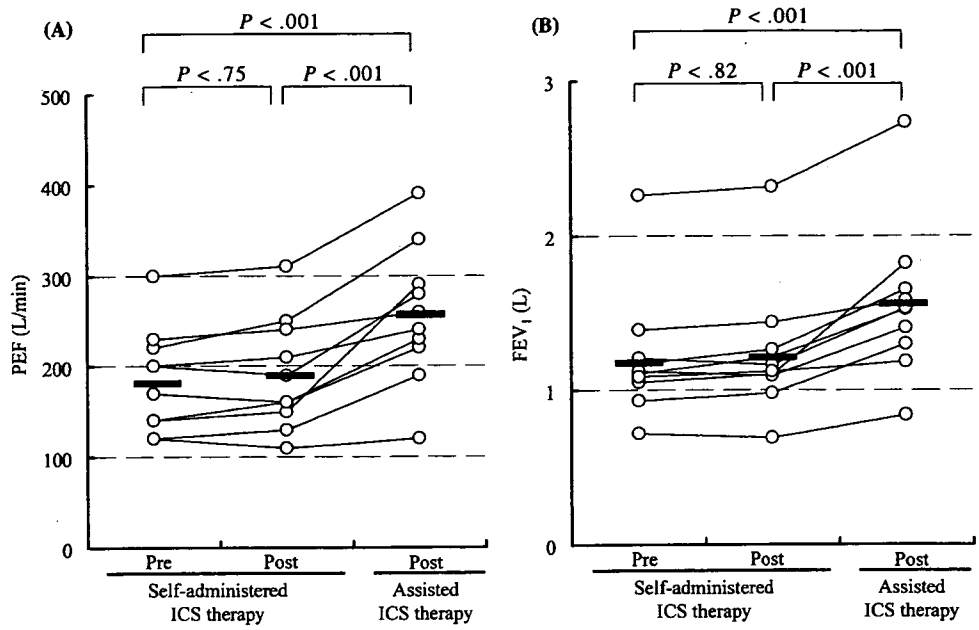

Figure 1. Changes in (A) peak expiratory flow (PEF) and (B) forced expiratory volume in 1 second (FEV_1) at the start and end of self-administered inhaled corticosteroid (ICS) therapy and at the end of assisted ICS therapy. Bold horizontal bars represent means of PEF and FEV_1 in each period.

asthma patient has, the lower the ICS prescription rate will be.[2] Intellectual dysfunction, such as Alzheimer's disease, can result in a poor understanding of the inhalation technique, and motor dysfunction, such as rheumatoid arthritis, will directly affect the physical ability to perform the inhalation procedure. It is assumed that, because the ICS therapy was not performed regularly, the improvement in asthma symptoms was limited, which in turn, led to poorer patient compliance. When asthma management is insufficient in spite of repeated inhalation guidance, assisted inhalation may be indicated. For assisted inhalation therapy, it is important to select inhalants that are easy for caregivers to use. Hydrofluoroalkane-BDP is considered appropriate for assisted ICS therapy, because it allows the caregiver to visually check the drug-spraying and inhalation conditions of the patient.

In conclusion, assistance by caregivers in ICS therapy is an important therapeutic strategy for elderly patients with asthma, especially those with complications that result in problems with the inhalation technique or compliance, and this strategy can be expected to expand the application of ICS therapy for elderly patients with asthma.

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Review

Agents against cytokine synthesis or receptors

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Abstract

Various cytokines play a critical role in pathophysiology of chronic inflammatory lung diseases including asthma and chronic obstructive pulmonary disease (COPD). The increasing evidence of the involvement of these cytokines in the development of airway inflammation raises the possibility that these cytokines may become the novel promising therapeutic targets. Studies concerning the inhibition of interleukin (IL)-4 have been discontinued despite promising early results in asthma. Although blocking antibody against IL-5 markedly reduces the infiltration of eosinophils in peripheral blood and airway, it does not seem to be effective in symptomatic asthma, while blocking IL-13 might be more effective. On the contrary, anti-inflammatory cytokines themselves such as IL-10, IL-12, IL-18, IL-23 and interferon-γ may have a therapeutic potential. Inhibition of TNF-α may also be useful in severe asthma or COPD. Many chemokines are also involved in the inflammatory response of asthma and COPD through the recruitment of inflammatory cells. Several small molecule inhibitors of chemokine receptors are now in development for the treatment of asthma and COPD. Antibodies that block IL-8 reduce neutrophilic inflammation. Chemokine CC3 receptor antagonists, which block eosinophil chemotaxis, are now in clinical development for asthma therapy. As many cytokines are involved in the pathophysiology of inflammatory lung diseases, inhibitory agents of the synthesis of multiple cytokines may be more useful tools. Several such agents are now in clinical development.

Keywords: Asthma; Chronic obstructive pulmonary disease; Cytokine; Chemokine; Chemokine receptor

Contents

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1. Introduction

Although cytokines are important for maintaining homeostasis, these proteins also play critical roles in the development of chronic airway inflammation in all diseases, including asthma and chronic obstructive pulmonary disease (COPD). Indeed, it has been demonstrated that various cytokines and chemokines are involved in the pathophysiology of asthma (Barnes et al., 1998; Chung and Barnes, 1999; Miller and Lukacs, 2004) and COPD (Barnes, 2004a). These cytokines and chemokines exert their effect through G-protein coupling receptor expressed on inflammatory cell surface. Therefore, these cytokines and their receptors may be a useful therapeutic target for asthma and COPD. Although the precise involvement and interaction of these cytokines in the pathogenesis of asthma and COPD are still unclear, intensive investigation and several clinical trials for new therapies as specific targets against these cytokines and their receptors are now ongoing. These include blocking antibody of proper cytokines and chemokines, specific receptor antagonists and small molecular receptor inhibitors (Adcock and Caramori, 2004a; Barnes, 2001a, 2002a,b, 2004b; Barnes and Stockley, 2005; Belvisi et al., 2004; Garcia et al., 2005; Ichinose and Barnes, 2004). In addition, there are another therapeutic options including anti-inflammatory cytokines, inhibition or modifier of inflammatory cytokine synthesis, and blocking various intracellular signaling pathways (Barnes and Lim, 1998; Barnes, 2000, 2004b; Ichinose and Barnes, 2004). This review focuses on the recent development of cytokine-inhibiting therapy for asthma and COPD.

2. Cytokine directed therapies for asthma

2.1. Inhibition of cytokines

Cytokines derived from T helper 2 (Th2) lymphocytes play a key role in pathophysiology of asthma through the induction of eosinophilic airway inflammation. These cytokines include interleukin (IL) -4, IL-5, IL-9, IL-13 and IL-25. In addition, pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α (TNF-α) may enhance the inflammatory response in asthma and may be linked to the disease severity. Therefore, blocking the release or effects of these cytokines may have therapeutic potential. This has been shown by several previous studies using animal models, including mice whose specific Th2 cytokine genes have been deleted.

On the other hand, there are several cytokines that suppress these inflammatory responses, which include IL-10, IL-12, IL-18, IL-23 and interferon-γ (IFN-γ). These cytokines per se may be useful therapeutic tools for asthma and COPD treatment (Barnes and Lim, 1998; Barnes, 2000, 2004b). Although its clinical benefits are still under investigation, it may be possible to develop drugs in the future that increase the release of these endogenous anti-inflammatory cytokines or activate their receptors and specific signal transduction pathways.

2.1.1. IL-1

IL-1 expression is increased in asthmatic airways (Sousa et al., 1996) and activates many inflammatory genes that are expressed in asthma. There are no small molecule inhibitors of IL-1, but a naturally occurring cytokine, IL-1 receptor antagonist, binds to IL-1 receptors to block the effects of IL-1 (Arend et al., 1998). In experimental animals IL-1 receptor antagonist reduced airway hyperresponsiveness induced by allergen. However, human recombinant IL-1 receptor antagonist does not appear to be effective in the treatment of asthma (Rosenwasser, 1998).

2.1.2. IL-4

IL-4 is critical for the synthesis of Immunoglobulin E (IgE) by B-lymphocytes and is also involved in eosinophil recruitment to the airways (Steinke and Borish, 2001). A unique function of IL-4 is to promote the differentiation of Th2 cells and therefore it acts at a proximal and critical site in the allergic response, making IL-4 an attractive target for inhibition.

IL-4 blocking antibodies inhibited allergen-induced airway hyperresponsiveness, goblet cell metaplasia and pulmonary eosinophilia in a murine model (Gavett et al., 1997). Inhibition of IL-4 may therefore be effective in treating allergic diseases, and soluble humanized IL-4 receptors have been tested in clinical trials. A single nebulized dose of soluble IL-4 receptor prevents the decrease in lung function induced by withdrawal of inhaled corticosteroids in patients with moderately severe asthma (Borish et al., 1999). In addition, weekly nebulization of soluble IL-4 receptor improved asthma control over a 12 week period (Borish et al., 2001). Subsequent studies in patients with milder asthma proved disappointing, however, and this

treatment has now been withdrawn. Another approach is blockade of IL-4 receptors with a mutated form of IL-4 (BAY 36-1677), which binds to and blocks IL-4 receptor α and IL-13 receptor α1, thus blocking both IL-4 and IL-13 (Shanafelt et al., 1998). However, because of its short duration of action, this treatment has also been withdrawn.

IL-4 and the closely related cytokine IL-13 signal through a shared surface receptor, IL-4 receptor α, which activates a specific transcription factor signal transducer and activator of transcription (STAT)-6 (Jiang et al., 2000). Deletion of the STAT-6 gene has an effect similar to that of IL-4 gene knockout (Foster, 1999). This has led to a search for inhibitors of STAT-6, and although peptide inhibitors that interfere with the interaction between STAT-6 and Janus kinases (JAK) linked to IL-4 receptor α have been discovered, it will be difficult to deliver these intracellularly. Thus, an endogenous inhibitor of STATs and suppressor of cytokine signaling (SOCS-1) that is a potent inhibitor of IL-4 signaling pathways may be a useful new therapeutic target (Jiang et al., 2000).

2.1.3. IL-5

IL-5 plays an essential role in orchestrating the eosinophilic inflammation of asthma (Greenfeder et al., 2001). In IL-5 gene knockout mice the eosinophilic response to allergen and the subsequent airway hyperresponsiveness are markedly suppressed, and yet the animals exhibit normal survival, validating the strategy to inhibit IL-5. This has also been achieved using blocking antibodies that block IL-5. Blocking antibodies to IL-5 inhibit eosinophilic inflammation and airway hyperresponsiveness in animal models of asthma, including primates (Egan et al., 1996). This blocking effect may last for up to 3 months after a single intravenous injection of antibody in primates, making the treatment of chronic asthma with such a therapy a feasible proposition. Humanized monoclonal antibodies to IL-5 have been developed and a single intravenous infusion of one of these antibodies (mepolizumab) markedly reduces blood eosinophils for several weeks and prevents eosinophil recruitment into the airways after allergen challenge in patients with mild asthma (Leckie et al., 2000) (Fig. 1). However, this treatment has no significant effect on the early or late response to allergen challenge or on the baseline airway hyperresponsiveness, suggesting that eosinophils may not be of critical importance for these responses in humans (Fig. 2). A clinical study in patients with moderate to severe asthma who had not been controlled using inhaled corticosteroids therapy confirmed a profound reduction in circulating eosinophils, but no significant improvement in either asthma symptoms or lung function (Kips et al., 2000). In both of these studies it would be expected that high doses of corticosteroids would improve these functional parameters. These surprising results cast doubt on the critical role of eosinophils in asthma and indicate that other strategies aimed at inhibiting eosinophilic inflammation might not be effective. More recently, a biopsy study has demonstrated that anti-IL-5 antibody, while profoundly reducing eosinophils in the circulation (by over 95%), is less effective at reducing eosinophils in bronchial biopsies (by ~50%), which may explain why this treatment is not clinically effective (Flood-Page et al., 2003b). However, further study shows that anti-IL-5 therapy reduces the deposition of extracellular matrix protein that contributes to airway remodeling in the bronchial subepithelial basement membrane (Flood-Page et al., 2003a). This anti-IL-5 effect may be due to the capacity of IL-5 to drive epithelial and fibroblast responses. Nevertheless, these results suggest that blocking IL-5 is not likely to be a useful approach in asthma therapy.

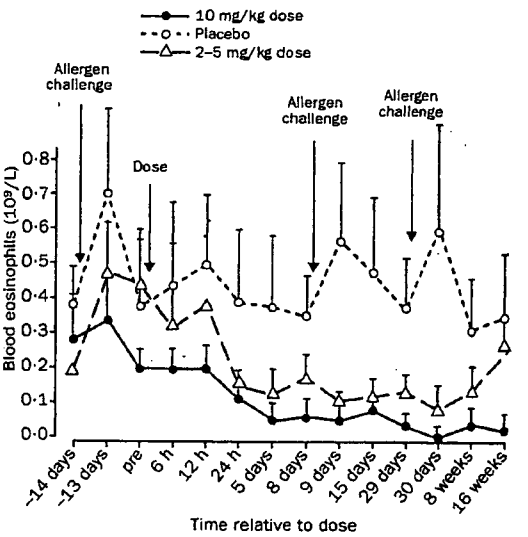

Fig. 1. The effect of a humanized monoclonal antibody against interleukin-5 (mepolizumab) on circulating eosinophils in patients with mild asthma, demonstrating a profound and very prolonged inhibitory effect. Reproduced from Leckie et al. (2000).

Somewhat similar findings have previously been reported in some studies in mice where anti-IL-5 antibodies reduced eosinophilic responses to allergen, but not airway hyperresponsiveness, whereas airway hyperresponsiveness was reduced by anti-CD4 antibody which depletes helper T cells (Hogan et al., 1998) suggesting that T cell derived cytokines other than IL-5 must be playing a more important role in airway hyperresponsiveness.

Non-peptidic IL-5 receptor antagonists would be an alternative strategy and there is a search for such compounds using molecular modeling of the IL-5 receptor α-chain and through large scale throughput screening. One such molecule, YM-90709, appears to be a relatively selective inhibitor of IL-5-receptors (Morokata et al., 2002). However, the lack of clinical benefit of anti-IL-5 antibodies has made this a less attractive approach. It is possible that eosinophils are associated with the more chronic aspects of asthma, such as airway remodeling, and in mice a blocking anti-IL-5 antibody prevented the increased collagen deposition in airways associated with repeated allergen exposure (Blyth et al., 2000). Eosinophils may be an important source of transforming growth factor-β in asthmatic airways, resulting in structural changes (Minshall et al., 1997). Indeed, more recently, it has been demonstrated that fibrotic lesions induced by antigen challenge are abolished in IL-5 receptor null mice, and that neutralizing anti-IL-5 antibody can almost completely prevent subepithelial and peribronchial fibrosis (Tanaka et al., 2004). Therefore, there is a possibility that IL-5

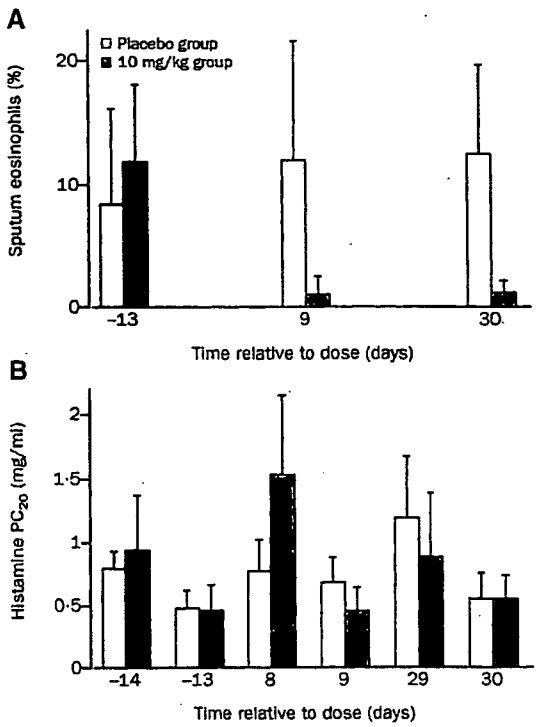

Fig. 2. Effect of a humanized monoclonal antibody against interleukin-5 (mepolizumab) on sputum eosinophils (A) and airway hyperresponsiveness (histamine PC_{20}) (B). Reproduced from Leckie et al. (2000).

may be a target for the more chronic asthmatic airway changes such as remodeling.

2.1.4. IL-9

IL-9 is a Th2 cytokine that may enhance Th2-driven inflammation and enhance mast cell mediator release and IgE production (Levitt et al., 1999). IL-9 may also enhance mucus hypersecretion (Longphre et al., 1999). IL-9 and its receptors show increased expression in asthmatic airways (Bhathena et al., 2000; Shimbara et al., 2000). A blocking antibody to IL-9 inhibited airway inflammation and airway hyperresponsiveness in a murine model of asthma (Cheng et al., 2002). Another study showed that anti-IL-9 antibody significantly reduced bone marrow eosinophilia, primarily by decreasing newly produced and mature eosinophils. In addition, in response to allergen, bone marrow cells over-express IL-9 (Sitkauskiene et al., 2005). These data suggest that IL-9 may participate in the regulation of eosinophils in allergic inflammation. Thus, IL-9 may be another therapeutic target for asthma. Strategies to block IL-9, including humanized blocking antibodies, are now in development (Zhou et al., 2001).

2.1.5. IL-10

IL-10 is a potent anti-inflammatory cytokine that inhibits the synthesis of many inflammatory proteins, including cytokines (TNF-α, GM-CSF, IL-5, chemokines) and inflammatory enzymes (inducible nitric oxide synthase) that are over-expressed in asthma (Ichinose et al., 2000a; Pretolani and Goldman, 1997). Indeed, there may be a defect in IL-10 transcription and secretion from macrophages in asthma, suggesting that IL-10 might be defective in atopic diseases (Barnes, 2001b; Borish et al., 1996; John et al., 1998). In sensitized animals, IL-10 is effective in suppressing the inflammatory response to allergen (Zuany-Amorim et al., 1995) and CD4+ cells engineered to secrete IL-10 suppressed airway inflammation in a murine model of asthma (Oh et al., 2002). Specific allergen immunotherapy results in the increased production of IL-10 by T helper cells and this may contribute to the beneficial effects of immunotherapy (Akdis et al., 1998).

Recombinant human IL-10 has proven to be effective in controlling inflammatory bowel disease and psoriasis, where similar cytokines are expressed, and may be given as a weekly injection (Fedorak et al., 2000). Although IL-10 is reasonably well tolerated, there are hematological side effects. In the future, drugs that activate the unique signal transduction pathways activated by the IL-10 receptor or drugs that increase the endogenous production of IL-10 may be developed. In mice, drugs that elevate cyclic AMP increase the IL-10 production, but this does not appear to be the case in human cells (Seldon et al., 1998).

2.1.6. IL-12

IL-12 is the endogenous regulator of Th1 cell development and determines the balance between Th1 and Th2 cells (Gately et al., 1998). IL-12 administration to rats inhibits allergen-induced inflammation (Gavett et al., 1995) and inhibits sensitization to allergens. IL-12 induces IFN-γ release, but has additional effects on T cell differentiation. The IL-12 levels released from whole blood cells are lower in asthmatic patients, indicating a possible reduction in IL-12 secretion (van der Pouw Kraan et al., 1997).

Recombinant human IL-12 has been administered to humans and has several toxic effects that are diminished by slow escalation of the dose (Leonard et al., 1997). In patients with mild asthma, weekly infusions of human recombinant IL-12 in escalating doses over 4 weeks caused a progressive fall in circulating eosinophils, and a reduction in the normal rise in circulating eosinophils after allergen challenge (Bryan et al., 2000) (Fig. 3). There was a concomitant reduction in eosinophils in induced sputum. However, there was no reduction in either the early or late response to inhaled allergen challenge or any reduction in airway hyperresponsiveness (as with anti-IL-5 therapy). Furthermore, most of the patients suffered from malaise and one out of the 12 subjects had an episode of cardiac arrhythmia, suggesting that IL-12 may not be a suitable treatment for asthma. In mice, administration of an IL-12-allergen fusion protein resulted in the development of a specific Th1 response to the allergen, with increased production of the allergen-specific IgG2, rather than the normal Th2 response with IgE formation (Kim et al., 1997). 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 atopic disease.

2.1.7. IL-13

There is increasing evidence that IL-13 in mice mimics many of the features of asthma, including airway hyperresponsiveness,

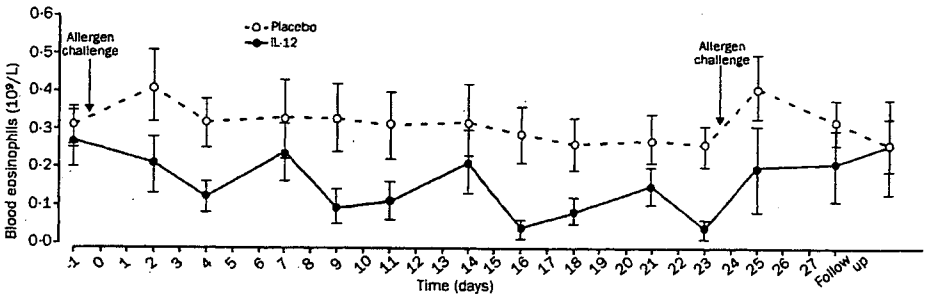

Fig. 3. Effect of interleukin-12 on peripheral blood eosinophils in patients with mild asthma. IL-12 was given in progressively increasing doses as an intravenous injection. Reproduced from Bryan et al., 2000.

mucus hypersecretion and airway fibrosis, independently of eosinophilic inflammation (Wills-Karp and Chiaramonte, 2003). It potently induces the secretion of eotaxin from airway epithelial cells (Li et al., 1999) and transforms airway epithelium into a secretory phenotype (Danahay et al., 2002). Knocking out the IL-13, but not the IL-4, gene in mice prevents the development of airway hyperresponsiveness after allergen challenge, despite a vigorous eosinophilic response (Walter et al., 2001), and the increase in airway hyperresponsiveness induced by IL-13 is only seen when the expression of STAT6 is lost in airway epithelial cells (Kuperman et al., 2002). IL-13 signals through the IL-4 receptor α, but may also activate different intracellular pathways via the activation of IL-13 receptor α1 (Jiang et al., 2000), so that it may be an important target for the development of new therapies. A second specific IL-13 receptor α2 exists in soluble form and has a high affinity for IL-13, thus acting as a decoy receptor for secreted IL-13. Soluble IL-13 receptor α2 is effective in blocking the actions of IL-13, including IgE generation, pulmonary eosinophilia and airway hyperresponsiveness in mice (Wills-Karp et al., 1998). In a murine model IL-13 receptor α2 is more effective than IL-4-blocking antibodies, highlighting the potential importance of IL-13 as a mediator of allergic inflammation. Blocking IL-13 may be more important in established asthma where the concentrations of IL-13 are much higher than those of IL-4.

Recently, it has been shown that neutralizing anti-IL-13 monoclonal antibody significantly suppresses airway hyperresponsiveness, eosinophil infiltration, the production of pro-inflammatory cytokines, serum IgE and airway remodeling induced by ovalbumin challenge in mice (Yang et al., 2004, 2005). In addition, a soluble murine anti-IL-13 receptor fusion protein that specifically binds to and neutralizes IL-13 has been demonstrated to prevent airway hyperresponsiveness induced by allergen challenge in mice (Leigh et al., 2004). These results confirm that IL-13 is critical for the development of airway hyperresponsiveness induced by allergen exposure, and that anti-human IL-13 treatment such as anti-IL-13 antibody or humanized IL-13 receptor α2 might be an effective therapeutic approach for asthma.

2.1.8. IL-18

IL-18 was originally described as an IFN-γ releasing factor, but has a different mechanism of action than IL-12 (Dinarello, 2000). IL-12 and IL-18 appear to have a synergistic effect on inducing IFN-γ release and for inhibiting IL-4-dependent IgE production and airway hyperresponsiveness (Hofstra et al., 1998), but no clinical studies have so far been reported. On the other hand, recent studies have shown that IL-18 can also promote Th2 cytokine production from T cells, NK cells, basophils, and mast cells (Nakanishi et al., 2001; Sugimoto et al., 2004). Thus, it is important to determine the precise role of IL-18 in bronchial asthma before considering its use as a relevant therapeutic target.

2.1.9. IL-23

IL-23, which is mainly expressed in dendritic cells, is structurally related to IL-12 and shares some of its biological effects, so should have a protective function in asthma (Oppmann et al., 2000). Although IL-23 induces the proliferation of memory T-cells and the secretion of IFN-γ, its precise clinical potential and role have not yet been examined.

2.1.10. IL-25

IL-25 is a recently described Th2 cell-derived cytokine that belongs to the IL-17 family and induces the production of IL-4, IL-5, IL-13 and eotaxin in the lung (Hurst et al., 2002). Transgenic over-expression of IL-25 results in the induction of airway hyperresponsiveness, airway eosinophilia and an increase in the serum levels of IL-5, IL-13, and IgE (Kim et al., 2002; Pan et al., 2001). These results suggest that IL-25 may play a role in allergic inflammation. It is released from mast cells via an IgE-dependent mechanism and is therefore a possible target for the treatment of asthma (Ikeda et al., 2003).

2.1.11. TNF-α

TNF-α is expressed in asthmatic airways and may play a key role in amplifying asthmatic inflammation through the activation of nuclear factor-κB (NF-κB), activator protein-1 (AP-1) and other transcription factors (Kips et al., 1993).

In rheumatoid arthritis and inflammatory bowel disease a humanized blocking monoclonal antibody to TNF-α (infliximab) and soluble TNF receptors (etanercept) have produced remarkable clinical responses, even in patients who are relatively unresponsive to steroids (Markham and Lamb, 2000; Jarvis and Faulds, 1999). Such TNF inhibitors are a logical approach to asthma therapy, particularly in patients with severe disease, and clinical trials are now underway.

Because of the problems associated with antibody-based therapies that have to be given by injection, there is a search for small molecule inhibitors of TNF. TNF-α-converting enzyme (TACE) is a matrix metalloproteinase-related enzyme critical for the release of TNF from the cell surface. Small molecule TACE inhibitors are in development as oral TNF inhibitors (Barlaam et al., 1999).

2.1.12. IFN-γ

Interferon-γ inhibits Th2 cells and should therefore reduce atopic inflammation. In sensitized animals nebulized IFN-γ inhibits eosinophilic inflammation induced by allergen exposure (Lack et al., 1996) and adenovirus-mediated gene transfer of IFN-γ inhibits allergic inflammation in mice (Behera et al., 2002). However, 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 (Boguniewicz et al., 1995). Interestingly, allergen immunotherapy increases IFN-γ production by circulating T cells in patients with clinical benefit (Benjaponpitak et al., 1999) and increases the numbers of IFN-γ expressing cells in nasal biopsies of patients with allergic rhinitis (Durham et al., 1996). A preliminary report suggested that IFN-α may be useful in the treatment of patients with severe asthma who have reduced responsiveness to corticosteroids (Gratzl et al., 2000).

2.2. Inhibition of chemokines

Many chemokines are involved in the recruitment of inflammatory cells in asthma and COPD (Lukacs, 2001). Over 50 different chemokines are now recognized and they activate up to 20 different surface receptors (Rossi and Zlotnik, 2000). Chemokine receptors belong to the 7 transmembrane receptor superfamily of G-protein-coupled receptors and this makes it possible to find small molecule inhibitors, which has not yet been possible for classical cytokine receptors (Proudfoot, 2002). Some chemokine receptors appear to be selective for single chemokines, whereas others are promiscuous and mediate the effects of several related chemokines. Chemokines appear to act in sequence in determining the final inflammatory response and so inhibitors may be more or less effective depending on the kinetics of the response (Gutierrez-Ramos et al., 2000).

2.2.1. Chemokine CC2 receptor

Monocyte chemoattractant protein-1 (MCP-1) activates chemokine CC2 receptor on monocytes and T lymphocytes. Blocking MCP-1 with neutralizing antibodies reduced the recruitment of both T cells and eosinophils in a murine model of ovalbumin-induced airway inflammation, with a marked reduction in airway hyperresponsiveness (Gonzalo et al., 1996). MCP-1 also recruits and activates mast cells, an effect that is mediated via chemokine CC2 receptor (Campbell et al., 1999). MCP-1 instilled into the airways induces marked and prolonged airway hyperresponsiveness in mice, associated with mast cell degranulation. A neutralizing antibody to MCP-1 blocks the development of airway hyperresponsiveness in response to allergen (Campbell et al., 1999). The MCP-1 levels are increased in the bronchoalveolar lavage fluid of patients with asthma (Holgate et al., 1997). This has led to a search for small molecule inhibitors of chemokine CC2 receptor.

2.2.2. Chemokine CC3 receptor

Several chemokines, including eotaxin, eotaxin-2, eotaxin-3, regulated on activation, normal T-cell expressed and secreted (RANTES) and monocyte chemoattractant protein-4 (MCP-4) activate a common receptor on eosinophils designated (Gutierrez-Ramos et al., 1999). Chemokine CC3 receptor has a critical role in allergic inflammation, and therefore, chemokine CC3 receptor inhibitors may be useful targets for asthma treatment.

A neutralizing antibody against eotaxin reduces eosinophil recruitment in the lung after allergen challenge and the associated airway hyperresponsiveness in mice (Gonzalo et al., 1996), and blocking eotaxin reduces the trafficking of Th2 cells and eosinophils (Lloyd et al., 2000). There is increased expression of eotaxin, eotaxin-2, monocyte chemoattractant protein-3 (MCP-3), MCP-4 and chemokine CC3 receptor in the airways of asthmatic patients and this is correlated with increased airway hyperresponsiveness (Ying et al., 1997, 1999). Several small molecule inhibitors of chemokine CC3 receptor, including UCB35625, SB-297006 and SB-328437, are effective in inhibiting eosinophil recruitment in allergen models of asthma (Sabroe et al., 2000; White et al., 2000), and drugs in this class are currently undergoing clinical trials for asthma. Although it was thought that chemokine CC3 receptors were restricted to eosinophils, there is some evidence for their expression on Th2 cells and mast cells, so that these inhibitors may have a more widespread effect than on eosinophils alone, making them potentially more valuable in asthma treatment.

RANTES, which shows increased expression in asthmatic airways (Berkman et al., 1996), also activates chemokine CC3 receptor, but has effects on chemokine CC1 receptor and chemokine CC5 receptor, which may play a role in T cell recruitment. Modification of the N-terminal of RANTES, met-RANTES, has a blocking effect on RANTES by inhibiting these receptors (Elsner et al., 1997). This Met-RANTES can prevent the recruitment of eosinophil in allergen-sensitized and -challenged mice (Elsner et al., 1999).

2.2.3. Chemokine CC4 receptor and chemokine CC8 receptor

Chemokine CC4 receptor and chemokine CC8 receptor are selectively expressed on Th2 cells. Chemokine CC4 receptor is activated by the monocyte-derived chemokine (MDC) and thymus and activation dependent chemokine (TARC) (Lloyd et al., 2000), and chemokine CC8 receptor is activated by I-309 (Roos et al., 1997; Tiffany et al., 1997). Neutralized antibody to MDC prevented airway hyperresponsiveness in a murine asthma model (Gonzalo et al., 1999). Blocking TARC also attenuates the airway eosinophilia and airway hyperresponsiveness induced by allergen challenge (Kawasaki et al., 2001). Blocking I-309 reduces airway eosinophilia, but not airway hyperresponsiveness and Th2 cytokine production (Bishop and Lloyd, 2003). Inhibitors of chemokine CC4 receptor and

chemokine CC8 receptor may therefore inhibit the recruitment of Th2 cells and thus the persistent eosinophilic inflammation in the airways. However, blockade of chemokine CC4 receptor has no effect on the recruitment of cells or the production of chemokines in guinea pig (Conroy et al., 2003), and chemokine CC8 receptor gene deletion does not have any effects on allergic inflammation in mice (Chung et al., 2003), suggesting that these receptors may not be an effective target. Chemokine CC7 receptor plays a role in the migration of dendritic cells to regional lymph nodes and therefore blocking this receptor might suppress antigen presentation (Sallusto and Lanzavecchia, 2000).

2.2.4. Chemokine CXC4 receptor

Chemokine CXC4 receptor is also selectively expressed on Th2 cells and is activated by stromal cell-derived factor 1 (SDF-1). Neutralized antibody to chemokine CXC4 receptor reduced airway eosinophilia and airway hyperresponsiveness in a murine model of allergic airway disease. In addition, blocking SDF-1 also reduced both airway inflammation and airway hyperresponsiveness (Gonzalo et al., 2000). A small molecule inhibitor, AMD3100, inhibited allergen-induced inflammation in a murine model of asthma (Lukacs et al., 2002).

2.3. Other approaches to cytokine inhibition

Although there have been several attempts to block specific cytokines, this may not be adequate to block chronic inflammation in asthma, as so many cytokines are involved and there is considerable redundancy in their effects. This suggests that the development of drugs that have a more general effect on cytokine synthesis may be more promising. However, these drugs also affect other inflammatory processes, so their beneficial effects cannot necessarily be ascribed to the inhibition of cytokine synthesis alone.

Corticosteroids are the most effective treatment for asthma (Ichinose et al., 2000b) and part of their efficacy is due to the inhibition of inflammatory cytokine production. This is mediated through an effect on glucocorticoid receptors to reverse the acetylation of core histones that is linked to the increased expression of inflammatory genes, such as those encoding cytokines and chemokines (Ito et al., 2000). New steroids have recently been developed, including prodrug (Reynolds and Scott, 2004) or dissociated corticosteroid (Belvisi et al., 2001).

Cyclosporin A, tacrolimus and rapamycin inhibit the transcription of nuclear factor of activated T-cells which regulates the secretion of IL-2, IL-4, IL-5, IL-13 and GM-CSF by T-lymphocytes (Rao et al., 1997). Although some beneficial steroid-sparing effects in asthma have been reported (Lock et al., 1996), the toxicity of cyclosporin A limits its usefulness, at least when given orally. More selective Th2 selective drugs may be safer for the treatment of asthma in the future. An inhibitor of Th2 cytokines, suplatast tosilate (Oda et al., 1999), has been reported to provide clinical benefits in asthma (Tamaoki et al., 2000).

Phosphodiesterase 4 (PDE4) inhibitors inhibit the release of cytokines and chemokines from inflammatory cells via an increase in intracellular cyclic AMP (Torphy, 1998). Their clinical use is limited in asthma by side effects such as nausea, which seems to be mainly due to the inhibition of PDE4D subtype (Lamontagne et al., 2001), while PDE4B is thought to be more important to reduce airway inflammation (Jin and Conti, 2002). Thus, a PDE4B selective inhibitor may be a more useful tool for asthma.

NF-κB that is a pro-inflammatory signaling molecule that regulates the expression of many cytokines and chemokines involved in asthma (Barnes and Karin, 1997). There are several possible approaches to the inhibition of NF-κB, including gene transfer of an inhibitor of NF-κB (IκB), inhibitors of IκB kinase-2 (IKK2), NF-κB-inducing kinase and IκB ubiquitin ligase, which regulate the activity of NF-κB, and the development of drugs that inhibit the degradation of IκB (Delhase et al., 2000). One concern about this approach is that effective inhibitors of NF-κB may result in immune suppression and impair host defenses, since knockout mice which lack NF-κB proteins succumb to septicemia. However, there are alternative pathways of NF-κB activation that might be more important in inflammatory disease (Nasuhara et al., 1999). Several small molecule inhibitors of IKK2 are now in development (Adcock and Caramori, 2004b; Castro et al., 2003).

Mitogen-activated protein (MAP) kinases play a key role in chronic inflammation, and several complex enzyme cascades have now been defined. p38 MAP kinase pathway is one of these kinases, which is involved in expression of several inflammatory cytokines and chemokines (Kumar et al., 2003; Meja et al., 2000; Underwood et al., 2000). Small molecule inhibitors of p38 MAP kinase, such as SB 203580, SB 239063 and RWJ 67657, also known as cytokine-suppressive anti-inflammatory drugs (CSAIDS), have been developed and these drugs have a broad range of anti-inflammatory effects (Lee et al., 2000). In addition, p38 MAP kinase inhibitors reduce eosinophil survival through the enhancement of apoptosis (Kankaanranta et al., 1999). It has been also shown that p38 MAP kinase is associated with steroid resistant asthma, and that p38 MAP kinase inhibitors may improve the response to steroid in asthma (Irusen et al., 2002). However, there may be issues of safety, as p38 MAP kinases are involved in host defense. It is possible that using the inhaled route of delivery may reduce the risk of side effects.

3. Cytokine directed therapies for COPD

3.1. Inhibition of cytokines and chemokines

Unlike asthma, Th2 cytokines do not play a critical role in the pathogenesis of COPD. There is no evidence that the levels of Th2 cytokine are elevated in COPD airways (Barnes, 2001a). Pro-inflammatory cytokines such as IL-1β and TNF-α may be involved in the inflammatory response not only in asthma but also in COPD. Although an IL-1 receptor antagonist is now in a clinical trial for some inflammatory diseases (Cohen, 2004),

there have been no published studies on the usefulness of an IL-1 receptor antagonist in COPD.

It has been reported that the levels of TNF-α and soluble TNF receptor are increased in the sputum of COPD (Keatings et al., 1996; Vernooy et al., 2002). TNF-α enhances airway inflammation through the induction of IL-8 and other chemokines via the activation of NF-κB. Therefore, TNF-α or its soluble receptor may be a target for reducing COPD inflammation. Trials of anti-TNF therapy in patients with the systemic features of COPD are now underway (Barnes and Stockley, 2005). TACE is required for soluble TNF-α release. Thus, small molecule of TACE inhibitors may be an attractive therapeutic target not only for asthma but also for COPD.

Various chemokines also play an important role in the recruitment of inflammatory cells in COPD airways and have been shown to be elevated in COPD. These include IL-8 and growth-related oncogene-α (GRO-α) (Keatings et al., 1996; Traves et al., 2002). The effects of these chemokines are mediated by chemokine CXC receptors, which are G-protein-coupled receptors. Neutrophils, the major contributors to the airway inflammation of COPD, express both chemokine CXC1 receptor (IL-8 specific low affinity receptor) and 2 (high affinity receptor for several chemokines). Thus, inhibitors of these chemokines or antagonists of chemokine CXC receptors may be a therapeutic target for COPD.

Blocking IL-8 reduces the neutrophil chemotactic activity of sputum from COPD patients (Beeh et al., 2003). A monoclonal antibody to IL-8 has been developed and tested in COPD. Although this antibody had a small effect in improving dyspnea, no significant differences were observed in the lung function and health status (Mahler et al., 2004). Antagonism of chemokine CXC2 receptor may be a more effective strategy. Several small molecule inhibitors of chemokine CXC2 receptor are now in clinical development for the treatment of COPD (Hay and Sarau, 2001; White et al., 1998). In chemokine CXC2 receptor knockout mice, there is a marked reduction in mucus secretion in response to viral infection, suggesting that this receptor may be also involved in mucus hypersecretion (Miller et al., 2003).

Growth related oncogene-α (GRO-α) is one of the CXC chemokines that is produced by several cells such as monocytes, endothelial cells and fibroblasts. GRO-α is also secreted in alveolar macrophages and airway epithelial cells by the stimulation with lipopolysaccharide, TNF-α and IL-17 (Becker et al., 1994; Schulz et al., 2004; Jones and Chan, 2002; Prause et al., 2003). GRO-α is a powerful activator and chemoattractant of neutrophils and exerts its effect through the activation of chemokine CXC2 receptor (Geiser et al., 1993). The levels of GRO-α are significantly increased in COPD sputum (Traves et al., 2002). In addition, the expression of chemokine CXC2 receptor is increased during exacerbations of COPD and there is a correlation between the airway neutrophilia and chemokine CXC2 receptor expression (Qiu et al., 2003). These data suggest that GRO-α and chemokine CXC2 receptor play a critical role in the recruitment of inflammatory cells in COPD. SB 225002, a small molecule antagonist of chemokine CXC2 receptor, which is now in clinical trials (Widdowson et al., 2004), potently inhibits the chemotaxis of neutrophils induced by IL-8 and GRO-α (White et al., 1998). This selective antagonist may be a useful tool for COPD treatment.

3.2. Inhibition of signal transduction

Like asthma, several signal transduction pathways are involved in the pathophysiology of COPD and some inhibitors of these pathways are now in clinical development (Barnes and Stockley, 2005; Cohen, 2002). Unlike asthma, corticosteroids are not effective in preventing the decline of the lung function and airway inflammation (Culpitt et al., 1999; Hattotuwa et al., 2002; Keatings et al., 1997).

PDE4 inhibitors may be useful for COPD treatment. Indeed, several PDE4 inhibitors have been developed and are in clinical trials. It has been demonstrated that PDE4 inhibitors reduce the production of TNF-α by LPS stimulation in a mononuclear cell line and in whole blood cells from COPD patients (Draheim et al., 2004; Ouagued et al., 2005).

NF-κB is one of the important regulators of the production of several cytokines involved in the pathophysiology of COPD including TNF-α, IL-6 and IL-8 (Tak and Firestein, 2001). The expression of NF-κB is increased in COPD airways and this increased expression is correlated with the disease severity (Di Stefano et al., 2002). Thus, NF-κB may be another therapeutic target for COPD. Small molecule inhibitors of IKK2 may be promising not only for the treatment of asthma but also for COPD (Adcock and Caramori, 2004b; Castro et al., 2003).

p38 MAP kinase pathway is also involved in the pathophysiology of COPD through the regulation of inflammatory cytokines such as TNF-α and IL-8 (Barnes and Stockley, 2005). One of the small molecule inhibitors, SB 239063, reduces neutrophil infiltration and IL-6 production in the lung of LPS stimulated rats (Underwood et al., 2000). SB 239063 also inhibits LPS-induced IL-6 production in alveolar macrophages from guinea pig (Underwood et al., 2000). These results suggest that the inhibition of the p38 MAP kinase pathway may be a useful target for COPD (Adcock and Caramori, 2004b).

More recently, it has been reported that CGH2466, a combined adenosine receptor antagonist, p38 mitogen-activated protein kinase and phosphodiesterase type 4 inhibitor, has potent anti-inflammatory activities (Trifilieff et al., 2005). CGH2466 inhibits the production of cytokines and oxygen radicals in human peripheral blood leucocytes, more potently than each inhibitor or antagonist alone. CGH2466 also inhibits LPS-induced airway inflammation in mice. Therefore, this novel compound may be a beneficial therapeutic tool for COPD.

Phosphoinositide 3-kinases (PI3K) have been shown to play an important role in neutrophil chemotaxis (Thomas et al., 2005; Wymann et al., 2003). Among several PI3K isoforms, PI3K gamma has a pivotal role in chemokine-dependent migration of neutrophils and macrophages (Hirsch et al., 2000), suggesting that the PI3K signaling pathway, especially the gamma isoform, may be a promising target for new therapies to treat COPD (Finan and Thomas, 2004). Small molecule

inhibitors of the PI3K family are now in development (Ward et al., 2003; Ward and Finan, 2003).

4. Conclusions

Several specific cytokine and chemokine inhibitors are now in development for the treatment of asthma and COPD. Inhibition of IL-4 with soluble IL-4 receptors showed promising early results for asthma, however, this was not confirmed in subsequent clinical trials. Antibodies that block IL-5 effectively inhibit peripheral blood and airway eosinophilia, but it does not also seem to be effective in symptomatic asthma. Inhibition of IL-13 appears to be more promising. Anti-inflammatory cytokines may also be useful, however, it would be necessary to develop efficient inhaled delivery systems to prevent systemic adverse effects. Inhibition of TNF-α may be useful in the treatment of severe asthma and COPD. As various chemokines are involved in the recruitment of inflammatory cells in asthma and COPD airways, small molecule inhibitors of chemokine receptors are also promising therapeutic targets. Antagonists against chemokine CC3 receptor or chemokine CXC2 receptor are now in development for the treatment of asthma and COPD. Many cytokines are involved in the complexity of the pathophysiology of asthma and COPD, therefore, agents that inhibit the synthesis of multiple cytokines may be more successful. Several such agents are now in clinical development, including PDE4, p38 MAP kinase, IKK2 and PI3K inhibitors. Using the inhaled delivery route may reduce the risk of adverse effects in these non-specific inhibitors.

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■ 鼻炎合併喘息の治療と ロイコトリエン受容体拮抗薬 ■

The effectiveness of leukotriene receptor antagonists for bronchial asthma with allergic rhinitis

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はじめに

上気道と下気道におけるアレルギー性疾患の病態生理には密接な関連性があることが示されてきており，"One airway, one disease"という概念が提唱されている[1]。本稿ではアレルギー性鼻炎と気管支喘息との関連についてこれまでの知見を紹介し，鼻炎合併喘息の治療におけるロイコトリエン受容体拮抗薬の役割について概説する。

Ⅰ．喘息とアレルギー性鼻炎の合併

これまでの疫学的調査によりアレルギー性鼻炎患者の約30～40%に気管支喘息が合併し，気管支喘息患者の約30～80%にアレルギー性鼻炎が合併することが報告されている[1)2)]。アレルギー性鼻炎と気管支喘息の罹患率は先進国において高い傾向にあり，各国での両疾患の罹患率は似通った傾向を示す[3)]。またアレルギー性鼻炎は喘息発症に先行することが多く，喘息発症の危険因子の1つと認識されている。成人を対象とした23年間の追跡調査によれば，アレルギー性鼻炎を有する患者は有さない患者に比べ約3倍の頻度で喘息を発症したことが報告されている[4)]。

Ⅱ．喘息とアレルギー性鼻炎の病態生理

アレルギー性鼻炎と気管支喘息の基本病態はアレルギー性炎症であり，両者の炎症はTリンパ球，好酸球，肥満細胞などの免疫細胞やヒスタミン，ロイコトリエン，IL-4, IL-5, GM-CSF, RANTESなどの炎症性メディエーターが関与する共通の免疫機序により生じる。喘息においては抗原吸入負荷により即時相，遅発相の二相性に1秒量の低下が認められるが，アレルギー性鼻炎においては鼻炎症状スコアの悪化が同様に二相性に認められる。喘息患者における鼻粘膜中の好酸球は鼻炎合併の有無にか

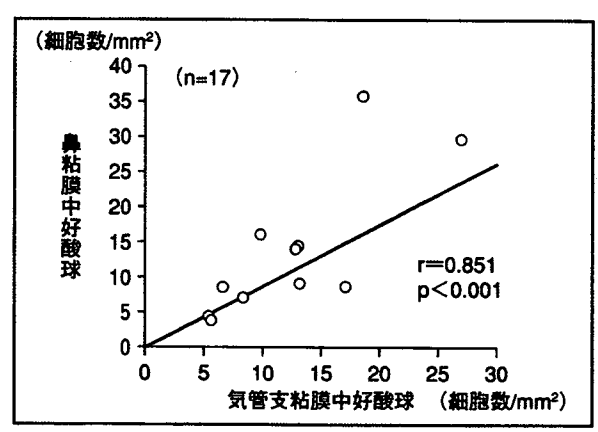

図1．喘息患者における鼻粘膜および気管支粘膜中の好酸球数の相関[5)]

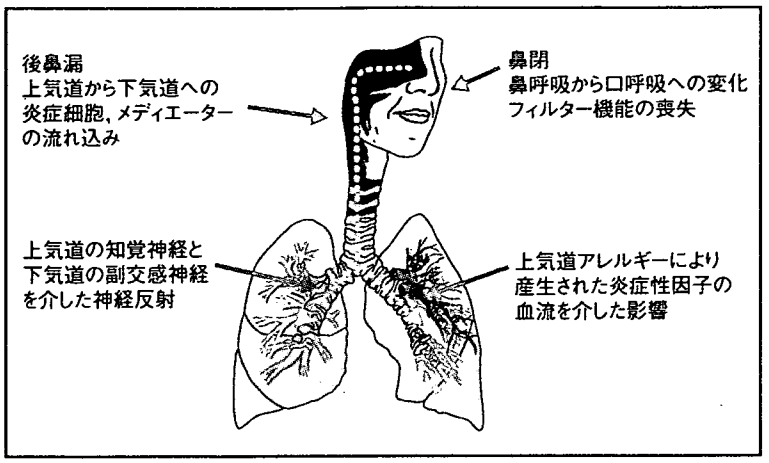

図2．上気道アレルギーが下気道に影響を及ぼす機序[6]

かわらず亢進しており，喘息患者の鼻粘膜と気管支粘膜中の好酸球数には有意な相関が認められる（図1）[5]。またアレルギー性鼻炎患者は花粉飛散期に気道過敏性が亢進することや，喘息のないアレルギー性鼻炎患者の気管支に抗原を滴下すると鼻粘膜の好酸球性炎症が誘導されることが示されている。これらの結果は上気道および下気道のアレルギー性炎症が連動して推移することを示唆している。

Ⅲ．One airway, one disease

以上述べてきたように気管支喘息とアレルギー性鼻炎は疫学的，病態生理学的に関連の深い気道の炎症性疾患であり，“One airway, one disease”と捉えて診断，治療することが提唱されている[1]。上気道アレルギーが下気道に影響を及ぼす機序の詳細は不明であるが，①後鼻漏による炎症細胞や炎症性メディエーターの上気道から下気道への流入，②上気道アレルギーにより産生された炎症性因子の血流を介した影響，③鼻閉に伴う口呼吸によるフィルター機能の喪失，④上気道の知覚神経と下気道の副交感神経を介した神経反射，などの因子が関与する可能性が推測されている（図2）[6]。

Ⅳ．鼻炎合併喘息の治療総論

喘息とアレルギー性鼻炎の基本病態は気道炎症である。両疾患のガイドラインにおいて，症状が通

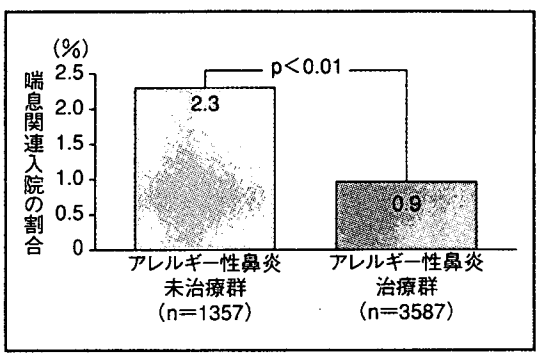

図3．アレルギー性鼻炎の治療による喘息関連入院の減少[7]

年性に認められる場合にはステロイド薬，ロイコトリエン受容体拮抗薬，抗アレルギー薬などの抗炎症薬による長期管理が重要であることが強調されている。喘息では吸入ステロイド薬が抗炎症治療の軸となるが，アレルギー性鼻炎では鼻閉などに伴い点鼻薬が鼻腔内に適切に分布しないことも多い。そのためアレルギー性鼻炎のガイドラインでは，すべての重症度における全身的な抗炎症治療が推奨されている。一方，気道閉塞の機序としてはアレルギー性鼻炎では豊富な血管網の充血が重要なのに対し，喘息では気管支平滑筋の収縮が重要である。そのため気道閉塞改善のためには，アレルギー性鼻炎ではα刺激薬などの血管収縮剤が，喘息ではβ刺激薬などの気管支拡張薬が有効である。鼻炎合併喘息においては喘息と鼻炎の両方を治療することが重要であり，アレルギー性鼻炎と喘息の両方

を治療した患者は喘息だけを治療した患者に比べ，喘息関連の入院が61%減少したことが報告されている(図3)[7]。

V．鼻炎合併喘息治療におけるロイコトリエン受容体拮抗薬

ロイコトリエン類(LT)は細胞膜のアラキドン酸から生成される脂質メディエーターであり，LTC_4, D_4, E_4などのシステイニルロイコトリエンには気道平滑筋収縮，好酸球遊走，血管透過性亢進などの生理活性がある。システイニルロイコトリエンはアレルギー性鼻炎患者の鼻汁中と喘息患者の喀痰中において産生が亢進している(図4)[8][9]。またヒト鼻粘膜と気管支粘膜にはシステイニルロイコトリエン受容体1が発現しており[10][11]，喘息患者における発現の亢進が確認されている(図5)[11]。ロイコトリエンの吸入刺激はアレルギー性鼻炎と喘息の症状を誘発し，ロイコトリエン受容体拮抗薬がその症状を抑制することからも，ロイコトリエンは両疾患の治療における重要な標的分子の1つと認識されている。

吸入ステロイド薬で喘息管理が不十分な症例において，吸入ステロイド薬を増量した群とロイコトリ

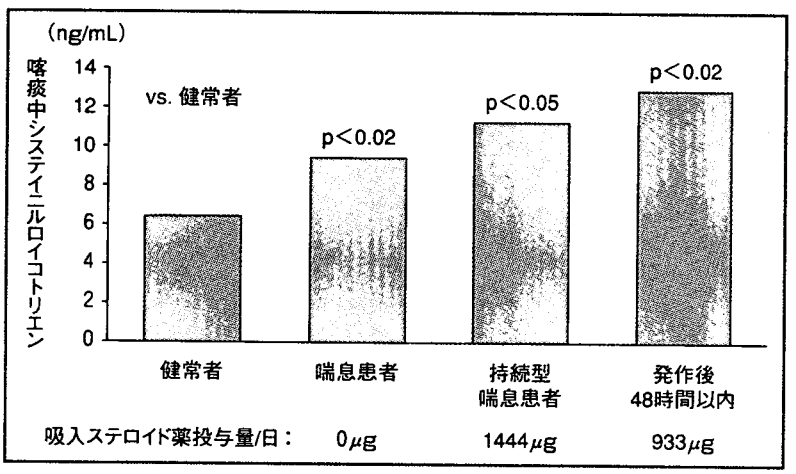

図4．喘息患者の誘発喀痰中のシステイニルロイコトリエン産生亢進[8]

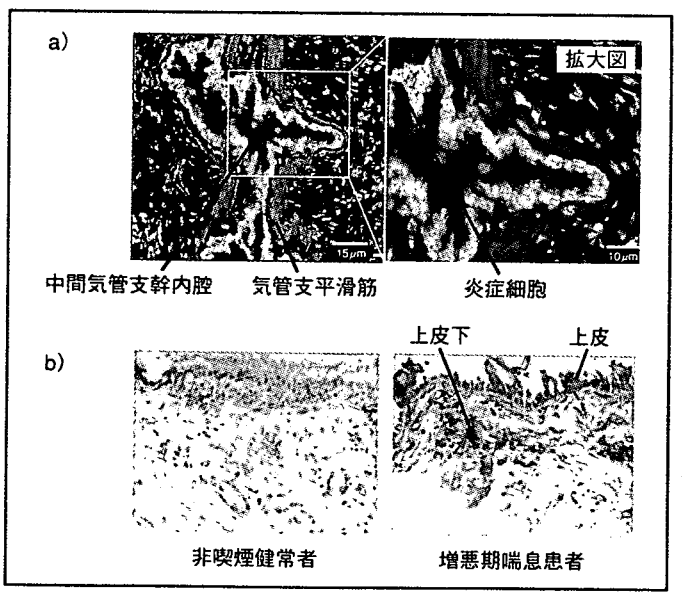

図5．気管支粘膜のシステイニルロイコトリエン受容体1発現状況[10][11]
a) 正常気管支における受容体発現
b) 喘息患者における気道上皮，上皮下の受容体発現亢進

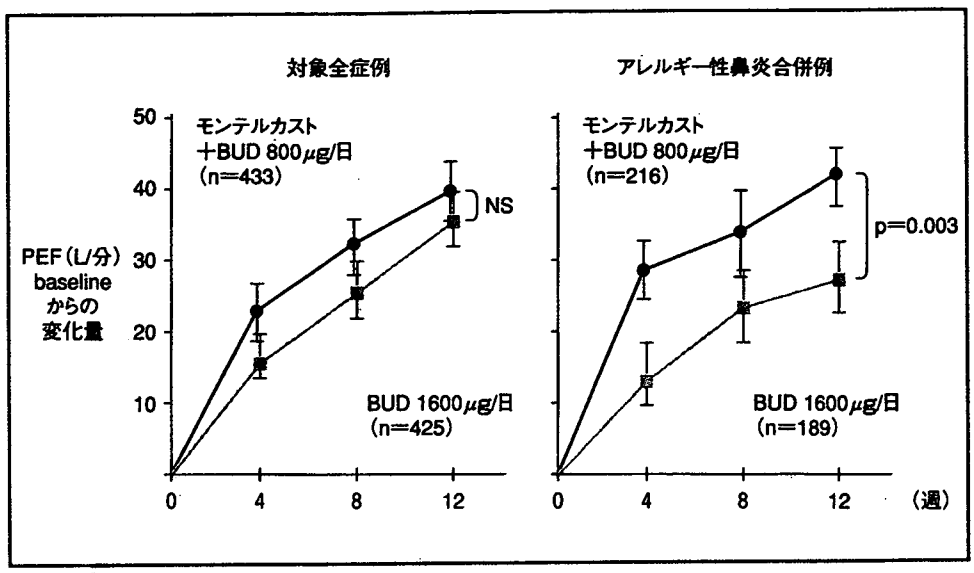

図6．鼻炎合併喘息に対するロイコトリエン受容体拮抗薬の併用効果[12)]
BUD：ブデソニド

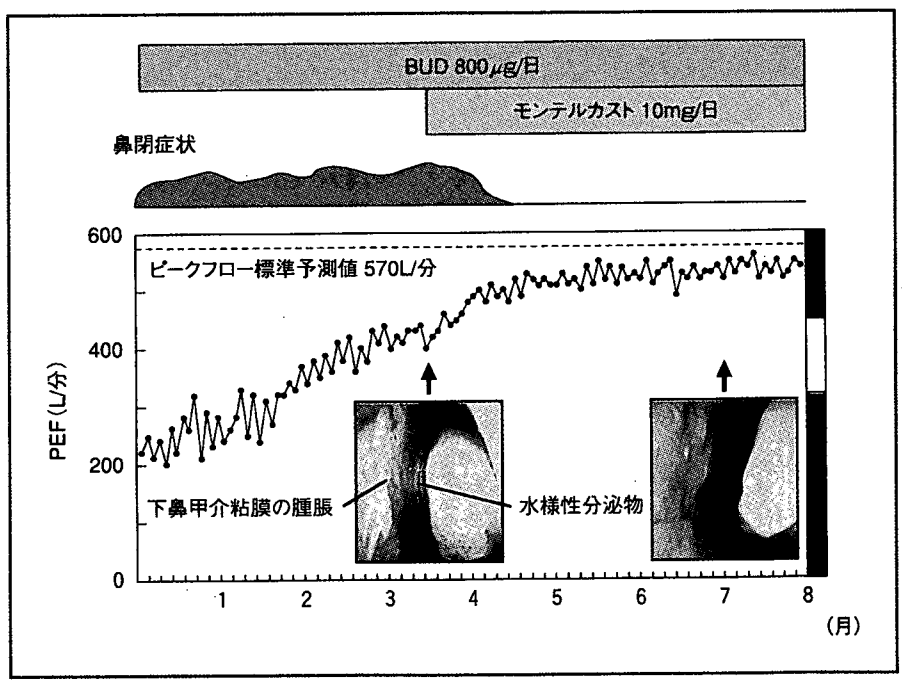

図7．ロイコトリエン受容体拮抗薬併用によりピークフロー値と鼻閉が改善した喘息症例(48歳，男性)
BUD：ブデソニド

エン受容体拮抗薬(モンテルカスト)を上乗せした群とを比較した場合，全症例での検討では両治療群の効果は同等であったが，アレルギー性鼻炎合併患者を対象としたサブ解析では，モンテルカストを上乗せした群のほうが有意なピークフローの改善が認められたことが報告されている(図6)[12)]。ステロイド薬は喘息気道におけるシステイニルロイコトリエンの産生を完全には抑制できないことも示されており，アレルギー性鼻炎を合併する喘息症例において吸入ステロイド薬の効果が不十分な場合には，ロイ

コトリエン受容体拮抗薬の併用が効果的であることが期待される。吸入ステロイド薬にモンテルカストを併用することにより，ピークフロー値，鼻炎症状と鼻閉所見(図7)が改善した症例を呈示する。

おわりに

関連の深い上気道と下気道のアレルギー性炎症の治療において，ロイコトリエンは共通の標的分子として重要である。鼻炎合併喘息では両疾患のアレルギー性炎症を同時に制御できる治療法が望ましく，吸入ステロイド薬に併用する薬剤としてロイコトリエン受容体拮抗薬の有効性が期待される。

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≪喘息の診断≫
気道炎症の評価

南方良章　一ノ瀬正和*

要旨

- 気管支喘息の気道炎症評価法として，誘発喀痰，呼気ガス，呼気凝縮液がある．
- 誘発喀痰は，細胞成分と液性成分の検討が可能で，前者では好酸球数が，後者では ECP，アルブミン，IL-5，RANTES，eotaxin，LTC4/D4/E4 などが炎症の指標となりうる．
- 呼気ガスでは，NO が気管支喘息で増加し，気流制限や気道過敏性との相関もみられ，炎症評価や病態管理の指標として用いうる．CO や炭化水素は，将来的に指標となりうる可能性はあるが，現状ではまだ不十分である．
- 呼気凝縮液は，まったくの無侵襲で将来有望な方法であることより，測定法の標準化や更なる報告の集積が期待される．

はじめに

喘息は気道の慢性炎症性疾患であり，病態の診断・管理には，この炎症をいかにして検出し評価するかが重要となる．喘息の炎症は，好酸球を中心とする細胞やサイトカイン，ケモカインなどが重要な役割を担っており[1]，これらを指標とすることで炎症を評価しうる可能性がある．従来，気道炎症の評価は病理学的手法，すなわち剖検組織あるいは軽症喘息患者に対する気管支鏡下生検組織によってなされていた．これに対し，近年誘発喀痰，呼気ガス，呼気凝縮液といった侵襲の少ない検査にて気道炎症を評価する試みが広がってきた．

本稿では，これら検査法による喘息の気道炎症評価の現状と可能性について述べる．

誘発喀痰(sputum induction)

1992 年 Pin ら[2]により開発され以来，喘息を含む炎症性気道疾患の病態解明に対する報告がみられるようになった．誘発喀痰はまったくの非侵襲的検査とはいえないが，気管支鏡下生検などに比較して低侵襲で，反復検査可能などの利点がある．

1．誘発喀痰採取法

採取 15 分前に短時間作動型 β_2刺激薬を吸入し気道を拡張したうえで，滅菌された 4% 程度の高張食塩水を超音波ネブライザーを用いて繰り返し吸入させる．吸入 5 分ごとに 1 回の咳嗽で喀痰を排出し，総量が約 1.0 m*l* になるまで 15〜30 分間繰り返す．ただし，高張食塩水により気道攣縮をきたす可能性と，1 秒量 1 *l* 未満の低肺機能患者に対する安全性が確認されていない点には注意が必要である．

採取した誘発喀痰は粘液を溶解し，細胞成分と液性成分に分離する．

2．誘発喀痰を用いた気道炎症の評価

細胞成分分析では，好酸球数の増加が気管支喘息患者で確認されている[3]．この好酸球数は気管支喘息の重症度と関連する(Fig. 1)[4]．ステロイド

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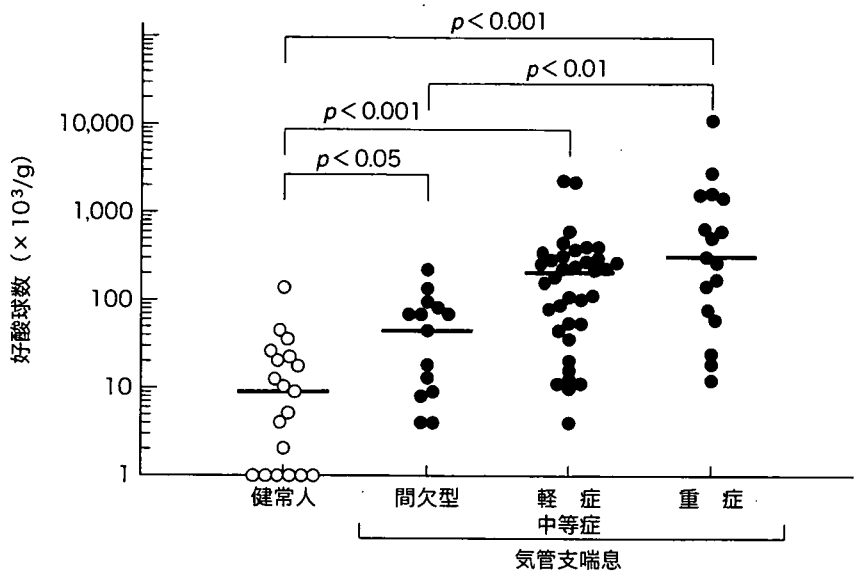

Fig. 1. 気管支喘息における誘発喀痰中好酸球数

気管支喘息患者では，健常人に比べ誘発喀痰中の好酸球数の有意な増加を認める．重症度が進むほど好酸球数の増加が顕著となる．

［文献 4）より引用］

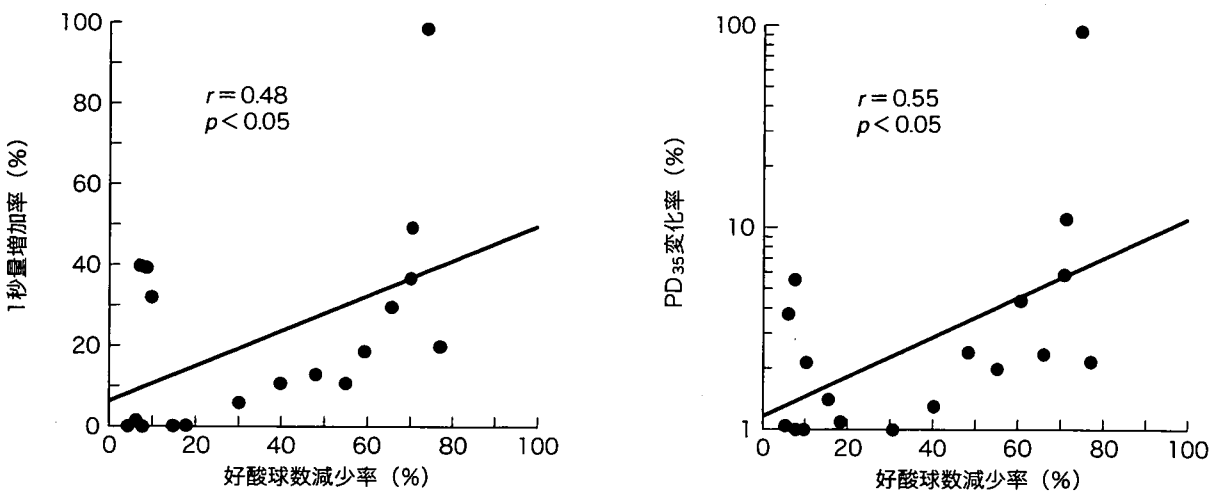

Fig. 2. ステロイド治療による好酸球数減少と気流制限・気道過敏性の改善率

誘発喀痰中の好酸球数は吸入ステロイド治療にて減少するが，その減少率は，1 秒量（気流制限），PD_{35}（気道過敏性）の改善率と有意な相関関係を示す．

［文献 3）より引用］

治療に反応して減少し，気流制限や気道過敏性の改善の程度と相関がみられることより（Fig. 2），診断ならびに治療効果の指標として有用である[3]．

また，急性発作時には顕著な好酸球増加とともに，好中球の増加も報告されている．

液性成分分析では，好酸球由来の蛋白質で，好酸球の活性化により放出される eosinophil cationic protein（ECP）が，喘息患者の誘発喀痰上清中で増加し，喘息の重症度との関連や，気流制限や気道過敏性の程度との相関も認められる[4]．微小血管の透過性亢進を示唆するアルブミン濃度は，上清中で高値を示す[4]．さらに，IL-5，RANTES，eotaxin などの増加や，leukotriene（LT）$C_4/D_4/E_4$の増加なども報告されている．