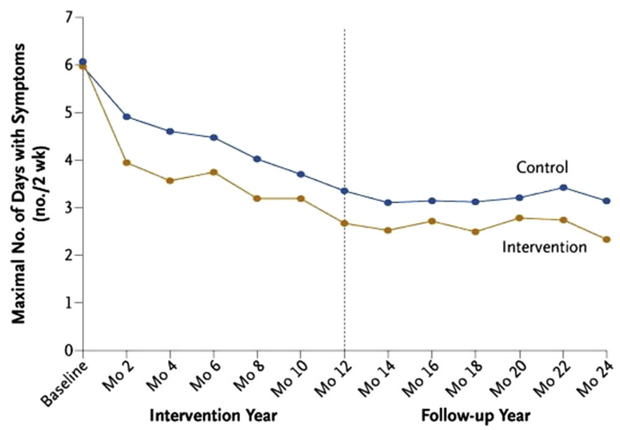


FIGURE 6. Mean maximal number of days with symptoms for every 2-week period before a follow-up assessment during the intervention year and follow-up year. The Inner-City Asthma Study evaluated the effectiveness of a multifaceted, home-based, environmental intervention for inner-city children with asthma. The difference between the 2 groups was significant in both the intervention year ($P < .001$) and the follow-up year ($P < .001$). Reproduced with permission from Morgan et al.[92]

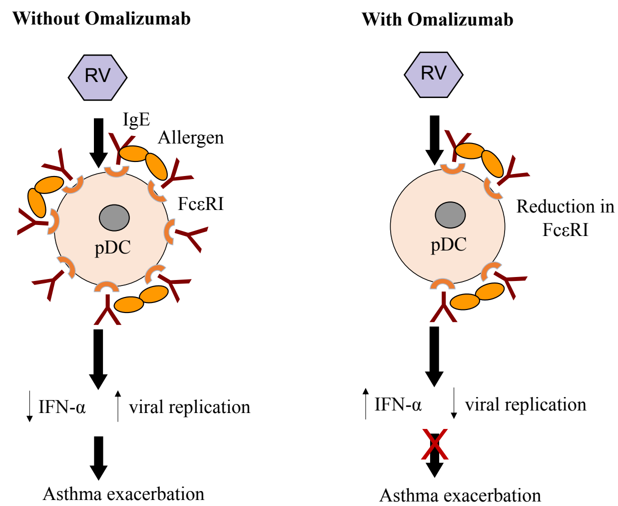


FIGURE 7. Effect of omalizumab on IgE-mediated functions in virus-provoked asthma exacerbations. *FcεRI*, High-affinity IgE receptor; *pDC*, plasmacytoid dendritic cell; *RV*, rhinovirus.

asthma, may indicate the need for a more comprehensive intervention.

TARGETED BIOLOGIC THERAPY

Anti-IgE (omalizumab)

Omalizumab is approved for use in patients 6 years of age and older with allergies and uncontrolled, persistent asthma despite moderate-to-high dose ICS. Omalizumab is a humanized monoclonal antibody directed against IgE and reduces the risk for asthma exacerbations in allergic asthmatic patients.[93-97] Omalizumab reduces asthma exacerbations when given with ICS[97] and shortens the duration of exacerbations[98] in adults and children.[99-101]

Some patients with asthma and allergy have a diminished interferon response to an *in vitro* challenge with respiratory viruses, and this reduction is related to IgE. In a study of inner-city children,[99] omalizumab reduced seasonal exacerbations in the fall and spring, without altering the rates of infections with respiratory viruses, suggesting that omalizumab may not prevent viral infections, but rather modify the consequences of the infection. Teach et al[20] showed that omalizumab improved antiviral defenses by increasing release of IFN-α from peripheral blood mononuclear cells to RV stimulation; in those subjects with a greater restoration of IFN responses, fewer exacerbations occurred (Figure 7). Thus, in addition to anti-inflammatory effects of omalizumab, a restoration of antiviral activity may prevent exacerbations.

Selecting patients most likely to benefit from omalizumab has been difficult. In a *post hoc* analysis, patients with elevated levels of fractional exhaled nitric oxide, blood eosinophils, and serum periostin, likely reflecting greater T2 inflammation, had a greater likelihood of benefitting from omalizumab.[102,103]

Anti-IL-5

Two anti-IL-5 monoclonal antibodies, mepolizumab and reslizumab, are approved as maintenance therapy for patients with uncontrolled, persistent eosinophilic asthma with an exacerbation phenotype despite high-dose ICS. IL-5 contributes to airway eosinophilic inflammation. Approximately 40% to 50% of patients with difficult-to-control asthma have persistent airway eosinophilia despite treatment with high-dose ICS. Although elevated sputum eosinophil counts predict the risk for asthma exacerbations, the use of sputum for routine measurements is impractical in clinical practice. Price et al[104] found a relationship between the intensity of peripheral blood eosinophilia and asthma-related outcomes; patients with asthma with blood eosinophil counts greater than 400 cells/μL experience more frequent severe exacerbations, and serves as a convenient biomarker for anti-IL-5 therapy.

Mepolizumab, given subcutaneously, reduces exacerbations by approximately 50% in patients with severe asthma who have blood eosinophil counts 150 cells/μL or greater (Figure 8).[65,66,105,106] It has been FDA-approved for add-on maintenance treatment of severe asthma in patients 12 years of age or older. Although clinical trial data suggest that efficacy requires an absolute eosinophil count of at least 150 cells/μL,[107] the National Institute for Health and Care Excellence recommends a threshold of 300 cells/μL. Reslizumab is also FDA-approved for add-on maintenance therapy of severe asthma in patients 18 years or older who have an eosinophil count of 400 cells/μL or higher. In clinical trials, intravenous reslizumab reduced asthma exacerbations by approximately 50%.[108,109]

RV infections lead to the generation of IL-5 and an increase in airway eosinophils, which correlate with exacerbation probability.[110] These relationships provide a probable explanation for why anti-IL-5 mAb treatment reduces asthma exacerbations.

Other biologics to prevent asthma exacerbations are under study.

TREATING EXACERBATIONS

Despite optimal maintenance therapy and asthma control, exacerbations occur. Therefore, early recognition and intervention are important to successfully stabilize asthma. A limited

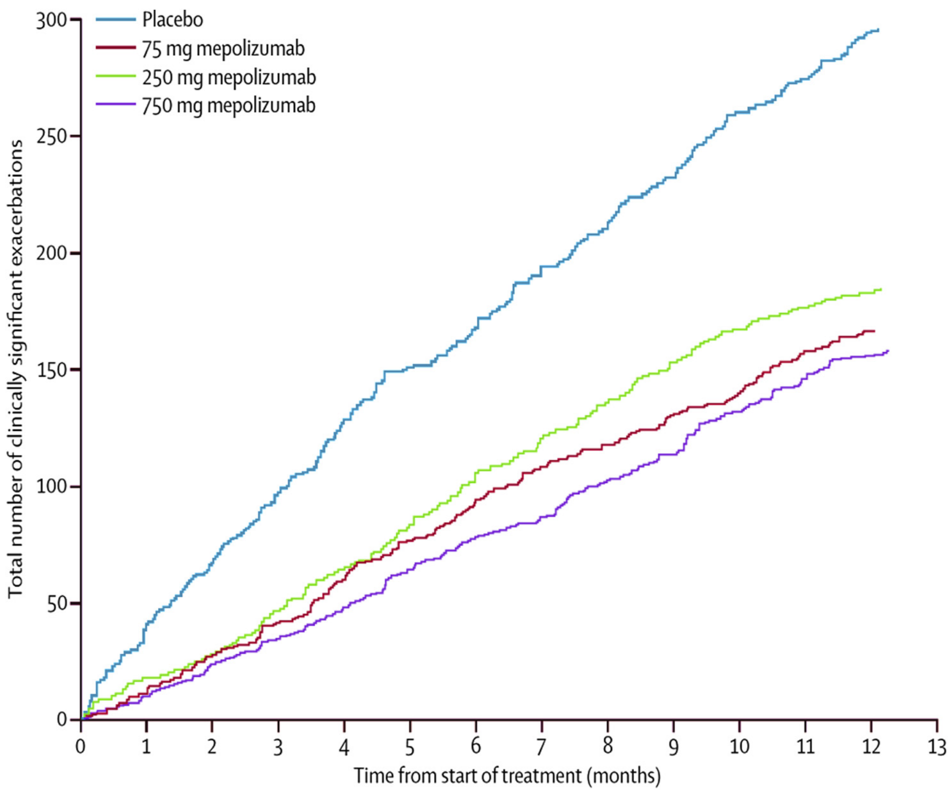


FIGURE 8. Reduction in the cumulative number of asthma exacerbations with mepolizumab versus placebo. Reproduced with permission from Pavord et al.[105]

number of treatments are currently available to alleviate asthma exacerbations, and the evidence supporting their use has limits.

Short-acting β2-agonists

Inhaled or nebulized short-acting β_2-agonists (SABAs), such as albuterol or levalbuterol, resolve acute symptoms of asthma and can initially be used every 15 to 20 minutes for the first hour during acute asthma.[107] Levalbuterol, the R-enantiomer of albuterol, and albuterol are equivalent.[111-113] Data are conflicting whether continuous nebulization with a SABA is superior to intermittent nebulization.[114,115] In very severe asthma exacerbations, continuous nebulization should be considered based on evidence of reduced admissions and improved pulmonary function.[114,116-118] SABAs provide symptomatic relief but have no effect on airway inflammation or sustained benefit.

Ipratropium bromide

Adding ipratropium bromide to an inhaled SABA in severe exacerbations decreases rates of hospitalizations and shortens ED stays for patients with severe or moderate-to-severe asthma exacerbations.[119-121] The benefit of ipratropium bromide to SABA therapy is seen primarily in more severe asthma exacerbations.[120,122]

Corticosteroids

An underlying component of exacerbations is an increase in airway inflammation.[103] Numerous studies evaluated ICS and oral corticosteroids (OCS) in asthma exacerbations, but the evidence for their efficacy remains limited. Moreover, because ICS often do not prevent exacerbations, it is unlikely that an increase in inflammation with an exacerbation will be fully responsive to corticosteroids. Nonetheless, their use is a reasonable and expected first step.

Inhaled corticosteroids. The administration of high-dose ICS for asthma exacerbations should be reserved for patients with mild or intermittent asthma and those unable to tolerate OCS because of side effects such as diabetes or psychiatric effects. A systematic review analyzed 8 studies comparing the efficacy of ICS with placebo in acute asthma exacerbations and found that ICS appeared superior to placebo, especially when given at high doses, that is, >1 mg of budesonide or fluticasone.[123] However, patients in these studies were heterogeneous in severity, ICS dose and administration frequency, and outcomes measured. The role of ICS for asthma exacerbations remains to be established.

Comparisons between ICS and systemic corticosteroids have also been conflicting. OCS were superior to ICS in reducing hospital admission rates in some studies[124-126] and others showed superiority of ICS.[127] A systematic review of 12 trials concluded that there was no benefit to the addition of ICS to systemic corticosteroids in reducing the relapse rate of acute asthma.[128] At present, insufficient evidence exists to support using ICS rather than OCS for exacerbations.

Systemic corticosteroids. Early administration of systemic corticosteroids for the treatment of acute exacerbations is standard guideline management with beneficial effects of systemic corticosteroids usually delayed for approximately 4 hours.[129] Systemic glucocorticoids accelerate the rate of improvement when persistent airflow obstruction exists despite bronchodilator treatment.[130] However, an evidence-based evaluation reported neither an improvement in airflow obstruction nor reduction in hospitalization rates with systemic corticosteroids.[112] In contrast, a systematic review by Rowe et al[113] concluded that the use of systemic corticosteroids in adults and children reduces the rate of hospital admission in ED treatment settings, especially in patients with severe asthma and those not currently receiving corticosteroids.

The optimal dose for systemic corticosteroids in asthma exacerbations also remains to be convincingly established. Doses above 2 mg/kg, or 60-80 mg/day, do not add benefit to improving pulmonary function, rates of hospital admission, or length of hospital stay.[131,132] Furthermore, no differences are found between oral and intravenous administration of comparable doses.[133,134]

Prescribing a short course of oral corticosteroids after ED treatment of acute asthma exacerbations reduces the rate of relapse.[113] Although the duration of therapy is not fully established, courses longer than 5 days did not provide additional benefit.[135,136] There is also no benefit from using a dose taper over a fixed-dose regimen and stopping.[122] Difficulties, however, arise in assessing approaches to treating exacerbations in patients already taking systemic corticosteroids. Optimal exacerbation treatment strategies for this patient population remain undefined and reflect the need for more targeted therapy.

A single dose of benralizumab, an anti-IL-5 receptor monoclonal antibody, reduces the rate and severity of subsequent exacerbations when given at the time of an initial exacerbation.[137] Thus, biologic therapy may also be beneficial in the acute treatment of asthma exacerbations to prevent subsequent events.

CONCLUSIONS

Asthma exacerbations can be prevented with ICS, ICS/LABA, and biologics in some patients. Exacerbations are more frequent in patients with severe disease and preventative strategies with biologics, such as anti-IgE and anti-IL-5, are seen. When exacerbations occur, systemic corticosteroids remain the primary intervention when bronchodilator therapy is not effective, but the evidence for their benefit has limitations. Prevention of exacerbations remains a major unmet need in asthma management. An improved understanding of the pathogenesis of asthma exacerbations will likely lead to new strategies to prevent and treat asthma exacerbations.

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