Respiratory Medicine (2006) **100**, 1139–1151

respiratoryMEDICINE

REVIEW

Uncontrolled asthma: A review of the prevalence, disease burden and options for treatment

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Received 14 November 2005; accepted 24 March 2006

KEYWORDS
Asthma;
Anti-IgE;
Omalizumab;
Inhaled corticosteroids;
Long-acting β_2-agonists

Summary An estimated 300 million people are affected by asthma worldwide and the burden is likely to rise substantially in the next few decades. Estimates of the prevalence of asthma range from 7% in France and Germany to 11% in the USA and 15–18% in the United Kingdom. Approximately 20% of these patients have severe asthma, of which 20% is inadequately controlled. Patients with inadequately controlled severe persistent asthma are at a particularly high risk of exacerbations, hospitalization and death, and often have severely impaired quality of life. Current management of asthma focuses on a stepwise approach tailored to disease severity. In addition to needing high-dose inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABAs), patients with severe persistent asthma often require additional controller medications, such as anti-leukotrienes, oral LABAs, oral corticosteroids and/or anti-IgE therapy. There is currently little evidence on which to base treatment decisions in patients with inadequately controlled severe persistent asthma already treated with ICS and LABAs. The anti-IgE monoclonal antibody omalizumab is the most recent addition to the list of treatment options for these patients and has been shown to reduce exacerbations and emergency visits and improve lung function, symptom scores and quality of life in patients with difficult-to-treat asthma whose symptoms remain inadequately controlled despite receiving ICS and LABAs. Comparative trials are needed to determine the merits of different treatments and strategies for patients with inadequately controlled severe persistent asthma and to identify patients likely to benefit from new treatment options.

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doi:10.1016/j.rmed.2006.03.031

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Introduction

Asthma affects 300 million people worldwide and is predicted to affect an additional 100 million people by 2025.[1] It causes approximately 239,000 deaths per year (0.4% of all deaths due to disease)[2] and results in a large burden of disability, accounting for a similar number of disability adjusted life years (DALYs) as osteoarthritis, cirrhosis, diabetes and schizophrenia.[1,2]

Inadequate control of asthma continues to present a serious problem, despite advances in our understanding of the inflammatory basis of asthma and a growing acceptance of disease management guidelines. Patients with inadequately controlled asthma often have limited therapeutic options and remain at a high risk of serious morbidity and mortality.[3–5] In this review, we will discuss current strategies for controlling asthma, describe the causes and consequences of inadequate control, and evaluate new options for improving asthma control.

Asthma control: guidelines and definitions

Global Initiative for Asthma (GINA) guidelines classify asthma severity into four steps according to clinical features before treatment, as well as by the daily medication regimen and the response to treatment (Fig. 1).[3,4] Thus, asthma is classified as intermittent, mild persistent, moderate persistent or severe persistent according to clinical features (Fig. 1). Treatment should be tailored to asthma severity. For example, patients with intermittent asthma should receive a rapid-acting inhaled β_2-agonist while those with mild persistent asthma should also receive a low-dose inhaled corticosteroid (ICS). Patients with moderate or severe asthma should receive inhaled long-acting β_2-agonists (LABAs) coadministered with an ICS (LABAs should never be used as monotherapy for the treatment of asthma).

The GINA guidelines define control of asthma as minimal chronic symptoms, minimal (infrequent)

	Current treatment step			
	Step 1 No controller	**Step 2** <500 µg BDP	**Step 3** 200–1,000 µg BDP + LABA	**Step 4** >1,000 BDP µg + LABA ± other
Clinical features				
Step 1 Symptoms <1 x week Nocturnal symptoms ≤2 x month Lung function normal between episodes	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Step 2 Symptoms >1 x week Nocturnal symptoms <1 x month Lung function normal between episodes	Mild persistent	Moderate persistent	Severe persistent	Severe persistent
Step 3 Symptoms daily Nocturnal symptoms ≥1 x week FEV_1 60–80% predicted	Moderate persistent	Severe persistent	Severe persistent	Severe persistent
Step 4 Symptoms daily Frequent nocturnal symptoms FEV_1 <60% predicted	Severe persistent	Severe persistent	Severe persistent	Severe persistent

Figure 1 GINA guidelines for the classification of asthma severity.[3]

exacerbations, no emergency visits, minimal use of as-needed (rapid-acting) β_2-agonists, no limitations on activities, daily peak expiratory flow (PEF) variation of less than 20%, near normal PEF and minimal adverse effects from medications.[3,4] In the stepwise approach to therapy recommended in the GINA guidelines, treatment should progress to the next step if control is not achieved or is lost with the current treatment and the patient is using medication correctly. Thus, a patient with mild persistent asthma despite step 2 treatment should be treated using step 3, proceeding to step 4 if control is still not achieved.

The response to treatment is also incorporated in various other terms used to categorize asthma at the severe end of the spectrum. For example, the European Respiratory Society (ERS) adopted a concept of 'difficult/therapy-resistant asthma' for patients whose asthma is not controlled despite high-dose ICS.[5] Adult patients are defined as having difficult/therapy-resistant asthma if their symptoms remain uncontrolled despite daily ICS doses in excess of 2000 μg beclometasone dipropionate (BDP), 1600 μg budesonide, 1000 μg fluticasone or equivalent. In children, the dose thresholds above which asthma is considered difficult to treat are 800 μg of BDP, 800 μg of budesonide or 400 μg of fluticasone.

The American Thoracic Society (ATS) describes 'refractory' asthma as encompassing several subgroups of patients with asthma that is severe, corticosteroid dependent/resistant, difficult to control, brittle or irreversible.[6] Patients with refractory asthma are those who require high doses of controller and reliever medications to maintain symptom control, or who have persistent symptoms, exacerbations or airflow obstruction despite near continuous high-dose medication use. They also have at least two of the following features: need for additional daily controller medication; need to use a short-acting inhaled β_2-agonist daily or near-daily; persistent airway obstruction (forced expiratory volume in 1 s (FEV_1) $<$ 80% predicted and PEF variability $>$ 20%); one or more urgent care visits per year; three or more oral steroid 'bursts' per year; prompt deterioration with reduction in steroid dose; or a near-fatal asthma event in the past.

Pathologic (airway and bronchoalveolar lavage) studies of severe asthma suggest that one-half to two-thirds of patients with severe asthma have persistent airway tissue eosinophilia, despite receiving high-dose oral and ICSs.[7] The presence of eosinophils (as measured by sputum, lavage, biopsy or exhaled nitric oxide) may represent another subtype of severe asthma, characterized by a higher level of active symptoms, reduced FEV_1 and a greater likelihood of exacerbations and near-fatal events occurring than in a subtype without eosinophils.[8] Differentiation by presence or absence of eosinophils has been applied to early and late-onset severe asthma, with indication for both similarities and differences in the eosinophilic process dependent on age onset.[9] In some, but not all, cases where eosinophils are absent there may be an increase in neutrophils. The increase in neutrophils does not always accompany the absence of eosinophils, and the two cell types may be concomitantly present in tissue.[8,10] The mechanisms or clinical implications for this neutrophilic inflammation are unclear.

Co-morbid risk factors for severe asthma

Certain co-morbidities are associated with severe or difficult-to-manage asthma.

Asthma co-exists with rhinitis in a large proportion of patients and epidemiological studies have estimated that the majority of patients with asthma (60–80%) also have rhinitis, with 20–40% of patients with rhinitis also having asthma.[11–13] A recent study conducted in the United Kingdom found that adults with asthma and documented concomitant allergic rhinitis experienced significantly more asthma-related hospitalizations and GP visits as well as incurring higher asthma-related drug costs compared with adults with asthma alone.[14] The high frequency of co-morbidity of rhinitis and asthma and the similarity of their epidemiological, pathological and physiological features have resulted in recommendations for a common approach to management.[15] Indeed, effective rhinitis management has been shown to improve asthma control[16] and two recent studies have shown that treating allergic rhinitis, particularly with intranasal steroids, confers significant protection against asthma exacerbations that result in emergency department visits for asthma.[17,18]

Gastroesophageal reflux disease (GERD) affects approximately 20% of adults in the United States on a weekly basis and 40% on a monthly basis.[19] GERD is also a trigger for asthma and the prevalence of GERD is higher in patients with asthma when compared with control groups, with 77% of asthma patients having reflux symptoms and 82% of asthmatics having abnormal esophageal acid contact times on 24-h esophageal pH testing.[19] Esophageal acid elicits respiratory responses including decreases in airflow, oxygen saturation, and increases in respiratory resistance, minute ventilation and

respiratory rate. Additionally, therapy of GERD improves asthma outcomes: in combined studies examining 326 asthma patients receiving drug therapy for GERD, asthma symptoms improved in 69% of these patients while surgical therapy trials to alleviate symptoms of GERD in 417 asthma patients showed that asthma symptoms improved in 79% of patients.[19]

A number of environmental factors have been shown to be associated with the onset of asthma. These include exposure to tobacco smoke, allergen sensitization, viral infection, occupational agents and air pollutants.[4] While these factors can precipitate exacerbations and prolong symptoms, their role in the development of severe asthma is not known. Aspirin and related drugs are more likely to act as specific triggers for asthma symptoms in susceptible individuals rather than being responsible for the development of asthma. However, the symptoms provoked by aspirin are often severe and patients with aspirin-sensitive asthma account for a substantial proportion of life-threatening exacerbations.[20]

Obesity has also been shown to be associated with asthma,[21] but it seems that asthma may predispose to later weight gain rather than vice versa, and a common other factor such as depression during critical periods of early life may be involved.[22] A link with severe disease has not been clearly established.

Increased stress is not only known to trigger worsening symptoms and exacerbations[23] but may also be associated with the development of asthma and atopy, possibly as early as in utero.[24] Possible pathways by which stress may exert an effect include neuroimmunoregulation and oxidative stress pathways.[24] Although asthma is not itself a psychosomatic condition, people with severe asthma are prone to anxiety and depression that can result in non-adherence to medication regimens and thus loss of asthma control.[25]

Prevalence and control of asthma

It is important to distinguish between the severity of asthma and the degree of control.[26] Severity can be used to describe the underlying nature or intensity of asthma in the absence of treatment. In patients receiving treatment, asthma severity can be estimated from the minimum level of treatment required to achieve good control and the intensity of exacerbations while on appropriate controller therapy. Asthma severity and control are distinct terms and it is important to note that patients with severe asthma can have good control, while patients with mild asthma can have poor control. The level of asthma control is particularly important to patients as it impacts directly on quality of life, while physicians need to determine the degree of control in order to decide whether treatment adjustments are required.

The recent European Community Respiratory Health Survey (ECRHS) estimated that 4.5% of people aged 20–44 years had asthma.[27] The overall prevalence of asthma in adults and children varies between countries, with estimates of 7% in France and Germany, 11% in the USA and 15–18% in the United Kingdom.[1]

A survey of 2803 European patients showed that asthma is frequently poorly controlled and that levels of control do not meet the goals of the GINA guidelines.[28] Forty-six percent of patients reported daytime symptoms and 30% had asthma-related sleep disturbances at least once a week. In the past year, 25% of patients with asthma had an unscheduled urgent care visit, 10% had an emergency room visit and 7% had an overnight hospitalization. Similarly, a survey of 7786 adults and 3153 children with asthma in Europe, North America and Asia showed that many patients failed to meet one or more of the GINA goals.[29] The GINA goal of minimal chronic symptoms was not met in a large percentage of patients, with 45–84% of patients having daytime symptoms and 33–70% having night-time awakenings during the previous 4 weeks. In addition, many patients did not meet the goal of minimal exacerbations and no emergency visits, with 9–31% having hospital admission due to asthma. The other GINA goals of minimal need for short-acting inhaled β_2-agonists and normal or near-normal lung function were also not met by a large proportion of patients. Similar findings were reported from a telephone survey of European asthma patients, which showed that only 35% had good asthma control (failed to meet $\leqslant$1 GINA goal), 40% had moderate control (failed to meet 2–3 GINA goals) and 25% had poor control (failed to meet 4–5 GINA goals).[30]

In many cases, the inadequate control of asthma reported in these surveys was associated with inadequate use of anti-inflammatory controller medication and differences between patient perceptions of control and actual symptoms.[28,29] However, studies have also shown that many patients have inadequate asthma control despite GINA step 4 therapy. For example, the Gaining Optimal Asthma Control (GOAL) study investigated whether treatment with fluticasone propionate or salmeterol/fluticasone combination therapy could achieve guideline-based asthma control in patients

with uncontrolled asthma.[31] The GOAL study looked at three categories of patients according to their corticosteroid usage: stratum 1, corticosteroid naive; stratum 2, $\leqslant$500 μg/day BDP or equivalent; and stratum 3, $>$500–1000 μg/day BDP. Patients were treated in two phases. During phase I, treatment was stepped up every 12 weeks until total control of asthma was achieved. Patients entered phase II if they achieved total control or if they had not achieved total control after 12 weeks at the maximum dose. In phase II, treatment was continued at the dose at which control was achieved (or at the maximum dose). At the end of phase II, 22% of salmeterol/fluticasone-treated patients in stratum 1, 25% in stratum 2 and 38% in stratum 3 did not achieve well controlled asthma, with higher percentages in the fluticasone arm. These results show that, although treatment goals can be met in many patients by guideline-based use of ICS and inhaled LABAs, many patients still fail to achieve adequate control of their asthma. Importantly, in patients with the most severe asthma, adding an oral corticosteroid at the end of the study, combined with the highest recommended dose of fluticasone and salmeterol, resulted in only another 7% of patients achieving well-controlled asthma.

The prevalence of severe asthma as a percentage of all asthma varies from country to country, with estimates of 18% in Western Europe, 19% in the USA and 32% in Central Europe.[28,29] An estimated 20% of these patients with severe asthma have uncontrolled disease.[29] It has also been estimated that approximately 50% of patients with severe asthma have a positive skin-prick test for common aeroallergens,[32] which would suggest that approximately 2% of all asthma patients have uncontrolled severe persistent allergic asthma. New treatments targeting this relatively small group of asthma patients might be expected to have a disproportionately large effect on the overall disease burden.

Personal, social and economic burdens of asthma

Patients with inadequately controlled severe persistent asthma despite GINA step 4 therapy are a particularly challenging patient population with significant unmet medical needs. These patients are at high risk of severe exacerbations and death[33,34] and have few therapeutic options available. In addition, patients with asthma often have co-morbid conditions, including psychiatric illness (depression, anxiety, panic, phobia or other psychiatric diagnoses).[35] The high prevalence of psychiatric illness was also apparent in a systematic assessment of patients with difficult-to-treat asthma.[36] Retrospective analyses of patients who have died of asthma suggest that psychosocial factors (including social isolation, marital problems, alcoholism, anxiety and depression) contributed to poor asthma control, although the relationship between the pathophysiology of asthma and psychosocial factors is difficult to determine.[5] The high prevalence of psychiatric illness is likely to add to the difficulty in maintaining patient compliance, which is a frequent underlying factor in poor asthma control.

Asthma adversely affects numerous aspects of daily life, including sleep, work, study, exercise and daily activities,[37] and causes a similar level of disability to diabetes.[1] An English survey in 2001 found that 16% of men and 20% of women with asthma symptoms said that their sleep was disturbed at least once a week and ~50% (46% of men, 54% of women) said that they were unable to carry out their everyday activities.[38] The degree of asthma-related impairment of quality of life increases with disease severity, with the most profound effects seen in patients with chronically uncontrolled severe disease.[39] These patients are frequently admitted to hospital and have regular absences from work or school. In surveys conducted during 1999–2001, 7% of Western Europeans with asthma were admitted to hospital due to asthma during the previous 12 months and 10% required an emergency room visit.[29] Between 80% and 85% of asthma deaths occur in patients with poorly controlled severe disease,[40] and there is a strong association between increased recurrences of hospitalization and asthma severity.[41]

The European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) investigated the characteristics of patients with poorly controlled severe asthma.[32] The 163 patients with severe asthma enrolled in the ENFUMOSA study had all had at least one exacerbation despite treatment with $\geqslant$1200 μg/day of BDP or equivalent and almost 40% had been hospitalized in the previous year. As well as ICS, 96% of patients were treated with inhaled LABAs, 46% required oral theophylline and a small proportion ($<$20%) were treated with anticholinergics, chromones or frequent nebulized short-acting β_2-agonists. In addition, 33% of the group also required oral corticosteroids (median prednisone dose 19 mg). Patients with uncontrolled severe asthma were more likely to be female and had

Table 1 Differences in clinical phenotype of patients with severe asthma and controlled asthma.[32]

	Controlled asthma ($n = 158$)	Severe asthma ($n = 163$)	P value
Sex ratio, female:male	1.6:1	4.4:1	<0.001
Weight (kg) (females)	66.5	70.9	<0.05
BMI, females	25.6	27.2	<0.05
Systolic BP (mmHg)			
Males	127.0	131.4	<0.01
Females	123.1	130.2	<0.01
Diastolic BP (mmHg)			
Males	79.6	83.1	<0.001
Females	76.8	82.0	<0.001
Heart rate (beats/min)			
Males	67.7	82.3	<0.001
Females	73.9	82.7	<0.001
Dose of ICS (μg/day)	666	1676	<0.001
Mean total serum IgE (IU/ml)	109	148	<0.05
$\geqslant 1$ positive allergen skin-prick test (%)	59	78	<0.05
FEV_1 (% predicted)	88.5	71.8	<0.001
FEV_1 post-salbutamol (% predicted)	97.6	80.9	<0.001
FVC (% predicted)	103.1	94.1	<0.001
FEV_1/FVC	89.7	79.9	<0.001
RV/TLC	104.2	113.4	<0.01
K_{CO}	95.0	90.6	<0.05
PaO_2 (kPa)	12.0	11.2	<0.001
$PaCO_2$ (kPa)	5.1	4.9	<0.01

Pulmonary function and blood gases were measured in 130 subjects with controlled asthma and 133–153 subjects with severe asthma. BMI, body mass index; BP, blood pressure; ICS, inhaled corticosteroid; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; K_{CO}, carbon monoxide transfer coefficient; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension.

a higher body mass index than patients with mild-to-moderate asthma (Table 1). In addition, aspirin sensitivity was more common in the severe group, reflected in higher urinary levels of the leukotriene LTE4.

The ongoing US multicentre TENOR study is currently investigating a cohort of patients with severe or difficult-to-treat asthma.[42] The ongoing study recruited 4756 patients aged $\geqslant 6$ years with difficult-to-treat asthma, defined as having high healthcare utilization in the past year ($\geqslant 2$ unscheduled visits or $\geqslant 2$ oral steroid bursts), or high medication use ($\geqslant 3$ medications or long-term daily high-dose ICS or $\geqslant 5$ mg/day prednisone). Consistent with ENFUMOSA, the majority of adult patients with severe or difficult-to-control asthma were female (71%), although the children and adolescents were more likely to be male (67% and 57%, respectively). Immunoglobulin E (IgE) levels were elevated in all age groups and increased with severity of asthma in children and adolescents but not adults. Patients with IgE levels $\geqslant 100$ IU/ml had a lower FEV_1 than those with IgE < 100 IU/ml, the difference in lung function being greatest in children.[43] In general, lower FEV_1 values were associated with greater healthcare utilization (Fig. 2).[44]

In addition to the impact on affected patients, asthma places a large economic burden on healthcare systems and society. In Europe, the total cost of asthma has been approximated at €17.7 billion per annum, of which an estimated €9.8 billion is accounted for by the indirect costs of lost productivity due to absence from work.[45] Severe asthma accounts for a large proportion of the overall costs,[46] with uncontrolled disease responsible for much of the economic burden.[47,48] In a Spanish study, patients with severe asthma accounted for 51% of total costs for the whole group.[49] Similar findings have been reported in France[50] and Italy[47] (Fig. 3). Patients with poorly controlled asthma utilize significantly greater amounts of healthcare resources than 'controlled' patients.[51,52] For example, a study of 13,241 UK asthma patients with varying degrees of severity showed that patients with 'poorly controlled' asthma had recurrent asthma exacerbations requiring emergency treatment and were around 3–4 times more costly to manage than well-controlled patients.[51]

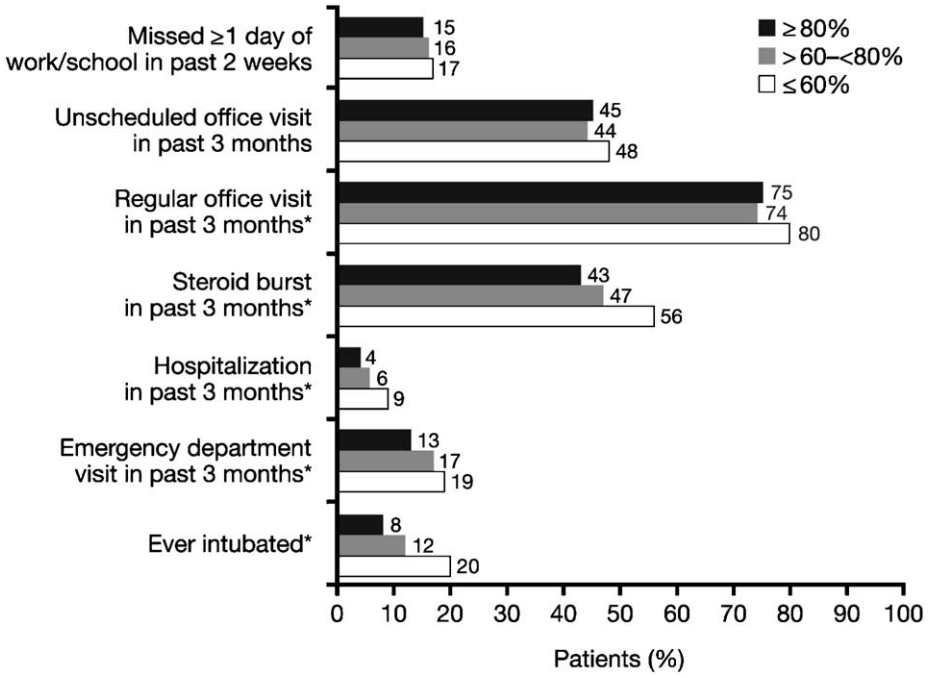

Figure 2 Healthcare utilization and missed days from work/school according to asthma severity in a cohort of 4756 patients with severe or difficult-to-treat asthma. *$P<0.05$ for difference in lung function (FEV_1).[44]

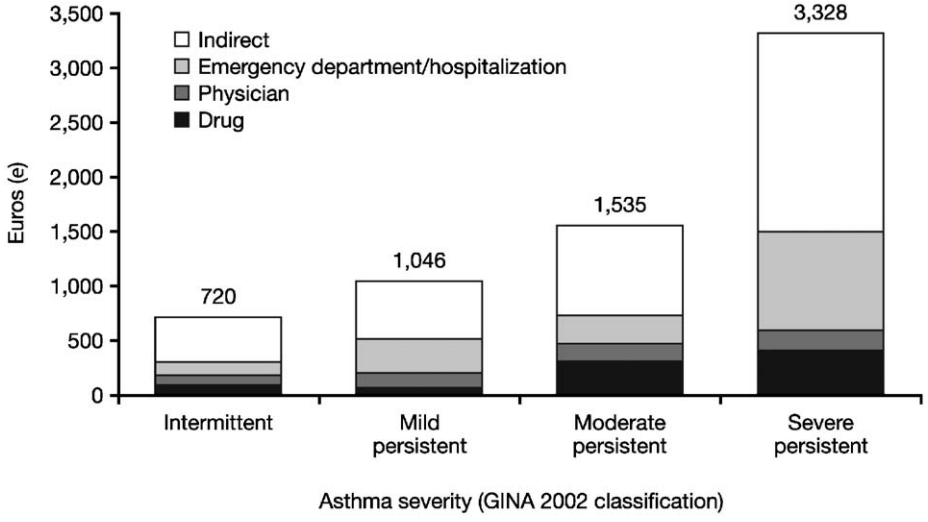

Figure 3 Direct and indirect costs increase with asthma severity.[47]

Management approaches for patients with poorly controlled severe asthma

Physicians face substantial challenges when treating patients with uncontrolled or severe asthma. The complexity of a multiple daily medication regimen is often a factor in patient non-adherence, which in turn affects asthma control. Patients with severe asthma may require particularly intensive patient education and referral to appropriate sources of support to assist in treatment compliance.

Patients with severe persistent asthma frequently require regular use of multiple controller medications, including high-dose ICS (>1000 μg/day of BDP or equivalent) plus a LABA twice daily. If needed, one or more of the following are often added: sustained-release theophylline, anti-leukotriene, oral LABA, oral corticosteroids or anti-IgE therapy (GINA step 4 therapy).[3,4]

There is currently little evidence on which to base management decisions in patients with uncontrolled asthma despite GINA step 3 or step 4 treatment. It is now recognized that addition of a LABA is associated with better outcomes than increasing corticosteroid doses.[31,53–55] However, there is a lack of comparative data to determine the relative merits of other agents when added to high-dose corticosteroid therapy. Anti-leukotrienes have been shown to provide clinical benefit in patients with chronic persistent asthma who were symptomatic despite ICS[56] and improve asthma control in patients receiving high-dose ICS,[57] perhaps reflecting the relatively high level of aspirin sensitivity among patients with severe asthma. In practice, as seen in the ENFUMOSA study, oral corticosteroids are used by approximately one-third of patients with severe asthma.[32] However, regular use of oral corticosteroids is associated with significant side effects.[6,26]

The anti-leukotrienes are a relatively new class of anti-asthma drugs that either block leukotriene synthesis by inhibiting 5-lipoxygenase (an example being zileuton), or are antagonists of the cysteinyl leukotriene 1 receptor (CysLT1), such as montelukast, zafirlukast and pranlukast. Hence, the major effect of the anti-leukotrienes is a selective anti-inflammatory one. Zafirlukast has been shown to improve asthma control in patients receiving high-dose ICSs,[57] and the benefit of anti-leukotrienes may be particularly apparent in the large percentage (20–25%) of patients with severe asthma who may be aspirin sensitive.[32,58]

Theophylline is a bronchodilator that may have extrapulmonary effects, including an anti-inflammatory action.[59] When given as a sustained-release preparation, it has a long duration of action and is useful in the control of nocturnal symptoms that persist despite regular treatment with anti-inflammatory therapy.[60] Theophylline is also a possible additional bronchodilator for use in patients with severe asthma, although as add-on therapy, it is less effective than LABAs.[61,62] It is, however, a less expensive option. In practice, the routine use of theophylline in patients hospitalized for asthma is no longer advocated in some countries due to the potential for serious adverse effects and the lack of benefit.[63] Further clinical research is needed to verify the value of theophylline in adults and children with severe asthma exacerbations and impending respiratory failure.

Omalizumab, a recently developed anti-IgE monoclonal antibody for the treatment of asthma has proven to be effective and well tolerated as add-on therapy in patients with severe persistent asthma. In a pooled analysis of 2511 omalizumab-treated patients and 1797 control patients in seven clinical trials, 93% of patients met the criteria for severe persistent asthma set out in the GINA 2002 guidelines.[64] Analysis of pooled data showed that addition of omalizumab to current asthma therapy significantly reduced the rate of asthma exacerbations by 38% (0.910 vs. 1.474, $P<0.0001$ vs. control) and total emergency visits by 47% ($P<0.0001$ vs. control; Table 2). Analysis of demographic subgroups showed that the efficacy of omalizumab on asthma exacerbations was unaffected by patient age, gender, baseline serum IgE (split by median) or by 2- or 4-weekly dosing schedule, although the greatest absolute benefit was observed in patients with poor baseline FEV_1 values.[64] Add-on omalizumab treatment in patients with co-morbid asthma and rhinitis has also been shown to lead to significantly fewer asthma exacerbations and significant improvements in both asthma and rhinitis-related quality of life, compared with placebo.[65] The anti-inflammatory effect of omalizumab produces a profound reduction in airway eosinophilia (observed in patients with mild-to-moderate asthma). Omalizumab also significantly reduces the number of T-lymphocytes (CD3+, CD4+, CD8+), B-cells, mast cells expressing the high-affinity IgE receptor, and cells showing surface IL-4.[66]

Omalizumab has been shown to be particularly effective in patients with severe asthma. Regression analysis of data from more than 1000 patients shows that baseline characteristics reflecting more severe asthma (high doses of ICS, history of frequent emergency asthma treatment, poor lung

Table 2 Hospitalizations and other unscheduled visits in patients receiving omalizumab.[64]

Type of visit	Rate per year			Ratio (95% CI)	*P* value
	Omalizumab	Control	Treatment difference		
Total emergency visits	0.332	0.623	0.291	0.533 (0.401, 0.709)	<0.0001
Hospital admission	0.030	0.062	0.032	0.489 (0.246, 0.972)	0.041
Emergency room visits	0.026	0.066	0.040	0.397 (0.192, 0.820)	0.013
Unscheduled doctor visits	0.252	0.443	0.191	0.568 (0.417, 0.774)	0.0003

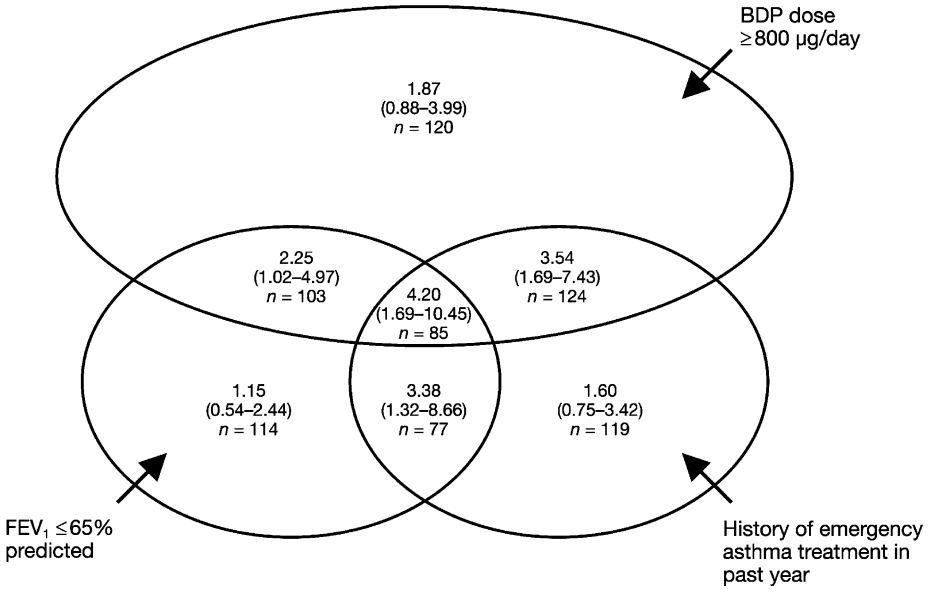

Figure 4 Venn diagram of odds ratios for response with omalizumab relative to placebo, according to three baseline high-severity covariates. Response was defined as at least one of the following: reduced symptoms with no increase in rescue use of β_2-agonist, reduced rescue use of β_2-agonist with no increase in symptoms, improved lung function, improved quality of life; *plus* no exacerbations during 16 weeks of treatment). The likelihood of response increases with the presence of more than one high-severity covariate.[67]

function) were predictive of the greatest response to omalizumab treatment (Fig. 4).[67] In addition, subgroup analyses have shown that omalizumab was particularly effective in reducing exacerbations in patients at high risk of death, as indicated by prior intubation or recent hospitalization/emergency treatment.[68]

The recently updated GINA guidelines recommend anti-IgE therapy (of which omalizumab is the only currently available option) for patients with severe allergic asthma.[4] Anti-IgE therapy is listed as an option in GINA step 4 therapy if additional control is needed beyond that achieved on high-dose ICS and LABAs. A recent 28-week study of omalizumab as add-on therapy (INNOVATE) exclusively enrolled patients with inadequately controlled severe persistent asthma despite GINA step 4 therapy.[69] All patients were receiving ICS plus LABAs and two thirds were receiving additional controller medication (including oral corticosteroids in 22% of patients). Statistically significant reductions were observed in the rate of clinically significant asthma exacerbations after adjustment for baseline exacerbation history (0.68 vs. 0.91, $P = 0.042$; Fig. 5a), severe exacerbation rate (0.24 vs. 0.48, $P = 0.002$; Fig. 5b), and emergency visit rates (0.24 vs. 0.43, $P = 0.038$). Omalizumab also provided significant improvements over placebo in morning PEF, FEV_1, asthma symptom scores and quality of life scores (Juniper AQLQ) and patients' and investigators' global evaluations of treatment effectiveness (both $P < 0.001$).

In addition to the clinical benefits that omalizumab provides in patients with severe persistent asthma, it is also relevant that the anti-IgE monoclonal antibody is administered by subcutaneous injection every 4 weeks (or every 2 weeks for patients requiring higher doses).[70] The relative simplicity of treatment may aid adherence for patients already on a complicated regimen of multiple inhaled and oral medications. The potential to improve adherence could be particularly important in poorly controlled and difficult-to-treat asthma given the strong association between compliance and treatment outcomes.[71]

Potential future therapies for severe asthma include anti-IL-5 monoclonal antibodies and agents that block interleukin synthesis or its effects. The anti-IL-5 monoclonal antibody SCH55700 was evaluated in a small study of different single doses in patients with severe persistent asthma and was shown to be biologically active (decrease in circulating eosinophils), with signs of an improvement in FEV_1.[72] Another anti-IL-5 antibody (SB240563, mepolizumab) was shown to deplete circulating eosinophils and partially reduce airway eosinophils without having an observable clinical effect.[73] Although mepolizumab had a marked effect on blood eosinophils (median 100% decrease, interquartile range 67–100%), the decrease in lung

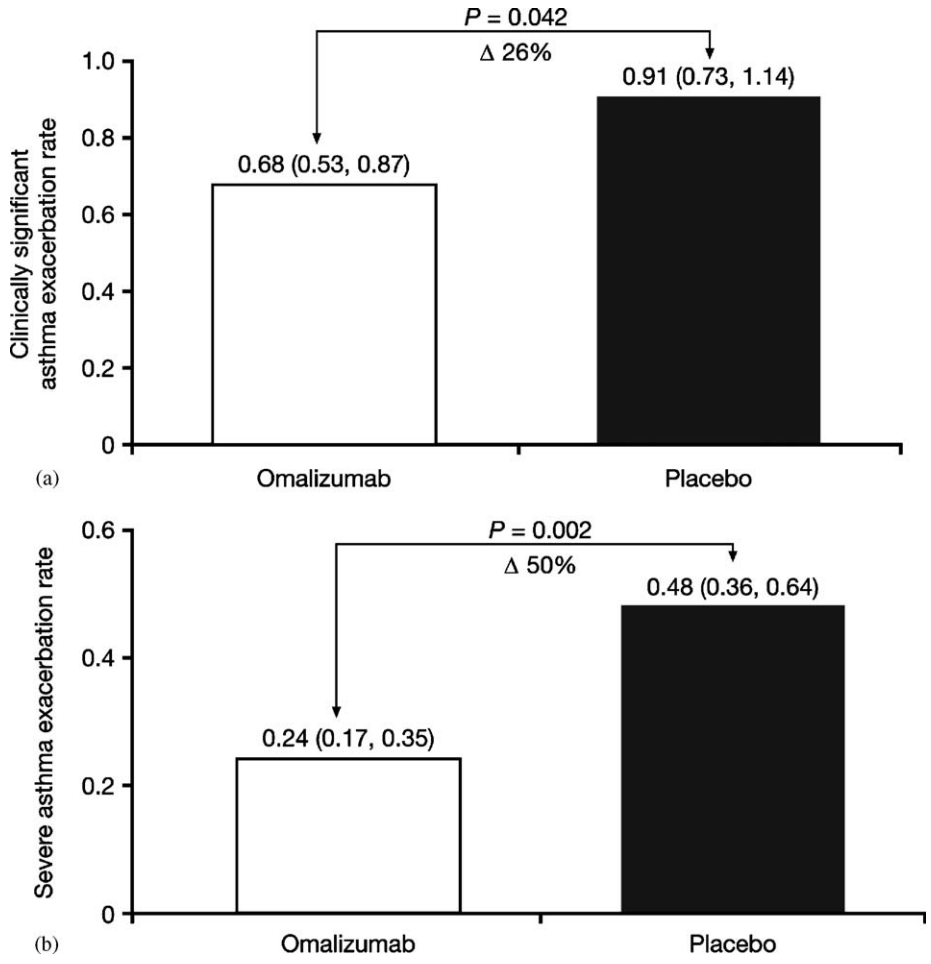

Figure 5 (a) Effect of omalizumab treatment on the rate of clinically significant asthma exacerbations (adjusted for baseline exacerbation history) during the 28-week treatment period (PITT population); mean (95% confidence interval).[69] (b) Effect of omalizumab treatment on severe exacerbations (PEF or $FEV_1 < 60\%$ of personal best) during the 28-week treatment period (PITT population).

eosinophils was considerably smaller (median 55%, interquartile range 29–89%),[73] which might explain the lack of clinical effect. In addition, mepolizumab had no effect on T-cell subsets or cytokine production.[74] It remains to be seen whether mepolizumab can achieve the degree of reduction in airway eosinophils required to produce a clinical response or even whether eosinophil depletion is capable of achieving clinical benefits.

In a study of 85 patients with moderate-to-severe asthma receiving high-dose ICS ($\geqslant$1500 μg/day BDP), suplatast (an orally administered agent that blocks the synthesis of cytokines, including IL-4 and IL-5, from Th2 cells) proved superior to placebo for symptoms and lung function when ICS doses were halved, although the level of exacerbations was not recorded.[75] Further investigation in a clearly defined group of patients with severe asthma is required to evaluate its usefulness in this population.

Other experimental drugs, including methotrexate,[76] cyclosporine,[77] gold salts,[78] troleandomycin,[79] azathioprine[80] and chloroquine[81] have failed to demonstrate an acceptable risk/benefit ratio.

Discussion

Despite improved understanding and adherence to recommended management strategies, many patients who have inadequately controlled asthma, particularly those with severe disease, are at high risk of exacerbations and asthma-related death. Patients who are not well controlled on high-dose ICS in combination with other available controller medications, or who require additional systemic corticosteroid treatment, have an identifiable need for a new therapy that can improve clinical outcomes, in particular life-threatening

exacerbations, without adding to the complexity or burden of adverse effects of medication.

The addition of omalizumab therapy is a promising new therapeutic option for patients with severe persistent asthma that is inadequately controlled despite best available therapy. Comparative trials are needed to determine the relative merits of different treatments and strategies as add-on therapy for patients with inadequately controlled asthma despite GINA step 4 therapy (i.e. high-dose ICS plus LABAs) and additional studies are needed to identify patients who may benefit from these new treatment options.

Acknowledgements

We thank medical writers Dr. Dominic Hague and Dr. Paul Hutchin for their assistance in drafting this article and Helen Venables for editorial support.

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