

Anti-TNF- α and Th1 cytokine-directed therapies for the treatment of asthma

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Purpose of review

This article examines recent work about the role of TNF- α and of selected Th1-related cytokines in asthma with particular emphasis on the therapeutic potential of blocking the biological activity of these mediators.

Recent findings

Current research endeavours suggest that asthma pathogenesis is driven by a mixed Th1/Th2 immune response. The contribution of individual Th1-associated and Th2-associated effector mechanisms to this mixed response profile is highly heterogeneous and variations in response patterns seem to be associated with heterogeneity in clinical phenotypes. In particular, it is now acknowledged that allergen-specific Th1 responses appear to be responsible for the pathogenetic effects seen in patients suffering from the more severe chronic forms of the disease. This is important because usual treatments for asthma appear to have limited effects on the more chronic severe forms of the disease and there is a pressing need for the development of new treatment strategies. The failure of topical corticosteroids to reduce TNF- α and Th1-derived cytokines to a significant level in asthmatic airways may explain to a certain extent why these drugs appear to have limited effects in the more severe forms of asthma.

Summary

It is likely that therapies blocking TNF- α and interfering with Th1-derived cytokines may be a considerable advance in the management of those asthma patients who are particularly resistant to typical treatment modalities.

Keywords

asthma, biological therapy, IFN- γ , IL-2, IL-12, IL-18, TNF- α

Abbreviations

AHR	airway hyperresponsiveness
BAL	bronchoalveolar lavage
COPD	chronic obstructive pulmonary disease
ICS	inhaled corticosteroid
LPS	lipopolysaccharide
TACE	TNF- α -converting enzyme

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Introduction

The so-called 'Th2 hypothesis' of asthma stems from the pioneering work by Mosmann *et al.* [1]. Their observations in mouse CD4+ lymphocytes *in vitro* revealed that these cells could be polarized into two distinct functional populations: Th1 cells and Th2 cells. Th1 cells produce IFN- γ , TNF- α , and interleukins IL-2, IL-12 and IL-18. These cytokines help to clear invading bacteria and viruses and are generally associated with cell-mediated immunity. Th2 cells, which produce IL-4, IL-5, IL-9 and IL-13, are important in fine-tuning B cell antibody production and defending against parasitic infections (especially helminths). As Th2 cytokines are known to induce eosinophilia, IgE production, mucus secretion and mast cell maturation/activation, they have been specifically linked to asthma pathogenesis.

Recent research endeavours have suggested, however, that asthma pathogenesis is rather driven by a mixed Th1/Th2 immune response [2]. Moreover, the contribution of individual Th1-associated and Th2-associated effector mechanisms to this mixed response profile is highly heterogeneous, and variations in response patterns seem to be associated with heterogeneity in clinical phenotypes [2]. Thus, despite the notion of the potential protective effects of Th1 immunity in relation to induction of atopic asthma [1–3] and of the widely accepted immunoregulatory role of Th2 cytokines in the pathogenesis of allergic asthma [4], an equally plausible case can be made for a role for Th1 cytokines in driving disease pathogenesis.

Indeed, several lines of evidence in model systems and in humans raise questions for the Th2 hypothesis as a conclusive explanation for asthma. Over the past years, the Th1/Th2 theory has been challenged for two main reasons: Th1 and Th2 cells are both pro-inflammatory; and Th1 cells do not always cross-regulate Th2 cells, but

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instead might exacerbate Th2-mediated diseases [5,6]. For example, Holtzman *et al.* [7] highlighted that Th1 as well as antigen-specific Th2 cells may be necessary for initiating the allergic response in mouse models of asthma. Furthermore, some features of the asthma phenotype, such as airway hyperresponsiveness (AHR) and mucus production, may develop in the absence of IgE production and tissue eosinophilia, which are well known Th2-mediated phenomena [8–10]. In murine models, AHR appears to be dissociated from eosinophilic inflammation because of variations in the genetic background [11,12]. In man, the development of clinical asthma appears to be independent of atopic status [13], with no evidence for linkage between asthma and candidate genes for atopy [14]. That Th2 cells may not be so critical in the pathogenesis of asthma is also underscored by the evidence that allergen-specific Th1 responses appear to be responsible for the pathogenetic effects seen in patients suffering from chronic forms of atopy [15,16].

These findings have important implications in relation to drug development, and provide one possible explanation for the equivocal results of the asthma trials using antagonists directed to Th2 cytokines. It may be argued that it is also necessary to interfere with Th1-mediated phenomena by means of potent and selective antagonists directed to Th1 cytokines for a completely successful therapeutic strategy. Human Th1 cells normally produce large amounts of IFN- γ and IL-2. As Th1 differentiation and IFN- γ production is critically controlled by IL-12 and IL-18, these pleiotropic cytokines are also worthy of consideration even though not released by CD4⁺ cells [17]. TNF- α is another pleiotropic cytokine produced by several proinflammatory (mainly macrophages, but also CD4⁺ cells) and structural cells known to be crucial in the pathogenesis of asthma. It may be considered a 'borderline' cytokine because it appears to enhance both types 1 and 2 immune responses.

In this article we will review the role of TNF- α and of selected Th1-related cytokines in asthma and we will discuss the recent research into the therapeutic potential of blocking the biological activity of these mediators.

Interferons

Among the Th1 cytokines, IFN- γ is known as the most potent in suppressing Th2-type allergic responses [18,19] with pleiotropic actions. The mechanisms underlying these pleiotropic actions include suppressing the release of Th2-type cytokines from activated T cells [18,20], suppressing differentiation of naive T cells to Th2 subtypes [21], facilitating apoptosis of T cells and eosinophils [22], and inducing nitric oxide production [23]. An inhibitory role for IFN- γ has been confirmed in several experimental models of asthma. The allergic inflammatory component of the airways persisted in IFN- γ -deficient

mice after allergen challenge compared with wild-type control mice [24]. In sensitized animals nebulized IFN- γ inhibited eosinophilic inflammation induced by allergen exposure [25]. Also, adenovirus-mediated gene transfer of IFN- γ was shown to inhibit allergic inflammation in mice [26]. IFN- γ , however, being a pleiotropic cytokine, is strongly involved in the up-regulation of ICAM-1 and other cytokines, suggesting a proinflammatory effect [27].

The complexity of regulation of IFN- γ in asthma has repeatedly been highlighted. Contrasting with the commonly decreased expression of IFN- γ in groups with atopic asthma [13], either elevated serum IFN- γ levels [28] or increased release from lung cells in adults with asthma have been reported [29]. Similar apparent discrepancies in the regulation of IFN- γ have also been observed in young children. Thus, studies have shown a relatively lower release of IFN- γ from peripheral blood-stimulated mononuclear cells in childhood atopic [30] and infantile asthma [31], but increased levels of IFN- γ in respiratory secretions from infants with persistent wheezing [32]. Recently Heaton *et al.* [2] showed that the wheal size from skin prick with allergen and AHR were positively associated with in-vitro IFN- γ responses.

Nonetheless, administration of IFN- γ by nebulization to asthmatic patients did not significantly reduce eosinophilic inflammation, possibly due to the difficulty in obtaining a high enough concentration locally in the airways [33]. Interestingly, allergen immunotherapy increases IFN- γ production by circulating T cells in patients with clinical benefit [34] and increased numbers of IFN- γ expressing cells in nasal biopsies of patients with allergic rhinitis [26]. A preliminary report suggests that IFN- γ may be useful in the treatment of patients with severe asthma who have reduced responsiveness to corticosteroids [35]. More recently it has been documented that a murine IFN- γ recombinant adenoviral vector is able to overexpress exogenous gene in murine lungs [36]. This IFN- γ overexpression can abrogate allergen-induced eosinophilic infiltration in lungs in an asthmatic model, which may suggest a new preventively therapeutic method for cytokine immunogenetic transfer in allergic asthma. This hypothesis, however, contrasts with the recent documentation that IFN- γ can lead to decreased epithelial barrier function and increased allergen influx and might thus augment immediate allergic reactions [37].

IL-2

Activated T cells, particularly Th0 and Th1 T cells, are major sources of IL-2 [38]. Binding of IL-2 to IL-2 receptors induces proliferation of T cells, secretion of cytokines, and enhanced expression of receptors for growth factors. The IL-2 receptor complex is composed of three chains (α , β and γ) and belongs to the family of

hematopoietic cytokine receptors [39,40]. IL-2 is a potent chemoattractant for eosinophils *in vitro* [41]. Its systemic infusion as part of chemotherapeutic treatment results in eosinophilia, with an associated increase in eosinophil colony-stimulating activity [42,43]. IL-2 enhances granulocyte macrophage colony stimulating factor production in peripheral blood mononuclear cells from asthmatics and IL-5 production in T cells from patients with the hypereosinophilic syndrome [44,45]. Repeated administration of IL-2 induces AHR in Lewis rats [46]. In ovalbumin sensitized Brown Norway rats, IL-2 led to a threefold increase in the late phase response, compared with the response in rats receiving only saline before allergen exposure [47]. IL-2 caused an inflammatory response around the airways, with a significant increase in eosinophils, lymphocytes, and mast cells. IL-2 is able to increase hydrogen peroxide production by normodense eosinophils isolated from patients with asthma thus contributing to bronchial epithelium damage and chronic inflammation [48].

The potential role of IL-2 in asthmatics is documented by the evidence that levels of IL-2 are increased in bronchoalveolar lavage (BAL) fluid from patients with symptomatic asthma [49,50]. Increased BAL cells expressing IL-2 mRNA are also present [51] and a non-significant increase in IL-2 mRNA-positive cells is also observed in asthmatics after allergen challenge [52]. Particularly high levels of IL-2 and IL-4 mRNA-positive bronchoalveolar lavage cells are observed in steroid-resistant asthmatic patients, compared with steroid-sensitive patients [53]; this increase is not abolished by pretreatment with oral prednisolone for the steroid-resistant patients, and there are no differences in the expression of IL-5 and IFN- γ mRNA between the two groups.

Daclizumab, a humanized monoclonal antibody directed against the IL-2 receptor α chain (CD25, Tac), dose-dependently inhibited secretion of all major Th2 cytokines IL-4, IL-5, IL-9, and IL-13 by activated T cells [54]. It also reduced the secretion of pro-inflammatory cytokines: TNF- α , IFN- γ , IL-6, and TNF- β . It has been recently reported that daclizumab improved asthma control in a phase II trial of 115 patients with moderate to severe chronic persistent asthma [55] and in a subset of 33 patients with refractory asthma [56]. Basiliximab, a chimeric anti-IL-2 receptor monoclonal antibody, can selectively block the bindings of IL-2 on the surface of activated T lymphocytes. It is used to prevent acute graft rejection, but it has the potential for also being tested in refractory asthma [57].

IL-12

IL-12 is a heterodimeric cytokine produced by phagocytes (monocytes, macrophages) and antigen-presenting cells (B cells, dendritic cells) [58,59]. It activates natural

killer cells, mast cells, and T lymphocytes, and seems particularly potent in its ability to induce production of IFN- γ and to downregulate IL-5 production, possibly through endogenous release of IL-10 [60]. IL-12 sends a powerful signal to naive precursor cells of the Th lineage, directing differentiation into Th1 cells *in vitro* and *in vivo*, and shifting the immune response toward cell-mediated immunity [61,62]. IL-12 knockout mice have defective IFN- γ production, diminished Th1 immune responses, and elevated IL-4 production [63]. In-vivo animal models have documented that exogenous administration of IL-12 during the primary sensitization process, suppresses allergen-induced Th2 development, favouring Th1 [64]. Furthermore, IL-12 inhibits AHR and airway eosinophilia after antigen challenge in sensitized animals [65]. When mouse-recombinant IL-12 is administered intraperitoneally to ovalbumin-sensitized mice, a marked reduction in the ovalbumin induced influx of eosinophils into the airway lumen was observed; this is compatible with the known modifying effects of this cytokine via IFN- γ on Th2 responses [66].

It is now known that levels of IL-12 released from whole blood cells are lower in asthmatic patients, indicating a possible intrinsic inability of these patients with regard to IL-12 secretion [67] and a predisposition to excessive production of IgE and IL-5. Moreover, IL-12 expression has been shown to be reduced in bronchial biopsy samples from asthmatic individuals [68].

On the basis of the above-mentioned studies, it has been suggested that IL-12 has the potential to mediate disease modification and exert long-term effects on the natural history of asthma. Recombinant human IL-12, however, induces several toxic effects in humans that are reduced by slow escalation of the dose [69]. Bryan *et al.* [70] tested the hypothesis that administration of recombinant IL-12 would reduce airway responses to allergen challenge. They administered intravenously four increasing doses of IL-12 or placebo at weekly intervals in a randomized, double-blind, parallel group design. Allergen challenges were performed before randomization, 24 h before the first injection and 24 h after the fourth injection. They measured the late allergic response, and airway responsiveness to histamine and sputum eosinophils, 24 h after allergen. Twenty-four hours before the first treatment injection, allergen challenge increased sputum eosinophilia in both groups. Twenty-four hours after the final injection, allergen induced sputum eosinophilia was significantly decreased by 55% in participants treated with IL-12, compared with 15% in placebo-treated participants. In contrast, there was no difference in the late response or AHR to histamine between the two study groups. Most importantly, four of the patients treated with IL-12 were withdrawn from the study because of serious adverse effects including marked elevation of

serum transaminase concentrations and in one patient because of cardiac arrhythmias.

These results indicate that treatment with IL-12 is not suitable for asthma. In mice, however, administration of an IL-12-allergen fusion protein results in the development of a specific Th1 response to the allergen, with increased production of an allergen-specific IgG2, rather than the normal Th2 response with IgE formation [71]. This indicates the possibility of using local IL-12 together with specific allergens to provide a more specific immunotherapy, which might even be curative if applied early in the course of the allergic disease. Recently, it has been shown that intranasal IL-12 significantly decreases pulmonary inflammation and airway reactivity thus indicating that topical IL-12 could be used as an adjuvant during allergen immunotherapy [72]. Intranasal IL-12 therapy combined with allergen therapy may be more effective, necessitate fewer injections and show fewer adverse reactions than conventional immunotherapy. Another treatment option that has the potential of inducing a Th1 cytokine response is the use of IL-12 linked to polyethylene glycol moieties. This mode of administration is likely to enhance cytokine delivery to the target organ, while decreasing its toxicity [73].

IL-18

IL-18, originally described as IFN- γ releasing factor, is a cytokine secreted by activated macrophages, and it shares some of its biologic activities with IL-12. It can induce both IFN- γ and IL-4 responses depending on its surrounding cytokine circumstances. Indeed, in presence of IL-12, IL-18 induces IFN- γ production from T lymphocytes, promoting differentiation of T cells to the Th1 subset [74], whereas IL-18 on its own induces IL-4 and IL-13 production [75^{*}]. Many animal and in-vitro studies have implicated IL-18 in the divergence of Th1 and Th2 immune responses [76,77]. Although an inherently low level of IL-18 may be associated with the pathogenesis of asthmatic airway inflammation in man [78], in a murine model of asthma IL-18 appears to increase IgE, Th2 cytokines, and airway eosinophilia [79]. Furthermore, various allergic conditions have been reported to be associated with increased serum levels of IL-18 [80–82].

Walter *et al.* [83] demonstrated that a single administration of IL-18 delivered as cDNA in an adenoviral vector prevented the development of AHR, and more importantly, reversed established AHR and shifted the balance of an established Th2 immune response towards a Th1-biased response in a murine model of asthma. It has also been shown that vaccination with a DNA vaccination plasmid containing cDNA for a prototypic allergen, OVA, fused to IL-18 cDNA protects against, and

reverses established, AHR in a murine asthma model [84].

TNF- α

TNF- α is an important pro-inflammatory cytokine that exerts its biological response by stimulating two structurally related receptors known as TNF-R1 (p55; CD120a) and TNF-R2 (p75; CD120b) [85]. These receptors are expressed on the surface of many cell types known to be crucial in the pathogenesis of asthma, and their activation results in a remarkably diverse set of cellular responses, including differentiation, activation, and apoptosis [85,86]. TNF- α is also a well known inducer of the inflammatory response and a regulator of immunity [86,87]. A strong argument exists for TNF- α being a critical cytokine in the pathogenesis of chronic inflammatory disorders of the airways [88^{*}].

Once released in the airways, TNF- α acts by inducing a general inflammatory response mainly through enhanced release of pro-inflammatory/chemotactic mediators and upregulation of adhesion molecules such as E-selectin, VCAM-1, and ICAM-1, thus facilitating the migration of neutrophils and eosinophils [89,90]. Eventually, this will lead to chronic inflammation and irreversible airway remodelling – an established feature in bronchial asthma. Indeed, TNF- α can induce proliferation and activation of sub-epithelial myofibroblasts/fibroblasts thus contributing to development of sub-epithelial fibrosis and to tissue remodeling [91,92]. TNF- α is also likely to have a more integrated role in airway remodeling, as it appears to modulate the EGFR-dependent stress and repair response that occurs as a result of the inflammatory response that is associated with airway epithelial injury [93].

That TNF- α plays a major role in the pathogenesis of human asthma has emerged from a number of recent experimental and clinical studies. TNF- α mRNA appears to be more frequently expressed in the airway of asthmatic patients than normal subjects and increased release of this cytokine has been shown from cells obtained from the BAL of asthmatic patients [94]. Also, elevated levels of TNF- α are present in the BAL fluid of asthmatic patients exposed to lipopolysaccharide (LPS) and they appear to correlate with the resultant increase in bronchial hyperresponsiveness [95]. Likewise, TNF- α was found to be increased in the BAL fluid of asthmatic patients in response to allergen challenge [96].

The role of TNF- α in the pathogenesis of asthma is not just limited to its biological effects in airway inflammation and remodelling; perhaps, its most prominent effect is that of induction/potential of airway hyperresponsiveness. Specifically, investigators have recently

demonstrated that TNF- α induces a hypercontractile phenotype in ASM cells by modulating the secretion of other cytokines or chemokines, by regulating the level of expression of adhesion molecules and by enhancing calcium-signalling pathways [97]. Earlier work by Kips *et al.* [98] showed that exposure to TNF- α causes AHR and inflammation in sensitized rats. In this model, exposure to LPS induced elevated TNF- α concentrations in the BAL fluid in association with airway hyperresponsiveness and pretreatment with anti-TNF- α antibodies before LPS exposure significantly diminished the increase in airway hyperresponsiveness. Likewise, in tracheal preparation of Dunkin–Hartley guinea-pigs, recombinant human TNF- α increased maximal isotonic contraction to methacholine and could be completely inhibited by co-incubation of the organ bath with a dimeric recombinant TNF-receptor p80 construct [99]. Using a TNF- α receptor fusion protein, Renzetti *et al.* [100] were the first to provide evidence for the involvement of TNF- α in allergen-induced airway hyperresponsiveness in sensitized guinea pigs. They also showed that the TNF- α receptor fusion protein is equally effective as dexamethasone in preventing allergen-induced responses, suggesting that a therapy directed against TNF- α may be useful in the management of asthma. Another argument for the importance of TNF- α in the development of airway inflammation and airway hyperresponsiveness is that derived from studies in man. In healthy human volunteers, exogenous TNF- α administered as an aerosol significantly increased airway reactivity in association with a neutrophil influx in the BAL fluid [101]. In a follow-up double blind, placebo controlled, randomized, crossover study of 10 participants with mild asthma treated with nebulized recombinant human TNF- α , Thomas *et al.* [102] were able to confirm their earlier observations in healthy volunteers. In view of these findings, it has been proposed that TNF- α may also play a pathogenetic role in the AHR associated with asthma.

Considering the critical role of TNF- α in the pathogenesis of asthma and the need for alternative treatments for those asthmatic patients with severe disease who are particularly resistant to conventional therapy, molecules targeted at blocking the effects of TNF- α are likely to constitute a considerable advance in the management of these difficult patients. The currently commercially available TNF- α blockers (infliximab, a chimeric mouse/human monoclonal anti-TNF- α antibody; etanercept, a soluble fusion protein combining two p75 TNF receptors with a Fc fragment of human IgG₁; and adalimumab, a fully human monoclonal anti-TNF- α antibody) have proven to be remarkably effective and well tolerated in well conducted clinical trials of patients with rheumatoid arthritis refractory to conventional therapy [103].

To date there is very limited information on the use of TNF- α blocking agents in asthma. In a retrospective analysis of rheumatoid arthritis patients receiving infliximab, Khalil *et al.* [104] were the first to report a significant improvement in forced expiratory volume in 1 s (FEV₁) and exercise tolerance in three patients who were also diagnosed with asthma or chronic obstructive pulmonary disease (COPD). All three patients showed an important clinical improvement whilst on infliximab and discontinued use of their maintenance inhaled corticosteroids. The notion that inhibition of TNF- α may be of prime importance in the control of airway inflammation with improved asthma outcomes was emphasized by subsequent observations by other researchers who investigated the effect of etanercept in 15 patients maximally treated for chronic severe asthma [105^{••}]. In this open labeled uncontrolled trial, 25 mg etanercept administered subcutaneously twice a week for a period of 12 weeks clearly improved lung function and had an important impact on the overall asthma symptoms scores with all but one of the patients discontinuing their regular bronchodilators by the end of the study. Of particular note is the remarkable attenuation in airway hyperresponsiveness that occurred after treatment with etanercept. These initial observations were recently confirmed in a small randomized placebo-controlled crossover trial of etanercept (25 mg; administered subcutaneously twice a week for a period of 10 weeks) in 10 patients with chronic severe asthma refractory to treatment with inhaled corticosteroids (ICS) [106]. Compared with placebo, an important attenuation in airway hyperresponsiveness was observed after etanercept. There was also a significant improvement in FEV₁ after bronchodilator and in overall asthma symptoms scores after treatment with etanercept compared with placebo. In patients with a mild form of the disease, however, the injection of etanercept, 25 mg subcutaneously, twice weekly for 2 weeks, failed to attenuate pulmonary eosinophilia and to reduce AHR to methacholine [107[•]]. This latter study underscores the current view that TNF- α is particularly important in the more severe chronic stages of the disease.

In view of the close similarities between chronic severe asthma and COPD and considering the important role of TNF- α in the induction and maintenance of airway inflammation in COPD [108], it has been suggested that blocking the biological effects of TNF- α may also be beneficial in the treatment of COPD. Regrettably, a recent phase II trial of infliximab in patients with mild-to-moderate COPD failed to reach any definite conclusions about its effectiveness in COPD [109]. It is likely that the observed lack of clinical response is to be ascribed to a number of problems with the study design and subject selection [110] and definite conclusions about effectiveness of anti TNF- α drugs in COPD will require

carefully designed studies with large numbers of patients with adequate disease severity.

Although no significant side effects were noted in the studies with asthmatic patients while on infliximab or etanercept, there is always the possibility of problems associated with antibody-based therapies that have to be given by injection. In order to make the use of drugs interfering with TNF- α more attractive, there has been a search for small molecule inhibitors of tumour necrosis factor. For example, it is possible to reduce the TNF- α level by inhibiting TNF- α -converting enzyme (TACE). Targeting TACE may result in similar efficacy to that seen with anti-TNF antibodies and soluble receptors. In an animal model of airway inflammation, PKF-242–484 and PKF-241–466, two TACE inhibitors, blocked TNF- α release into the airways and inflammatory cell influx [111]. The treatment of patients with inhibitors of TNF- α production such as SB-210313, CJ-14877, CJ-14897 [112], or with antisense oligonucleotides directed against their RNA molecules encoding TNF- α such as ISIS-104838 and ISIS-25302 can be viewed as alternative strategies [113].

Conclusion

Atopic disease is associated with a shift in immune responses away from a Th1 pattern toward a Th2 profile. Although a correction in the imbalance between Th1 and Th2 may contribute to disease resolution, studies on the role of Th1 cells and their cytokines in allergic asthma have resulted in conflicting findings. Nonetheless, despite disparate results, Th1 cells and their secreted products appear to predominantly downmodulate Th2 responses. Specifically, it appears that blockade of a Th1 cytokine in clinical asthma is highly efficacious at the severe end of the disease spectrum. This simply reflects the fact that asthma is a heterogeneous syndrome with heterogeneity in disease pathogenesis and treatment response; thus viewing this disease simply as a Th2 inflammatory response is inadequate, especially as the disease becomes chronic and severe. Regrettably, the common drugs used for treating asthma appear to have limited effects on the more chronic severe forms of the disease and there is a pressing need for the development of new treatment strategies for patients at the more severe end of the disease spectrum who do not respond well to current therapy. The failure of ICS to reduce TNF- α and Th1-derived cytokines to a significant level in asthmatic airways may explain to a certain extent why ICS appear to have limited effects in the more severe forms of asthma. Therefore, it is likely that therapies blocking TNF- α and interfering with Th1-derived cytokines may be a considerable advance in the management of those asthma patients who are particularly resistant to typical treatment modalities.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 70).

- 1 Mosmann TR, Cherwinski H, Bond MW, *et al.* Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* 1986; 175:5–14.
- 2 Heaton T, Rowe J, Turner S, *et al.* An immunoepidemiological approach to asthma: identification of in-vitro T-cell response patterns associated with different wheezing phenotypes in children. *Lancet* 2005; 365:142–149.
- 3 Romagnani S. The role of lymphocytes in allergic disease. *J Allergy Clin Immunol* 2000; 105:399–408.
- 4 Umetsu DT, McIntire JJ, Akbari O, *et al.* Asthma: an epidemic of dysregulated immunity. *Nat Immunol* 2002; 3:715–720.
- 5 Hansen G, Berry G, DeKruyff RH, Umetsu DT. Allergen-specific Th1 cells fail to counterbalance Th2 cell-induced airway hyperreactivity but cause severe airway inflammation. *J Clin Invest* 1999; 103:175–183.
- 6 Randolph DA, Carruthers CJ, Szabo SJ, *et al.* Modulation of airway inflammation by passive transfer of allergen-specific Th1 and Th2 cells in a mouse model of asthma. *J Immunol* 1999; 162:2375–2383.
- 7 Holtzman MJ, Agapov E, Kim E, *et al.* Developing the epithelial, viral, and allergic paradigm for asthma. *Chest* 2003; 123:377S–384S.
- 8 Hogan SP, Mould A, Kikutani H, *et al.* Aeroallergen-induced eosinophilic inflammation, lung damage, and airways hyperreactivity in mice can occur independently of IL-4 and allergen-specific immunoglobulins. *J Clin Invest* 1997; 99:1329–1339.
- 9 Mehlhop PD, van de Rijn M, Goldberg AB, *et al.* Allergen-induced bronchial hyperreactivity and eosinophilic inflammation occur in the absence of IgE in a mouse model of asthma. *Proc Natl Acad Sci U S A* 1997; 94:1344–1349.
- 10 Wills-Karp M, Luyimbazi J, Xu X, *et al.* Interleukin-13: central mediator of allergic asthma. *Science* 1998; 282:2258–2261.
- 11 Corry DB, Folkesson HG, Warnock ML, *et al.* Interleukin 4, but not interleukin 5 or eosinophils, is required in a murine model of acute airway hyperreactivity. *J Exp Med* 1996; 183:109–117.
- 12 Foster PS, Hogan SP, Ramsay AJ, *et al.* IL-5 deficiency abolishes eosinophilia, airways hyperreactivity, and lung damage in a mouse asthma model. *J Exp Med* 1995; 183:195–201.
- 13 Holtzman MJ, Sampath D, Castro M, *et al.* The one-two of T helper cells: does interferon- γ knockout the Th2 hypothesis for asthma? *Am J Respir Cell Mol Biol* 1996; 14:316–318.
- 14 Hakonarson H, Bjornsdottir US, Ostermann E, *et al.* Allelic frequencies and patterns of single-nucleotide polymorphisms in candidate genes for asthma and atopy in Iceland. *Am J Respir Crit Care Med* 2001; 164:2036–2044.
- 15 Hales BJ, Shen H, Thomas WR. Cytokine responses to Der p 1 and Der p 7: house dust mite allergens with different IgE-binding activities. *Clin Exp Allergy* 2000; 30:934–943.
- 16 Oldfield WL, Kay AB, Larche M. Allergen-derived T cell peptide-induced late asthmatic reactions precede the induction of antigen-specific hyperresponsiveness in atopic allergic asthmatic subjects. *J Immunol* 2001; 167:1734–1739.
- 17 Okamura H, Kashiwamura S, Tsutsui H, *et al.* Regulation of interferon- γ production by IL-12 and IL-18. *Curr Opin Immunol* 1998; 10:259–264.
- 18 Tang C, Inman MD, van Rooijen N, *et al.* Th type 1-stimulating activity of lung macrophages inhibits Th2-mediated allergic airway inflammation by an IFN- γ -dependent mechanism. *J Immunol* 2001; 166:1471–1481.
- 19 Lack G, Bradley KL, Hamelmann E, *et al.* Nebulized IFN- γ inhibits the development of secondary allergic responses in mice. *J Immunol* 1996; 157:1432–1439.
- 20 Swain SL, Bradley LM, Croft M, *et al.* Helper T-cell subsets: phenotype, function and the role of lymphokines in regulating their development. *Immunol Rev* 1991; 123:115–144.
- 21 Gajewski TF, Fitch FW. Anti-proliferative effect of IFN- γ in immune regulation, I: IFN- γ inhibits the proliferation of Th2 but not Th1 murine helper T lymphocyte clones. *J Immunol* 1988; 140:4245–4252.
- 22 Morita M, Lamkhouiou B, Soussi Gounni A, *et al.* Induction by interferons of human eosinophil apoptosis and regulation by interleukin-3, granulocyte/macrophage-colony stimulating factor and interleukin-5. *Eur Cytokine Netw* 1996; 7:725–732.

- 23 Barnes PJ, Liew FY. Nitric oxide and asthmatic inflammation. *Immunol Today* 1995; 16:128–130.
- 24 Yoshida M, Leigh R, Matsumoto K, *et al*. Reversing effect of interferon on T_H2 responses after allergen challenge in sensitized interferon-deficient mice. *Am J Respir Crit Care Med* 2002; 166:451–456.
- 25 Benjaponpitak S, Oro A, Maguire P, *et al*. The kinetics of change in cytokine production by CD4 T cells during conventional allergen immunotherapy. *J Allergy Clin Immunol* 1999; 103:468–475.
- 26 Durham SR, Ying S, Varney VA, *et al*. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon- γ . *J Allergy Clin Immunol* 1996; 97:1356–1365.
- 27 Dery RE, Bissonnette EY. IFN- γ potentiates the release of TNF- α and MIP- α by alveolar macrophages during allergic reactions. *Am J Respir Cell Mol Biol* 1999; 20:407–412.
- 28 Ten Hacken NHT, Oosterhoff Y, Kauffman HF, *et al*. Elevated serum interferon- γ in atopic asthma correlates with increased airways responsiveness and circadian peak expiratory flow variation. *Eur Respir J* 1998; 11:312–316.
- 29 Krug N, Madden J, Redington AE, *et al*. T-cell cytokine profile evaluated at the single cell level in BAL and blood in allergic asthma. *Am J Respir Cell Mol Biol* 1996; 14:319–326.
- 30 Warner JA, Miles EA, Jones AC, *et al*. Is deficiency of interferon γ production by allergen triggered cord blood cells a predictor of atopic eczema? *Clin Exp Allergy* 1994; 24:423–430.
- 31 Renzi PM, Turgeon JP, Marcotte JE, *et al*. Reduced interferon- γ production in infants with bronchiolitis and asthma. *Am J Respir Crit Care Med* 1999; 159:1417–1422.
- 32 van Schaik SM, Tristram DA, Nagpal IS, *et al*. Increased production of IFN- γ and cysteinyl leukotrienes in virus-induced wheezing. *J Allergy Clin Immunol* 1999; 103:630–636.
- 33 Boguniewicz M, Martin RJ, Martin D, *et al*. The effects of nebulized recombinant interferon-gamma in asthmatic airways. *J Allergy Clin Immunol* 1995; 95:133–135.
- 34 Benjaponpitak S, Oro A, Maguire P, *et al*. The kinetics of change in cytokine production by CD4 T cells during conventional allergen immunotherapy. *J Allergy Clin Immunol* 1999; 103:468–475.
- 35 Gratzl S, Palca A, Schmitz M, Simon HU. Treatment with IFN- α in corticosteroid-unresponsive asthma. *J Allergy Clin Immunol* 2000; 105:1035–1036.
- 36 Gao Z, Kang Y, Xu Y, *et al*. Inhibition of allergic responsiveness in a murine asthma model via IFN- γ transgene expression. *Chin Med J* 2002; 115:1470–1474.
- 37 Reisinger J, Triendl A, Kuchler E, *et al*. IFN- γ -enhanced allergen penetration across respiratory epithelium augments allergic inflammation. *J Allergy Clin Immunol* 2005; 115:973–981.
- 38 Morgan DA, Ruscetti FW, Gallo R. Selective in vitro growth of T lymphocytes from normal human bone marrows. *Science* 1976; 193:1007–1008.
- 39 Taniguchi T, Minami Y. The IL-2/IL-2 receptor system: a current overview. *Cell* 1993; 73:5–8.
- 40 Weiss A, Littman DR. Signal transduction by lymphocyte antigen receptors. *Cell* 1994; 76:263–274.
- 41 Rand TH, Silberstein DS, Kornfeld H, Weller PF. Human eosinophils express functional interleukin 2 receptors. *J Clin Invest* 1991; 88:825–832.
- 42 Sedgwick JB, Frick WE, Sandel PM, *et al*. The appearance of hypodense eosinophils during interleukin-2 treatment. *J Allergy Clin Immunol* 1990; 85:557–566.
- 43 Macdonald D, Gordon AA, Kajitani H, *et al*. Interleukin-2 treatment-associated eosinophilia is mediated by interleukin-5 production. *Br J Haematol* 1990; 76:168–173.
- 44 Nakamura Y, Ozaki T, Kamei T, *et al*. Increased granulocyte/macrophage colony-stimulating factor production by mononuclear cells from peripheral blood of patients with bronchial asthma. *Am Rev Respir Dis* 1993; 147:87–89.
- 45 Enokihara H, Furusawa S, Nakakubo H, *et al*. T cells from eosinophilic patients produce interleukin-5 with interleukin-2 stimulation. *Blood* 1989; 73:1809–1813.
- 46 Renzi PM, Du T, Sapienza S, *et al*. Acute effects of interleukin-2 on lung mechanics and airway responsiveness in rats. *Am Rev Respir Dis* 1991; 143:380–385.
- 47 Renzi PM, Sapienza S, Wasserman S, *et al*. Effect of interleukin-2 on the airway response to antigen in the rat. *Am Rev Respir Dis* 1992; 146:163–169.
- 48 Conesa A, Tassinari P, Aldrey O, *et al*. Interleukin-2 induces peroxide production by primed normodense eosinophils of patients with asthma. *Allergy Asthma Proc* 2003; 24:27–33.
- 49 Walker C, Bode E, Boer L, *et al*. Allergic and non-allergic asthmatics have distinct patterns of T-cell activation and cytokine production in peripheral blood and bronchoalveolar lavage. *Am Rev Respir Dis* 1992; 146:109–115.
- 50 Broide D, Paine MM, Firestein GS. Eosinophils express interleukin 5 and granulocyte-macrophage colony-stimulating factor mRNA at sites of allergic inflammation in asthmatics. *J Clin Invest* 1992; 90:1414–1424.
- 51 Robinson DS, Hamid Q, Ying S, *et al*. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992; 326:298–304.
- 52 Bentley AM, Meng Q, Robinson DS, *et al*. Increases in activated T lymphocytes, eosinophils and cytokine mRNA expression for interleukin-5 and granulocyte/macrophage colony-stimulating factor in bronchial biopsies after allergen inhalation challenge in atopic asthmatics. *Am J Respir Cell Mol Biol* 1993; 8:35–42.
- 53 Leung DYM, Martin RJ, Szeffler SJ, *et al*. Dysregulation of interleukin 4, interleukin 5, and interferon γ gene expression in steroid-resistant asthma. *J Exp Med* 1995; 181:33–40.
- 54 Sornasse TR, Hong W, Schreck R, *et al*. Daclizumab in vitro inhibits the secretion of pro-asthmatic and pro-inflammatory cytokines by activated T cells [abstract]. *J Allergy Clin Immunol* 2005; 115:S73.
- 55 Busse WW, Baker JW, Charous BL, *et al*. Preliminary safety and efficacy of daclizumab in the treatment of patients with moderate to severe chronic persistent asthma [abstract]. *J Allergy Clin Immunol* 2004; 113:S286–S287.
- 56 Nelson HS, Busse WW, Israel E, *et al*. Daclizumab improves asthma control in patients with refractory asthma [abstract]. *J Allergy Clin Immunol* 2005; 115:S134.
- 57 Tan J, Yang S, Wu W. Basiliximab (Simulect) reduces acute rejection among sensitized kidney allograft recipients. *Transplant Proc* 2005; 37:903–905.
- 58 Trinchieri G. Interleukin-12: a cytokine produced by antigen-presenting cells with immunoregulatory functions in the generation of T-helper cells type 1 and cytotoxic lymphocytes. *Blood* 1994; 84:4008–4027.
- 59 Trinchieri G. Interleukin-12: a proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. *Annu Rev Immunol* 1995; 13:251–276.
- 60 Lee Y, Fu C, Chiang B. Administration of interleukin-12 exerts a therapeutic instead of a long-term preventive effect on mite Der p 1 allergen-induced animal model of airway inflammation. *Immunology* 1999; 97:232–240.
- 61 Hsieh CS, Macatonia S, Tripp C, *et al*. Development of Th1 CD4⁺ T cells through IL-12 produced by Listeria-induced macrophages. *Science* 1993; 260:547–549.
- 62 Paul WE, Seder RA. Lymphocyte responses and cytokines. *Cell* 1994; 76:241–251.
- 63 Magram J, Connaughton SE, Warrier RR, *et al*. IL-12-deficient mice are defective in IFN γ production and type 1 cytokine responses. *Immunity* 1996; 4:471–481.
- 64 Kips JC, Brusselle GJ, Joos GF, *et al*. Interleukin-12 inhibits antigen-induced airway hyper-responsiveness in mice. *Am J Respir Crit Care Med* 1996; 153:535–539.
- 65 Schwarze J, Hamelmann E, Cieslewicz G, *et al*. Local treatment with IL-12 is an effective inhibitor of airway hyperresponsiveness and lung eosinophilia after airway challenge in sensitized mice. *J Allergy Clin Immunol* 1998; 102:86–93.
- 66 Sur S, Bouchard P, Holbert D, Van Scott MR. Mucosal IL-12 inhibits airway reactivity to methacholine and respiratory failure in murine asthma. *Exp Lung Res* 2000; 26:477–489.
- 67 van der Pouw Kraan TC, Boeijs LC, de Groot ER, *et al*. Reduced production of IL-12 and IL-12-dependent IFN- γ release in patients with allergic asthma. *J Immunol* 1997; 158:5560–5565.
- 68 Naseer T, Minshall EM, Leung DY, *et al*. Expression of IL-12 and IL-13 mRNA in asthma and their modulation in response to steroid therapy. *Am J Respir Crit Care Med* 1997; 155:845–851.
- 69 Leonard JP, Sherman ML, Fisher GL, *et al*. Effects of single-dose interleukin-12 exposure on interleukin-12-associated toxicity and interferon- γ production. *Blood* 1997; 90:2541–2548.
- 70 Bryan SA, O'Connor BJ, Matti S, *et al*. Effects of recombinant human interleukin-12 on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000; 356:2149–2153.
- 71 Kim TS, DeKruyff RH, Rupper R, Maeccker HT, *et al*. An ovalbumin-IL-12 fusion protein is more effective than ovalbumin plus free recombinant IL-12 in inducing a T helper cell type 1-dominated immune response and inhibiting antigen-specific IgE production. *J Immunol* 1997; 158:4137–4144.

- 72 Matsuse H, Kong X, Hu J, *et al*. Intranasal IL-12 produces discrete pulmonary and systemic effects on allergic inflammation and airway reactivity. *Int Immunopharmacol* 2003; 3:457–468.
- 73 Leonard P, Sur S. Interleukin-12: potential role in asthma therapy. *BioDrugs* 2003; 17:1–7.
- 74 Yoshimoto T, Takeda K, Tanaka T, *et al*. IL-12 up-regulates IL-18 receptor expression on T cells, Th1 cells and B cells: synergism with IL-18 for IFN- γ production. *J Immunol* 1998; 161:3400–3407.
- 75 El-Mezayen RE, Matsumoto T. In vitro responsiveness to IL-18 in combination with IL-12 or IL-2 by PBMC from patients with bronchial asthma and atopic dermatitis. *Clin Immunol* 2004; 111:61–68.
- This elegant study provided documentation about the role of IL-18 in increasing IFN- γ production through an IL-12-dependent pathway.
- 76 Suemoto Y, Okamoto I, Usui M, *et al*. IFN- γ -inducing factor (IGIF) is a co-stimulatory factor on the activation of Th1 but not Th2 cells and exerts its effect independently of IL-12. *J Immunol* 1997; 158:1541–1550.
- 77 Hofstra CL, Van Ark I, Hofman G, *et al*. Prevention of Th2-like cell responses by co-administration of IL-12 and IL-18 is associated with inhibition of antigen-induced airway hyperresponsiveness, eosinophilia, and serum IgE levels. *J Immunol* 1998; 161:5054–5060.
- 78 Ho LP, Davis M, Denison A, *et al*. Reduced interleukin-18 levels in BAL specimens from patients with asthma compared to patients with sarcoidosis and healthy control subjects. *Chest* 2002; 121:1421–1426.
- 79 Kumano K, Nakao A, Nakajima H, *et al*. Interleukin-18 enhances antigen-induced eosinophil recruitment into the mouse airways. *Am J Respir Crit Care Med* 1999; 160:873–878.
- 80 Wong CK, Ho CY, Ko FW, *et al*. Proinflammatory cytokines (IL-17, IL-6, IL-18 and IL-12) and Th cytokines (IFN- γ , IL-4, IL-10 and IL-13) in patients with allergic asthma. *Clin Exp Immunol* 2001; 125:177–183.
- 81 Tanaka H, Miyazaki N, Oashi K, *et al*. IL-18 might reflect disease activity in mild and moderate asthma exacerbation. *J Allergy Clin Immunol* 2001; 107:331–336.
- 82 Tanaka T, Tsutsui H, Yoshimoto T, *et al*. Interleukin-18 is elevated in sera from patients with atopic dermatitis and from atopic dermatitis model mice. *NC/Nga Int Arch Allergy Immunol* 2001; 125:236–240.
- 83 Walter DM, Wong CP, DeKruyff RH, *et al*. IL-18 gene transfer by adenovirus prevents the development of and reverses established allergen-induced airway hyperactivity. *J Immunol* 2001; 166:6392–6398.
- 84 Maecker HT, Hansen G, Walter DM, *et al*. Vaccination with allergen-IL-18 fusion DNA protects against, and reverses established, airway hyperactivity in a murine asthma model. *J Immunol* 2001; 166:959–965.
- 85 Bazzoni F, Beutler B. The tumor necrosis factor ligand and receptor families. *N Engl J Med* 1996; 334:1717–1725.
- 86 Wajant H, Henkler F, Scheurich P. The TNF-receptor-associated factor family: scaffold molecules for cytokine receptors, kinases and their regulators. *Cell Signal* 2001; 13:389–400.
- 87 Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. *Nat Rev Immunol* 2003; 3:745–756.
- 88 Russo C, Polosa R. TNF- α as a promising therapeutic target in chronic asthma: a lesson from rheumatoid arthritis. *Clin Sci (Lond)* 2005; 109:135–142.
- This is one of the first review articles underscoring the importance of TNF- α signaling in the context of asthma and bronchial hyperresponsiveness. The potential role of TNF- α as a therapeutic target in severe chronic asthma is also reviewed here.
- 89 Lassalle P, Gosset P, Delneste Y, *et al*. Modulation of adhesion molecule expression on endothelial cells during the late asthmatic reaction: role of macrophage-derived tumor necrosis factor- α . *Clin Exp Immunol* 1993; 94:105–110.
- 90 Yamamoto H, Sedgwick JB, Busse WW. Differential regulation of eosinophil adhesion and transmigration by pulmonary microvascular endothelial cells. *J Immunol* 1998; 161:971–977.
- 91 Paulsson Y, Austgulen R, Hofslie E, *et al*. Tumor necrosis factor-induced expression of platelet-derived growth factor A-chain messenger RNA in fibroblasts. *Exp Cell Res* 1989; 180:490–496.
- 92 Palombella VJ, Mendelsohn J, Vilcek J. Mitogenic action of tumor necrosis factor in human fibroblasts: interaction with epidermal growth factor and platelet-derived growth factor. *J Cell Physiol* 1988; 135:23–31.
- 93 Polosa R, Sapsford RJ, Dokic D, *et al*. Induction of the epidermal growth factor receptor and its ligands in nasal epithelium by ozone. *J Allergy Clin Immunol* 2004; 113:120–126.
- 94 Cembrzynska-Nowak M, Szklarz E, Inglot AD, Teodorczyk-Injeyan JA. Elevated release of tumor necrosis factor- α and interferon- γ by bronchoalveolar leukocytes from patients with bronchial asthma. *Am Rev Respir Dis* 1993; 147:291–295.
- 95 Michel O, Ginanni R, Le Bon B, *et al*. Inflammatory response to acute inhalation of endotoxin in asthmatic patients. *Am Rev Respir Dis* 1992; 146:352–357.
- 96 Gosset P, Tsicopoulos A, Wallaert B, *et al*. Increased secretion of tumor necrosis factor α and interleukin-6 by alveolar macrophages consecutive to the development of the late asthmatic reaction. *J Allergy Clin Immunol* 1991; 88:561–571.
- 97 Amrani Y, Chen H, Panettieri RA Jr. Activation of tumor necrosis factor receptor 1 in airway smooth muscle: a potential pathway that modulates bronchial hyper-responsiveness in asthma? *Respir Res* 2000; 1:49–53.
- 98 Kips JC, Tavernier J, Pauwels RA. Tumor necrosis factor causes bronchial hyper-responsiveness in rats. *Am Rev Respir Dis* 1992; 145:332–336.
- 99 Pennings HJ, Kramer K, Bast A, *et al*. TNF- α induces hyperreactivity in tracheal smooth muscle of the guinea-pig in vitro. *Eur Respir J* 1998; 12:45–49.
- 100 Renzetti LM, Paciorek PM, Tannu SA, *et al*. Pharmacological evidence for tumor necrosis factor as a mediator of allergic inflammation in the airways. *J Pharmacol Exp Ther* 1996; 278:847–853.
- 101 Thomas PS, Yates DH, Barnes PJ. Tumor necrosis factor alpha increases airway responsiveness and sputum neutrophilia in normal human subjects. *Am J Respir Crit Care Med* 1995; 152:76–80.
- 102 Thomas PS, Heywood G. Effects of inhaled tumour necrosis factor alpha in subjects with mild asthma. *Thorax* 2002; 57:774–778.
- 103 Toussiot E, Wendling D. The use of TNF- α blocking agents in rheumatoid arthritis: an overview. *Expert Opin Pharmacother* 2004; 5:581–594.
- 104 Khalil Saadeh C, Brown DM, Chumney-Malacara J, Crow J. Infliximab therapy for rheumatoid arthritis (RA) induced significant control of asthma in patients with both RA and asthma or asthma/COPD in addition to improving RA status [abstract]. *J Allergy Clin Immunol* 2002; 109:s243.
- 105 Howarth PH, Babu KS, Arshad HS, *et al*. Tumour Necrosis Factor (TNF α) as a novel therapeutic target in symptomatic corticosteroid-dependent asthma. *Thorax* 2005 Sep 15 [Epub ahead of print].
- This was the first study to show that TNF- α blocking agents can improve symptoms, lung function and bronchial hyperresponsiveness in chronic severe asthma. It also provides evidence that TNF- α production is increased in these patients.
- 106 Berry MA, Hargadon B, Shelley M, *et al*. Etanercept in refractory asthma: a randomised controlled trial [abstract]. *Am J Respir Crit Care Med* 2005; 171:A63.
- 107 Rouhani FN, Meitin CA, Kaler M, *et al*. Effect of tumor necrosis factor antagonism on allergen-mediated asthmatic airway inflammation. *Respir Med* 2005; 99:1175–1182.
- This work indirectly supports the view that only when asthma becomes more severe and chronic, with the acquisition of an altered inflammatory profile towards a Th1-type response, may anti-TNF- α strategies become useful.
- 108 Chung KF. Cytokines in chronic obstructive pulmonary disease. *Eur Respir J Suppl* 2001; 34:50s–59s.
- 109 van der Vaart H, Koeter GH, Postma DS, *et al*. First study of infliximab treatment in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172:465–469.
- 110 Russo C, D'Angelo F, Polosa R. Study of infliximab treatment in smokers with COPD: What next? *Am J Respir Crit Care Med* (in press).
- 111 Trifileff A, Walker C, Keller T, *et al*. Pharmacological profile of PKF242-484 and PKF241-466, novel dual inhibitors of TNF- α converting enzyme and matrix metalloproteinases, in models of airway inflammation. *Br J Pharmacol* 2002; 135:1655–1664.
- 112 Boehm JC, Smietana JM, Sorenson ME, *et al*. 1-substituted 4-aryl-5-pyridinylimidazoles: a new class of cytokine suppressive drugs with low 5-lipoxygenase and cyclooxygenase inhibitory potency. *J Med Chem* 1996; 39:3929–3937.
- 113 Nyce J. Respirable antisense oligonucleotides: a new, third drug class targeting respiratory disease. *Curr Opin Allergy Clin Immunol* 2002; 2:533–536.