Expert Opinion

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Anti-inflammatory

Targeted interventions for difficult-to-treat asthma

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Chronic persistent asthma has a significant burden in terms of healthcare-related expenses, decreased productivity and reduced quality of life for patients. Currently available guideline-directed therapy can control the majority of patients, but roughly one-third of patients will require additional care. This article reviews the barriers that hinder the ability of practitioners and patients to gain and maintain control of asthma, including inaccurate assessment measures, variability in patient response, and poor adherence. Strategies aimed at controlling difficult-to-treat disease, such as the use of biomarkers to assess control, are discussed. Newer and developing therapies that cater to specific types of asthmatic patients and may lead to improved outcomes in those patients for whom standard care is insufficient are also looked at.

Keywords: asthma control, biomarker, difficult asthma, persistent asthma

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1. Introduction

According to the Global Initiative for Asthma (GINA) guidelines, 'It is reasonable to expect that in most patients with asthma, control of the disease can and should be achieved and maintained.' [101] In reality, however, millions of patients with asthma are not well controlled, despite using maximum doses of controller medications. This review focuses on this subset of the patient population, and discusses the latest management strategies and pharmacological treatments for these patients with 'difficult' asthma.

1.1 Defining asthma control: NAEPP Guidelines

The National Institutes of Health (NIH) in 1997 put forth the National Asthma Education and Prevention Programme (NAEPP) guidelines, which define control of asthma as:

- preventing chronic and troublesome symptoms;
- maintaining (near) 'normal' pulmonary function;
- maintaining normal activity levels;
- preventing asthma exacerbations, emergency department visits and hospitalizations;
- minimizing adverse events from pharmacotherapy.

The guidelines recommend that control be maintained with the least amount of medication possible. Therefore, the above parameters should ideally be assessed at each encounter to guide the progress of treatment. If control has been achieved, treatment is maintained or stepped down; if the patient is not well controlled, treatment is stepped up [102].

The most accepted definition of uncontrolled asthma, in both adults and children, is asthma that does not respond to maximum guideline-directed therapy. However, it is important to note that there is no universally acceptable definition of asthma severity. A search for alternative diagnoses, stressing adherence to therapy,

attempting to control comorbid conditions and addressing underlying psychiatric illness are requisite to maximum chances for control. Also, difficult-to-control patients may not only present with symptoms that are refractory to therapy, but with mild indolent symptoms that are associated with severe exacerbations [1].

1.2 Achieving asthma control: the GOAL, AIRE and AIR studies

The Gaining Optimal Asthma ControL (GOAL) study set out to answer the question of whether or not guideline-defined asthma control, as delineated above, can be achieved. The GOAL study was a 1-year, randomized, stratified, double-blind, parallel-group study of 3421 patients with uncontrolled asthma at baseline. Patients were randomized to either monotherapy with fluticasone, an inhaled corticosteroid (ICS), or combination therapy with fluticasone plus salmeterol, a long-acting β_2-agonist (LABA). During Phase I of the study, treatment with either regimen was stepped up every 12 weeks until either total control was achieved or a maximum dose of 500 µg fluticasone (with or without LABA) was reached. During Phase II, patients were maintained on the dose they had reached during Phase I until the end of the 1-year treatment period.

At the end of 1 year, 63% of patients using fluticasone monotherapy and 71% of patients using fluticasone/salmeterol had gained control of their asthma as defined by NAEPP guidelines. These are promising results, indicating that control of asthma is possible and is facilitated by combination therapy. However, as the results also indicate, roughly one-third of patients did not gain control, despite using the highest recommended dose of therapy. Thus, the GOAL study demonstrates that a need exists for improved methods of treating patients with difficult asthma [2].

Rabe and co-workers found similar results in two surveys, the Asthma Insights and Reality in Europe (AIRE) survey conducted in 1999, and the worldwide Asthma Insights and Reality (AIR) survey conducted in 2004. In the AIRE study, 344 households with 2803 patients were surveyed. A total of 48% reported regular daytime symptoms and 30% reported sleep-related symptoms each week. A total of 50% of the patients who had symptoms consistent with severe persistent asthma felt they were well or completely controlled. The burden of this illness was reinforced by 25% of the patients requiring unscheduled visits (10% emergency room visits and 7% hospitalizations). In the last month before the study, 63% used short-acting medications versus 23% using ICS [3]. A subsequent study was published in 2004, where 7786 adults and 3153 children from 29 countries were surveyed. As in the previous study, asthma control was achieved in < 45% of the patients [4].

1.3 Consequences of uncontrolled asthma: the TENOR Study

Although patients with difficult-to-treat asthma represent a minority of asthma patients, they account for much of the morbidity, mortality and cost of disease. The goal of The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study was to better understand the natural history of asthma in these patients. Comprising the TENOR cohort were 4756 patients, 96% of which were considered difficult-to-treat by their physician. Patients were assessed at baseline and followed-up at 12 and 24 months, although continuing to receive usual asthma treatment as determined by their asthma specialist.

During the course of the 2-year study, most patients had uncontrolled asthma (83% uncontrolled at all study visits, 16% inconsistent control, 1.3% controlled at all visits). To assess the burden of controlled and uncontrolled asthma, data on work and school absences, health service use and medication use were collected. At all assessments, the annual mean number of work and school days lost was significantly higher for patients with uncontrolled asthma. Patients with uncontrolled asthma required more hospitalizations, ER visits, scheduled and unscheduled physician visits, and courses of systemic steroids [5]. Also, the total mean cost for patients with uncontrolled asthma over the 24-month study period was more than double that for patients with controlled asthma (US$14,212 versus US$6452) [6].

2. Barriers to achieving asthma control

2.1 Inaccurate assessment

There are a number of barriers hindering an accurate assessment of the degree of asthma control. First, there is a general tendency among both patients and physicians to overestimate control. In a study conducted by Boulet and co-workers, 66% of patients and 43% of physicians rated asthma symptom control as 'adequate' to 'very good' when the patient was actually poorly controlled according to NAEPP guidelines [7]. Parents of children with asthma also overestimate control. Halterman and co-workers found that roughly three-quarters of parents of asthmatic children experiencing significant impairments described their children as having good control [8].

Second, selection of asthma control criteria among physicians varies and is not always in keeping with current asthma guidelines. In Boulet's study, some physicians employed criteria such as fatigue, need to clear throat, colored sputum, headache and dizziness during evaluation. Also problematic is the reliance upon single, rather than composite, measures of control. For example, many physicians assess control through the sole use of pulmonary function tests. However, studies have shown that pulmonary function tests alone are poor indicators of asthma status [9-11]. Also established is the poor correlation between control measures. In a separate study, Boulet and co-workers examined the relationship between symptoms, forced expiratory volume in one second (FEV_1) and inflammation (as measured by airway eosinophilia), and reported no significant correlation ($p > 0.05$) [12]. Other studies have corroborated this finding. Thus, when evaluating asthma control using single

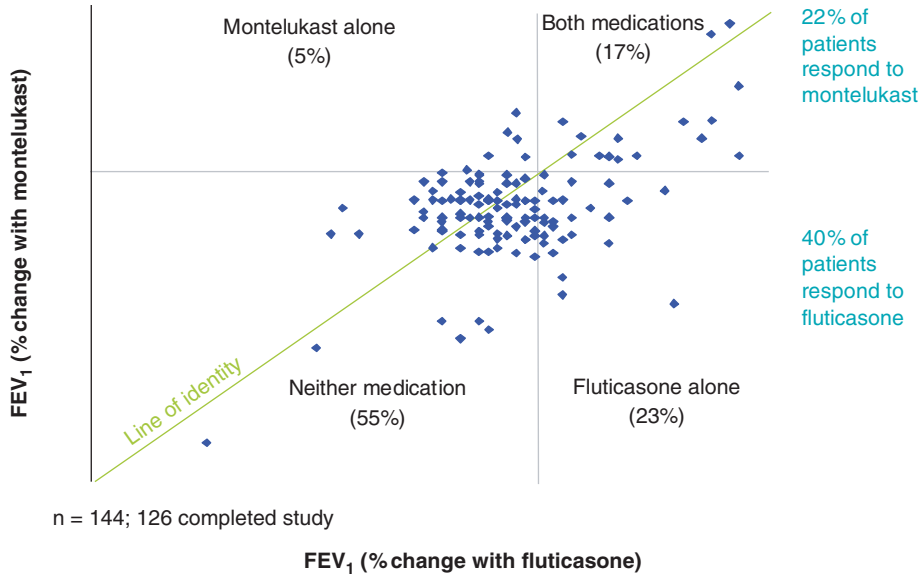


Figure 1. Patient responsiveness to ICS and LTRA is highly variable. Szefler *et al*. [13] studied the variability of response to fluticasone and montelukast, assessed by changes in the subjects FEV_1 in 144 children, ages 6 – 17 years, with mild-to-moderate persistent asthma. This graph illustrates 4 regions that show categories of response, defining a favorable response as ≥ 7.5%. Important observations: i) 5% of patients responded to montelukast but not fluticasone, ii) 40% of patients responded to fluticasone, but not montelukast, iii) 17% of patients responded to both medications, and iv) 55% did not respond to either medication. In a study by Zeiger *et al*. [58] of response profiles of pediatric patients with moderate-to-severe persistent asthma, they reported that there was a more favorable clinical, pulmonary and inflammatory responses to an ICS than to an LTRA. They stated that this evidence provides pediatric-based group evidence to support ICSs as the preferred first-line therapy for mild-to-moderate persistent asthma in children. Furthermore, they stated that expired nitric oxide might help to identify individual children not receiving controller medication who achieve a greater improvement in asthma control days with an ICS compared with an LTRA.
Figure adapted from Szefler SJ *et al*.: Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J. Allergy Clin. Immunol.* (2005) **115**:233-242 [13].
FEV_1: Forced expiratory volume in one second; ICS: Inhaled corticosteroid; LTRA: Leukotriene receptor antagonist.

parameters, the conclusion may vary depending on which control measure is employed.

2.2 Variability in response to therapy

A primary barrier to gaining control of asthma is the highly variable nature of patient responsiveness to therapy. A multicenter, double-blind, 18-week study conducted by Szefler and co-workers illustrates this point from a clinical perspective. The investigators studied responses to fluticasone (an ICS) and montelukast (a leukotriene receptor antagonist [LTRA]) in 126 children with mild-to-moderate persistent asthma. Responses were measured in terms of percentage change in FEV_1, with a favorable response defined as a change of ≥ +7.5%. They found that 5% of patients responded to montelukast but not fluticasone, 23% of patients responded to fluticasone but not montelukast, 17% responded to both, and 55% responded to neither (**Figure 1**) [13].

The mechanism behind such variability in response is genetic polymorphism. Genetic variations can alter the pharmacokinetic and/or pharmacodynamic properties of a drug, or may produce idiosyncratic reactions. As a result of polymorphism, large inter-individual variation, including a significant number of non-responders, exists in the treatment response to each of the major classes of asthma medications.

ICSs, the cornerstone of long-term asthma treatment, are ineffective in a significant number of patients, as reported in several studies [14,15]. Research has found that variation in one gene, corticotropin-releasing hormone receptor 1 (*CRHR1*) may be associated with enhanced response to ICS therapy. Tantisira and co-workers demonstrated that individuals homozygous for particular variants in the *CRHR1* gene manifested a doubling to quadrupling of lung function response (as measured by FEV_1) to corticosteroids compared with individuals lacking the variants [16].

Similarly, response to long-acting β_2-agonists may be genetically determined. It has been repeatedly shown that patients with a genetic polymorphism that results in homozygosity for arginine (Arg/Arg), rather than glycine (Gly/Gly), at amino acid residue 16 of the β_2-adrenergic receptor, experience a reduction in lung function with continuous use of both albuterol [17,18] and salmeterol [19]. These patients also experience a further reduction in lung function after LABA discontinuation. The Arg/Arg polymorphism occurs in approximately one sixth of the population and may

be disproportionately present in some racial or ethnic groups, such as African-Americans [20]. In addition to this particular polymorphism, other genetic variations have been investigated as potential explanations for the variability in LABA responsiveness.

Finally, the variable nature of patient response to LTRAs, and the significant prevalence of non-responders, has been linked with a genetic polymorphism. Lima and co-workers showed that a series of DNA sequence variants in the promoter regions of the arachidonate 5-lipoxygenase (*ALOX5*) gene were associated with a decreased response to montelukast and an increased risk of exacerbations [21].

2.3 Adherence

In addition to the difficulty practitioners face in assessing the degree of asthma control and predicting the response of a patient to therapy, poor adherence hinders the achievement of asthma control in many cases. Poor adherence is by no means unique to the treatment of asthma; however, its consequences in the difficult-to-treat population merit discussion, as patients with difficult asthma are likely to be prescribed a regimen of daily controller medications. This regimen may include an ICS, an LABA, an LTRA and others. Studies have repeatedly shown that these daily controller medications are particularly susceptible to poor adherence. For example, one study found that 39% of patients prescribed an LTRA, 60% of patients prescribed a LABA and 69% of patients prescribed an ICS failed to ever refill their prescription [22].

This issue becomes additionally complicated by the fact that many patients use improper inhaler technique, and thus may fail to reap the benefits of their medications when they do use them. Although it is recommended that practitioners reinforce proper inhaler technique at each encounter, studies have repeatedly indicated that many patients use their inhaler incorrectly. In an observational study, Kofman and co-workers found that 36% of patients using a metered-dose inhaler and 58% of patients using a dry powder inhaler made mistakes that were considered to affect drug output significantly [103].

3. Strategies and newer therapies

3.1 Biomarkers

To improve the assessment and maintenance of asthma control, a number of biomarkers are being evaluated, including sputum eosinophilia, exhaled nitric oxide and airway hyper-responsiveness. Preliminary evidence indicates that these biomarkers may have a role in asthma care, particularly in patients with difficult-to-treat asthma for whom standard care is often insufficient.

In a study of 15 subjects with stable asthma, Jatakanon and co-workers attempted to induce mild asthma exacerbations by decreasing the ICS dose of the subjects. Eight subjects did not develop exacerbations during the 8-week study, whereas seven subjects developed mild exacerbations. The only significant difference between these two groups was a higher baseline sputum eosinophil count in subjects with subsequent exacerbations ($p < 0.05$). Multiple regression analysis suggested that sputum eosinophilia is a potentially useful marker in predicting asthma control [23]. In another study, monitoring sputum eosinophil counts to predict which individuals would maintain asthma control allowed 48% of subjects with mild-to-moderate asthma to discontinue ICS therapy without deterioration [24].

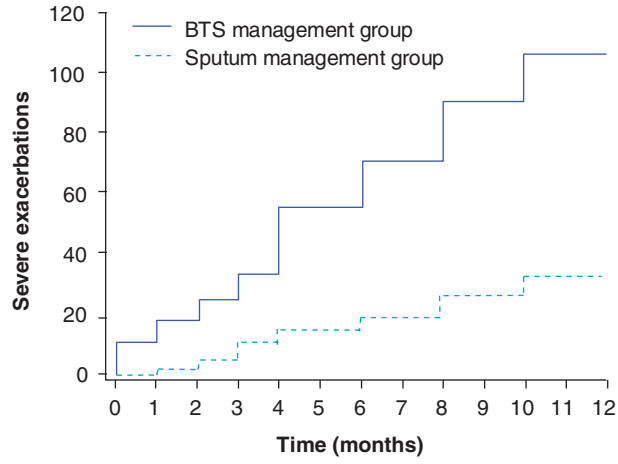
Supporting these results is a study by Green and co-workers in which 74 patients with moderate-to-severe asthma were randomly allocated to management either by British Thoracic Society asthma guidelines (BTS management group) or by normalization of the induced sputum eosinophil count (sputum management group). Patients in the sputum management group had significantly fewer asthma exacerbations and significantly fewer hospital admissions than patients in the BTS management group. There was no difference between the two groups in the average daily dose of inhaled or oral corticosteroids. Thus, the authors concluded that a treatment strategy directed at normalization of the induced sputum eosinophil count can reduce asthma exacerbations and admissions without the need for additional anti-inflammatory treatment (**Figure 2**) [25].

Fractional exhaled nitric oxide (FE_{NO}) has been shown to be a marker of airway inflammation. In a study of 59 children and adults, 5 consecutive days of measurements demonstrated that FE_{NO} was consistently higher in the subjects with asthma than in controls, and that the elevated levels were free from diurnal or day-to-day fluctuations [26]. Another study reported a significantly positive relationship between FE_{NO} and eosinophilic airway inflammation [27].

Furthermore, monitoring of FE_{NO} may reduce exacerbations and ICS use. Smith and co-workers conducted a single-blind, placebo-controlled trial of 97 patients with asthma, in which stepwise adjustments to ICS therapy were made in response to FE_{NO} measurements. The decrease in exacerbations in patients managed with the FE_{NO} strategy was measurable, but not statistically significant. However, the FE_{NO} management strategy did result in a clinically and statistically significant reduction in the daily dose of ICS. The investigators concluded that FE_{NO} measurements allow for decreased maintenance doses of ICS without compromising the degree of disease control (**Figure 3**) [28].

Finally, investigators have found that management strategies based upon airway hyper-responsiveness (AHR) can improve asthma control. In a 2-year trial conducted by Sont and co-workers, 75 adults with asthma were randomized to either a management strategy aimed at reducing AHR (AHR strategy) or a management strategy based on current guideline recommendations (reference strategy). The AHR strategy group had a 1.8-fold lower rate of asthma exacerbations than the reference strategy group, and also experienced a significantly greater improvement in FEV_1. The authors suggest that this implies a role for the monitoring of AHR in the long-term treatment of asthma [29].

- 74 patients with moderate-to-severe asthma
- ICS Rx titrated by British Thoracic Society (BTS) guidelines or sputum eosinophils
- Sputum eosinophils guided Rx: 48% reduction ICS therapy



Overall ICS use similar: sputum eosinophilia identified subjects needing ICS and those that do not

Figure 2. Asthma management guided by sputum eosinophils. Green *et al.* [25] studied 74 patients with moderate-to-severe asthma allocated randomly to management either by standard British Thoracic Society asthma guidelines (BTS management group) or by normalization of the induced sputum eosinophil count and reduction of symptoms (sputum management group). The sputum eosinophil count was 63% (95% CI: 24 – 100) lower over 12 months in the sputum management group than in the BTS management group ($p = 0.002$). Patients in the sputum management group had significantly fewer severe asthma exacerbations than did patients in the BTS management group (35 versus 109; $p = 0.01$) and significantly fewer patients were admitted to hospital with asthma (1 versus 6, $p = 0.047$). There were no differences between the groups in the average daily dose of inhaled or oral corticosteroids. A treatment strategy directed at normalization of the induced sputum eosinophil count as an inflammatory surrogate count reduces asthma exacerbations and admissions without the need for additional anti-inflammatory treatment.
Figure adapted from Green RH *et al.*: Asthma exacerbations and sputum eosinophil counts: a randomized controlled trial. *Lancet* (2002) **360**:1715-1721 [25].
BTS: British Thoracic Society; ICS: Inhaled corticosteroid.

Although the use of biomarkers such as these may lead to improved assessment of asthma control, it is important to keep in mind that there is no single preferred guide to therapy. For asthma there is no hemoglobin A_{1c}, blood pressure measurement, cholesterol level or glomerular filtration rate that will clearly define the severity or status of the illness. Rather a complete measure of asthma control including symptoms, pulmonary function, quality of life, healthcare utilization, burden of illness, adverse events and biomarkers should be employed.

3.2 Newer and evolving therapies

3.2.1 Anti-IgE: omalizumab

In the allergic cascade, inhaled allergens stimulate B lymphocytes to release IgE antibodies. The free IgE circulates in the blood, is eventually bound by the high-affinity IgE receptor FcεRI, and is subsequently expressed on the surface of mast cells and basophils. Upon re-encounter, the offending allergen causes the crosslinking of two adjacent surface-expressed IgE molecules, which initiates an intracellular signalling pathway that induces the release of inflammatory mediators, ultimately leading to the bronchoconstriction characteristic of an asthma exacerbation.

Omalizumab is a recombinant, humanized, monoclonal IgE antibody that works by selectively binding the CH_3 domain of the IgE molecule, which is conserved among all IgE molecules, and is the same site to which FcεRI binds. The binding of omalizumab to free serum IgE forms a soluble complex which is cleared by the reticuloendothelial system. Administration of omalizumab results in a rapid and substantial decrease in free serum IgE. The effects of this reduction in serum IgE are twofold: both the amount of surface-expressed IgE and the expression of FcεRI on mast cells and basophils are decreased [30,31].

The INNOVATE study was a 28-week, randomized, double-blind, parallel-group study to determine the effects of omalizumab on clinically significant asthma exacerbations (i.e., requiring systemic corticosteroids). Following a run-in phase, 419 adults who were inadequately controlled, despite therapy with high-dose ICS and LABA, were randomized to receive either omalizumab or placebo. Treatment with omalizumab reduced the clinically significant exacerbation rate by 26% (0.68 versus 0.91 for placebo). Omalizumab also reduced the severe exacerbation rate (0.24 versus 0.48) and emergency visit rate (0.24 versus 0.43), and significantly improved asthma-related quality of life, morning peak expiratory flow and asthma symptom scores [32].

In a recent report, Bousquet and co-workers pooled data from 7 studies to determine the effect of omalizumab on asthma exacerbations in 4308 patients with severe persistent

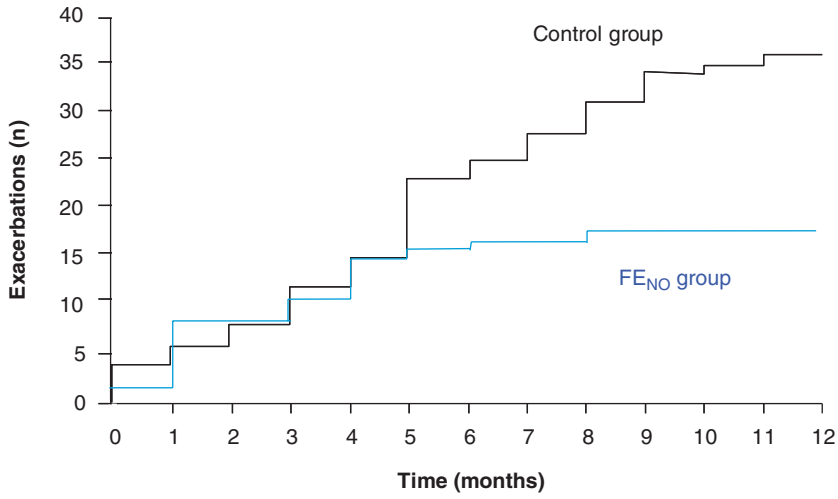


Figure 3. Monitoring of FE_{NO} may reduce exacerbations. Smith *et al*. [28] conducted a single-blind, placebo-controlled trial of stepwise adjustment of ICS therapy in response to FE_{NO} in 97 patients with asthma who had been regularly receiving treatment with inhaled corticosteroids. The FE_{NO} strategy decreased exacerbations, although this was not statistically significant. Although the changes in exacerbations were not statistically significant, use of the FE_{NO} resulted in a clinically and statistically significant decrease in the daily dose of the ICS. The investigators concluded that with FE_{NO} measurements, maintenance doses of ICS can be significantly reduced without compromising the degree of disease control.

Figure adapted from Smith AD *et al*.: Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N. Engl. J. Med.* (2005) **352**:2163-2173 [28].
FE_{NO}: Fractional exhaled nitric oxide; ICS: Inhaled corticosteroid.

asthma according to GINA guidelines. Omalizumab significantly reduced the rate of asthma exacerbations by 38% ($p < 0.0001$) and the rate of total emergency visits by 47% ($p < 0.0001$) when compared with controls. Benefits of the drug extended across subgroups by patient age, gender and baseline serum IgE [33].

In addition to omalizumab, other agents are now in development to modulate T_H2 cytokine production (suplatast tosilate), cytokine nuclearization (soluble IL-4 receptor antagonist and IL-5 antibody) and T_H2 blockers (IL-12) [34]. Most recently, immunostimulatory sequences of DNA were used to treat allergic rhinitis (ragweed Toll-like receptor 9 agonist vaccine). This allowed for two years of control of ragweed allergic rhinitis symptoms with six injections given during the first year. The long-term affects of application of this vaccine and treatment of IgE-mediated disease are not yet known [35].

3.2.2 *TNF-α inhibitors: etanercept*

TNF-α is a pro-inflammatory cytokine that regulates the pathogenetic mechanisms of chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis and Crohn's disease. Agents that block TNF-α suppress inflammation, slow disease progression, and in some cases, induce remission. In recent years, it has been shown that TNF-α is present in increased amounts in the bronchoalveolar fluid of patients with asthma, especially in patients with more severe disease [36,37], and that TNF-α plays a critical role in the initiation and amplification of airway inflammation [38,39].

Research has also indicated that etanercept, the soluble TNF-α receptor fused to human IgG, may be of benefit in the treatment of severe or difficult-to-treat asthma. Berry and co-workers studied the effects of treatment with etanercept in patients with difficult asthma in a placebo-controlled, double-blind, crossover pilot study [37]. Patients treated with etanercept for 10 weeks experienced a significant increase in: postbronchodilator FEV_1, the concentration of methacholine required to provoke a 20% decrease in FEV_1, and asthma-related quality of life score (**Figure 4**).

Etanercept has been approved by the FDA for the treatment of other chronic inflammatory diseases, but not for the treatment of asthma. Further research will determine whether or not this therapeutic agent will play a role in the management of difficult-to-treat asthma. In particular, longer studies involving larger patient populations are needed to determine the adverse effects that may result from etanercept therapy.

Furthermore, TNF-α is not the only T_H1 cytokine that may be operative in the pathogenesis of difficult-to-treat asthma. Further research is needed to characterize the effects of other T_H1-derived inflammatory factors in the course of the disease, as these factors represent a potential therapeutic target in the difficult-to-treat patient, for whom standard treatments are often ineffective.

3.2.3 *Improved ICSs: ciclesonide*

ICSs are the preferred treatment for the long-term care of patients with asthma. However, prolonged use in persistent asthma and increased doses in severe cases may result in

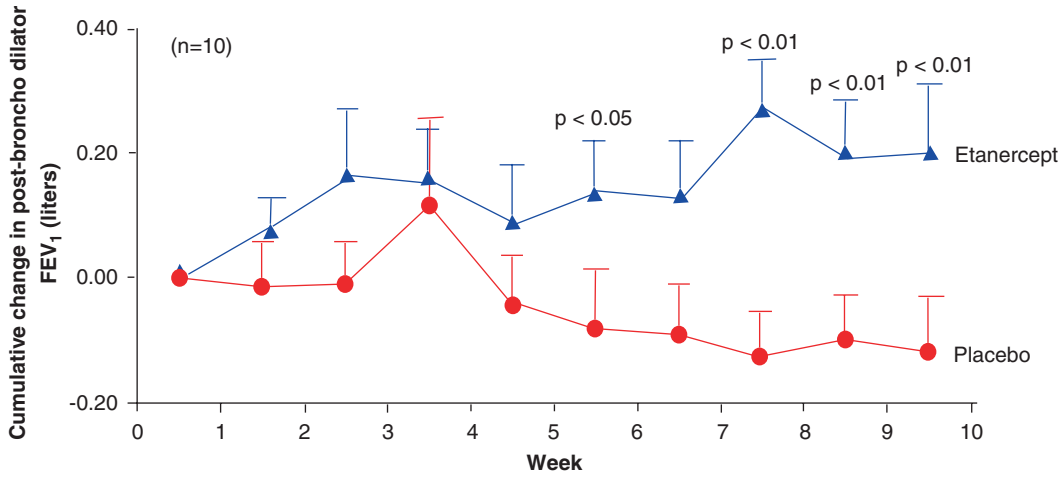


Figure 4. Etanercept in severe asthma: post-bronchodilator FEV_1. Berry *et al*. [37] measured markers of TNF-α activity on peripheral-blood monocytes in 10 patients with refractory asthma, 10 patients with mild-to-moderate asthma, and 10 control subjects. They also studied the effects of treatment with the soluble TNF-α receptor etanercept (25 mg twice weekly) in the patients with refractory asthma in a placebo-controlled, double-blind, crossover pilot study. Compared with controls, patients with mild-to-moderate asthma had increased expression of membrane-bound TNF-α, TNF-α receptor 1 and TNF-α-converting enzyme by peripheral-blood monocytes. 10 weeks of treatment with etanercept was associated with a significant increase in: i) The concentration of methacholine required to provoke a 20% decrease in FEV_1, and ii) the asthma-related quality-of-life score (by 0.85 point; 95% CI: 0.16 – 1.54 on a 7-point scale; p = 0.02) 0.32 liter increase in post-bronchodilator FEV_1.
Figure adapted from Berry MA *et al*.: Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N. Engl. J. Med.* (2006) **354**:697-708 [37].
FEV_1: Forced expiratory volume in one second.

suppression of the hypothalamic pituitary adrenal (HPA) system. HPA suppression might cause growth impairment in children (including premature closure of the epiphyses of long bones), disturbed glucose tolerance, decreased mineralization of bone (increasing the risk of fractures), ocular problems such as glaucoma and cataracts, and thinning of the skin [40,41]. Local adverse affects, even at low doses, may include dysphonia, pharyngitis and oral candidiasis [42].

Ciclesonide is a new ICS, licensed only for the treatment of persistent asthma in adults (≥ 18 years). Ciclesonide has little anti-inflammatory activity itself and requires cleavage by endogenous carboxyl esterases in the lung, which creates the active metabolite desisobutryl-ciclesonide (des-ciclesonide) [43]. This targets activity at the desired location. Des-ciclesonide undergoes rapid hepatic metabolism into inactive metabolites on leaving the lung [44]. These factors, together with the fact that ciclesonide has very low oral bioavailability due to almost complete first pass metabolism [45] would seem to create conditions favoring the maximization of therapeutic effect in the lung and minimization of the risk of systemic adverse effects, especially suppression of the HPA system.

Preliminary research has focused on demonstrating the therapeutic equivalence of ciclesonide with the three most commonly used ICSs: fluticasone, budesonide and beclomethasone. So far, ciclesonide has not been found to be any more or less effective than other ICSs for the outcomes of lung function, symptoms, quality of life, airway responsiveness to a provoking agent, or inflammatory markers [46].

Preliminary research also seems to indicate the potential for reduced local and systemic side effects with ciclesonide. Weinbrenner and co-workers found no clinically relevant effects of ciclesonide, administered for 1 week at a dose of 640 µg/day, on the HPA axis, independent of the time of administration [47]. In a study comparing treatment with ciclesonide and fluticasone, Derom and co-workers found that 24-h cortisol secretion (a measure of HPA suppression) did not change significantly from baseline in patients treated with ciclesonide, whereas treatment with low- and high-dose fluticasone suppressed cortisol secretion by 29% and 59%, respectively [48]. Other studies have found similar results [49,50].

Compared to currently available ICSs, ciclesonide has been shown to be as effective with potentially less side effects. The use of ciclesonide may also improve adherence, as it is dosed only once per day, rather than twice per day as with other ICSs. However, as with all new products, the advantages witnessed in clinical trials will need to be studied on a long-term basis and on a large scale. Many studies of this sort are already underway.

3.2.4 *Once-daily LABAs*

A number of once-daily LABAs are currently under development for the treatment of asthma and chronic obstructive pulmonary disease, including arformoterol, carmoterol, indacaterol, GSK-159797 and GSK-597901 [51]. As with once-daily ICS therapy, once-daily LABAs have the potential to enhance adherence to therapy and lead to improved clinical

outcomes, especially if given in a combination product with a once-daily ICS.

Twice-daily LABAs currently in clinical use are given as a racemic mixture, and it has been established that only the (*R*)-enantiomer is pharmacologically active. However, it has long been debated whether the adverse effects on disease progression that have been seen with regular use of β_2-agonists may be due to undesirable effects of the accompanying (*S*)-enantiomer, which has pharmacological properties that are unrelated to β_2-adrenoceptor activity and also has a 12-fold slower rate of metabolism than the (*R*) form [52]. To avoid the potentially unwanted effects of the (*S*)-enantiomer, the majority of the once-daily LABAs are being developed as the pure (*R*) form.

3.2.5 Phosphodiesterase 4 inhibitors: roflumilast

Phosphodiesterases (PDEs) are enzymes involved in the degradation of cAMP, which is a natural modulator of inflammation. PDE4 is expressed in inflammatory cells involved in the pathophysiology of asthma (T lymphocytes, eosinophils and macrophages), and thus represents a potential target for new anti-inflammatory therapeutics.

Roflumilast is an oral PDE4 inhibitor that has been found to reduce TNF-α synthesis, T cell proliferation and cytokine production [53,54]. The high systemic availability of orally administered roflumilast and the prolonged half-life of its active metabolite, roflumilast *N*-oxide, favor a once-daily dosing regimen [55]. In a recent study comparing roflumilast (500 µg once daily) and budesonide (200 µg twice daily) in patients with moderate-to-severe persistent asthma, Bousquet and co-workers found that both therapies were equally effective for improving FEV_1, decreasing symptoms, and decreasing use of rescue medications. The investigators concluded that roflumilast was comparable to budesonide in regard to outcome measures and safety [56].

The side effects of roflumilast, which are primarily nausea and headache, may limit its wide acceptance for asthma therapy. Further research is needed to determine whether the oral, once-daily dosing of roflumilast will improve patient adherence and, thereby, play a role in the management of difficult asthma, despite side effects. Alternatively, ongoing research includes inhibitors of other PDE families (such as PDE7) that are also expressed in immune and pro-inflammatory cells in the hope that the beneficial activity can be retained at the expense of side effects.

4. Expert opinion

No single evaluation paradigm or intervention strategy exists that will control all patients with asthma. Guideline-based therapy should be implemented first, but patients with a less than complete response will require additional intervention. The selection of one of these newer therapies will depend on the nature of the patient's asthma.

Currently available ICSs may have significant systemic presence and an unacceptable side effect profile, especially in patients using maximum doses. In these patients, the use of a safer ICS, such as ciclesonide, may be warranted. For patients with atopic asthma, omalizumab has been shown to decrease exacerbations and ICS dose, and to improve quality of life. When primarily non-allergic inflammation is predominant, antagonizing TNF-α with a treatment such as etanercept may be useful. Roflumilast may be especially effective in patients with lung disease related to smoking, as the upregulation of histone deacetylase may help to improve ICS responsiveness.

A recent intriguing observation suggests that natural killer T cells may play an important immunomodulatory role in patients with asthma. Natural killer T cells can promote the polarization of CD4 T cells into T_H1 and T_H2 cells, and asthma is thought to have a T_H2-driven immunological basis. Much has been learned in recent years about mouse models of asthma in this regard, but research in humans has only just begun. More research in this area may lead to future immunotherapies which, by controlling the immune response to infections and allergens, may shift the focus of asthma treatment towards preventing the development of the disease [57].

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