weekly nebulization of sIL-4r improves asthma control over a 12 week period [20]. Subsequent studies in patients with milder asthma proved disappointing, however, and this treatment has now been withdrawn.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-4Rα and IL-13Rα1, thus blocking both IL-4 and IL-13 [21]. This treatment has also been withdrawn.

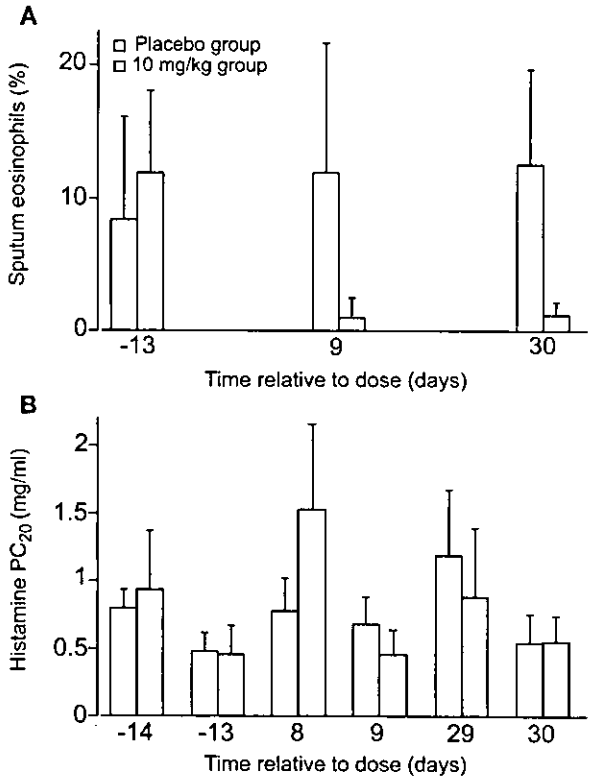

Fig. (3). Effect of a humanized monoclonal antibody against interleukin-5 (mepolizumab) on sputum eosinophils (upper panel) and airway hyperresponsiveness (histamine PC_{20}) (lower panel). Reproduced from reference [10].

IL-4 and the closely related cytokine IL-13 signal through a shared surface receptor, IL-4Rα, which activates a specific transcription factor STAT-6 [22]. Deletion of the STAT-6 gene has a similar effect to IL-4 gene knock-out [23]. This has led to a search for inhibitors of STAT-6, and although peptide inhibitors that interfere with the interaction between STAT-6 and JAKs linked to IL-4Rα have been discovered, it will be difficult to deliver these intracellularly. An endogenous inhibitor of STATs, suppressor of cytokine signaling (SOCS-1), is a potent inhibitor of IL-4 signaling pathways and offers a new therapeutic target [22].

3. Anti-IL-13

There is increasing evidence that IL-13 in mice mimics many of the features of asthma, including AHR, mucus hypersecretion and airway fibrosis, independently of eosinophilic inflammation [24]. It potently induces the secretion of eotaxin from airway epithelial cells [25] and transforms airway epithelium into a secretory phenotype [26]. Knocking out the IL-13, but not the IL-4, gene in mice prevents the development of AHR after allergen, despite a vigorous eosinophilic response [27], and the increase in AHR induced by IL-13 is only seen when the expression of STAT6 is lost in airway epithelial cells [28]. IL-13 signals through the IL-4Rα, but may also activate different intracellular pathways via activation of IL-13Rα1 [22], so that it may be an important target for the development of new therapies. A second specific IL-13 receptor, IL-13Rα2 exists in soluble form and has a high affinity for IL-13, thus acting as a decoy receptor for secreted IL-13. Soluble IL-13Rα2 is effective in blocking the actions of IL-13, including IgE generation, pulmonary eosinophilia and AHR in mice [29]. In the murine model IL-13Rα2 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 concentrations of IL-13 are much higher than those of IL-4. Humanized IL-13Rα2 is now in clinical development as a therapeutic approach for asthma.

4. Anti-IL-9

IL-9 is a Th2 cytokines that may enhance Th2-driven inflammation and amplify mast cell mediator release and IgE production [30]. IL-9 may also enhance mucus hypersecretion [31]. IL-9 and its receptors show an increased expression in asthmatic airways [32, 33]. A blocking antibody to IL-9 inhibits airway inflammation and AHR in a murine model of asthma [34]. Strategies to block IL-9, including blocking humanized antibodies are now in development [35].

5. Anti-IL-25

IL-25 is a newly described cytokine that stimulates the release of Th2 cytokines IL-4, IL-5 and IL-13, suggesting that it may play a role in

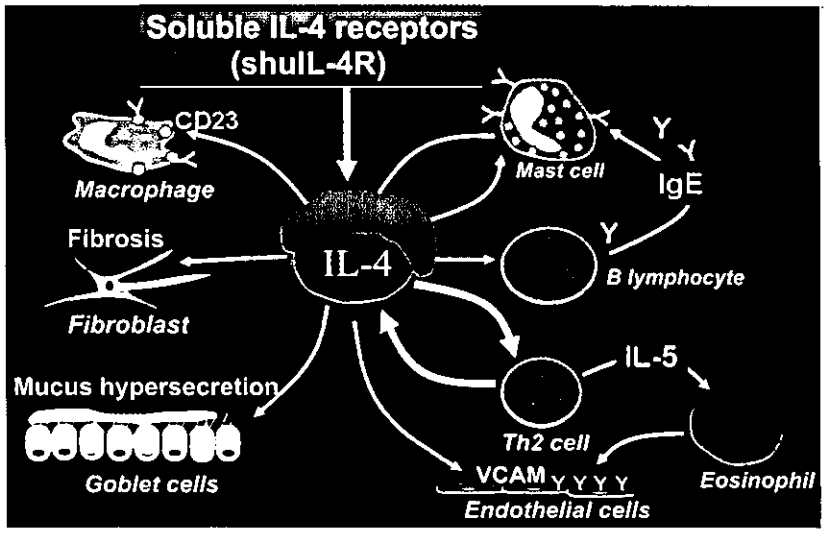

Fig. (4). Effects of blocking interleukin(IL)-4 in asthma. IL-4 has multiple effects relevant to allergic inflammation in asthma, including differentiation of type 2 T-helper lymphocytes (Th2), production of immunoglobulin E (IgE) from B-lymphocytes, increased expression of the low-affinity receptor for IgE (FcεRII) on several inflammatory cells, increased mucus secretion and fibrosis. IL-4 may be blocked by a high-affinity soluble receptor (shuIL-4R). VCAM: vascular cell adhesion molecule.

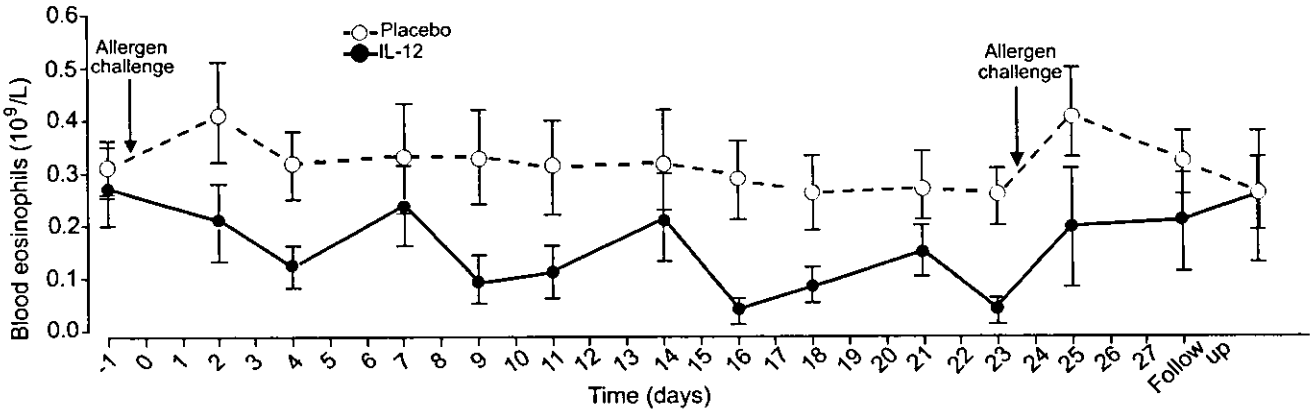

Fig. (5). Effect of interleukin-12 on peripheral blood eosinophils in patients with mild asthma. IL-12 was given in progressively increasing doses as an intravenous injection. Reproduced from reference [65].

allergic inflammation [36]. It is released from mast cells via an IgE-dependent mechanism and is therefore a possible target for inhibition in the treatment of asthma [37].

II. INHIBITION OF PROINFLAMMATORY CYTOKINES

Pro-inflammatory cytokines, particularly IL-1β and tumor necrosis factor-α (TNF-α), may amplify the inflammatory response in asthma and may be linked to disease severity. This suggests that blocking IL-1β or TNF-α may have beneficial effects, particularly in severe airway disease.

1. Anti-IL-1

IL-1 expression is increased in asthmatic airways [38] 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 (IL-1ra) binds to IL-1 receptors to block the effects of IL-1 [39]. In experimental animals IL-1ra reduces AHR induced by allergen. However, human recombinant IL-1ra does not appear to be effective in the treatment of asthma [40].

2. Anti-TNF

TNF-α is expressed in asthmatic airways and may play a key role in amplifying asthmatic inflammation, through the activation of NF-KB, AP-1 and other transcription factors [41].

In rheumatoid arthritis and inflammatory bowel disease a blocking humanized 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 [42, 43]. 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 [44].

III. ANTI-INFLAMMATORY CYTOKINES

Some cytokines have anti-inflammatory effects in inflammation and therefore have therapeutic potential [6, 7]. While it may not be feasible or cost-effective to administer these proteins as long-term therapy, it may be possible to develop drugs in the future that increase the release of these endogenous cytokines or activate their receptors and specific signal transduction pathways.

1. 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 (iNOS) that are over-expressed in asthma [45, 46]. 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 [47-49]. In sensitized animals IL-10 is effective in suppressing the inflammatory response to allergen [50] and CD4+ cells engineered to secrete IL-10 suppress airway inflammation in a murine model of asthma [51]. Specific allergen immunotherapy results in increased production of IL-10 by T helper cells and this may contribute to the beneficial effects of immunotherapy [52].

Recombinant human IL-10 has proved to be effective in controlling inflammatory bowel disease and psoriasis, where similar cytokines are expressed, and may be given as a weekly injection [53]. Although IL-10 is reasonably well tolerated, there are hematological side effects. In the future, drugs which activate the unique signal transduction pathways activated by the IL-10 receptor or drugs that increase endogenous production of IL-10 may be developed. In mice drugs that elevate cyclic AMP increase IL-10 production, but this does not appear to be the case in human cells [54].

2. Interferons

Interferon-γ (IFN-γ) inhibits Th2 cells and should therefore reduce atopic inflammation. In sensitized animals nebulized IFN-γ inhibits eosinophilic inflammation induced by allergen exposure [55] and adenovirus-mediated gene transfer of IFN-γ inhibits allergic inflammation in mice [56]. 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 [57]. Interestingly, allergen immunotherapy increases IFN-γ production by circulating T cells in patients with clinical benefit [58] and increased numbers of IFN-γ expressing cells in nasal biopsies of patients with allergic rhinitis [59]. A preliminary report suggests that IFN-α may be useful in the treatment of patients with severe asthma who have reduced responsiveness to corticosteroids [60].

3. IL-12

IL-12 is the endogenous regulator of Th1 cell development and determines the balance between Th1 and Th2 cells [61]. IL-12 administration to rats inhibits allergen-induced inflammation [62] and inhibits sensitization to allergens. IL-12 releases IFN-γ, but has additional effects on T cell differentiation. IL-12 levels released from whole blood cells are lower in asthmatic patients, indicating a possible reduction in IL-12 secretion [63].

Recombinant human IL-12 has been administered to humans and has several toxic effects that are diminished by slow escalation of the dose [64]. 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 [65] (Fig. 5). There was a concomitant reduction in eosinophils in induced sputum. However, there was no reduction in either early or late response to inhaled allergen challenge or any reduction in AHR (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. This suggests that IL-12 in not a suitable treatment for asthma. In mice 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 [66]. This

Table 2. Chemokine Receptor Antagonists in Asthma

Chemokine receptors	Cell types	Agonists	Antagonists
CCR3	Eosinophil	Eotaxin	Met-RANTES
	Th2 cell	Eotaxin-2	UCB35625
	Mast cell	RANTES	SB297006
		MCP-4	SB328437
CCR2	Monocyte	MCP-1	
	Mast cell		
	T-lymphocyte		
CCR4	Th2 cell	MDC	
		TARC	

There are three major chemokine receptor targets in asthma, CCR3, which is most advanced in terms of low-molecular-weight inhibitor development, and also CCR2 and CCR4, for which low-molecular-weight inhibitors are currently developed.

Abbreviations: Th2: type 2 T-helper lymphocyte; RANTES: regulated on activation, normal T-cell expressed and secreted; MCP-4: macrophage chemoattractant protein-4; MDC: monocyte-derived chemokine; TARC: thymus and activation-dependent chemokine; Met-RANTES: N-terminally modified RANTES.

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.

4. IL-18

IL-18 was originally described as IFN-γ releasing factor, but has a different mechanism of action to IL-12 [67]. 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 AHR [68], but no clinical studies have so far been reported.

5. IL-23

IL-23 is structurally related to IL-12 and shares some of its biological effects, so should have a protective function in asthma [69]. Its clinical potential has not yet been explored.

IV. CHEMOKINE INHIBITORS

Many chemokines are involved in the recruitment of inflammatory cells in asthma and COPD [70]. Over 50 different chemokines are now recognized and they activate up to 20 different surface receptors [71]. Chemokine receptors belong 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 [72]. Some chemokines appear to be selective for single chemokines, whereas others are promiscuous and mediate the effects of several related chemokines (Table 2). 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 [73].

1. CCR3 Inhibitors

Several chemokines, including eotaxin, eotaxin-2, eotaxin-3, RANTES and macrophage chemoattractant protein-4 (MCP-4) activate a common receptor on eosinophils designated CCR3 [74]. A neutralizing antibody against eotaxin reduces eosinophil recruitment in to the lung after allergen and the associated AHR in mice [75]. There is an increased expression of eotaxin, eotaxin-2, MCP-3, MCP-4 and CCR3 in the airways of asthmatic patients and this is correlated with increased AHR [76, 77]. Several small molecule inhibitors of CCR3, including UCB35625, SB-297006 and SB-328437 are effective in inhibiting eosinophil recruitment in allergen models of asthma [78, 79] and drugs in this class are currently undergoing clinical trials in asthma. Although it was though that CCR3 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 [80] also activates CCR3, but also has effects on CCR1 and CCR5, 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 [81].

2. CCR2 Inhibitors

MCP-1 activates CCR2 on monocytes and T lymphocytes and blocking MCP-1 with neutralizing antibodies reduces recruitment of both T cells and eosinophils in a murine model of ovalbumin-induced airway inflammation, with a marked reduction in AHR [75]. MCP-1 also recruits and activates mast cells, an effect that is mediated via CCR2 [82]. MCP-1 instilled into the airways induces marked and prolonged AHR in mice, associated with mast cell degranulation. A neutralizing antibody to MCP-1 blocks the development of AHR in response to allergen [82]. MCP-1 levels are increased in bronchoalveolar lavage fluid of patients with asthma [83]. This has led to a search for small molecule inhibitors of CCR2.

3. Other CCR Inhibitors

CCR4 and CCR8 are selectively expressed on Th2 cells and are activated by the chemokines monocyte-derived chemokine (MDC) and thymus and activation dependent chemokine (TARC) [84]. Inhibitors of CCR4 and CCR8 may therefore inhibit the recruitment of Th2 cells and thus persistent eosinophilic inflammation in the airways. CCR8 gene deletion does not have any effects on allergic inflammation in mice, suggesting that this receptor may not be an effective target [85]. CXCR4 are also selectively expressed on Th2 cells and a small molecule inhibitor AMD3100 inhibits allergen-induced inflammation in a murine model of asthma [86].

CCR7 plays a role in the migration of dendritic cells to regional lymph nodes and therefore blocking this receptor might suppress antigen presentation [87].

V. 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 or COPD, as so many cytokines are involved and there is considerable redundancy of effects. This has suggested that the development of drugs that have a more general effect on cytokines synthesis may be more successful. However, these drugs also affect other inflammatory processes, so their beneficial effects cannot necessarily be ascribed to inhibition of cytokine synthesis alone.

1. Corticosteroids

Corticosteroids are by far the most effective treatments for asthma [88] and part of their efficacy is due to inhibition of inflammatory cytokine

expression. This is mediated via an effect on glucocorticoid receptors to reverse the acetylation of core histones that is linked to increased expression of inflammatory genes, such as those encoding cytokines and chemokines [89].

2. Immunomodulatory Drugs

Cyclosporin A, tacrolimus and rapamycin inhibit the transcription factor NF-AT that regulates the secretion of IL-2, IL-4, IL-5, IL-13 and GM-CSF by T-lymphocytes [90]. Although it has some reported beneficial steroid-sparing effects in asthma [91], 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 [92], is reported to provide clinical benefit in asthma [93].

3. Phosphodiesterase 4 Inhibitors

PDE4 inhibitors inhibit the release of cytokines and chemokines from inflammatory cells via an increase in intracellular cyclic AMP [94]. Their clinical use is limited in asthma by side effects such as nausea.

4. NF-κB Inhibitors

NF-κB regulates the expression of many cytokines and chemokines involved in asthma [95]. There are several possible approaches to inhibition of NF-κB, including gene transfer of the inhibitor of NF-κB (IκB), inhibitors of IκB kinase-2 (IKK2), NF-κB-inducing kinase (NIK) and IκB ubiquitin ligase, which regulate the activity of NF-κB, and the development of drugs that inhibit the degradation of IκB [96]. One concern about this approach is that effective inhibitors of NF-κB may result in immune suppression and impair host defenses, since knock-out 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 [97]. Several small molecule inhibitors of IKK2 are now in development.

5. p38 MAP Kinase Inhibitors

Mitogen-activated protein (MAP) kinases play a key role in chronic inflammation and several complex enzyme cascades have now been defined. One of these, the p38 MAP kinase pathway, is involved in the expression of inflammatory cytokines and chemokines [98, 99]. 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 now been developed and these drugs have a broad range of anti-inflammatory effects [100]. There may be issues of safety, as p38 MAP kinases are involved in host defense. It is possible that the inhaled route of delivery may reduce the risk of side effects, however.

CONCLUSIONS

There are several specific cytokine and chemokine inhibitors now in development for the treatment of asthma. Inhibition of IL-4 with soluble IL-4 receptors in asthma showed promising early results, but this was not confirmed in larger trials and IL-13 inhibition is more promising. Anti-IL-5 antibody is very effective at inhibiting peripheral blood and airway eosinophils, but does not appear to be effective in symptomatic asthma. Inhibitory cytokines, such as IL-10, interferons and IL-12 are less promising, as systemic delivery produces side effects and it may be necessary to develop inhaled delivery systems. Inhibition of TNF-α may be useful in the treatment of severe asthma. Many chemokines are involved in the inflammatory response of asthma and small molecule inhibitors of chemokine receptors are now in development. CCR3 antagonists are now being developed for the treatment of asthma. Because so many cytokines are involved in these complex diseases, drugs that inhibit the synthesis of multiple cytokines may be more successful. Several such classes of drug are now in clinical development, including PDE4, p38 MAP kinase and IKK2 inhibitors. The risk of side effects in these non-specific inhibitors may be reduced by inhaled route of delivery.

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Original Article

Effect of a leukotriene receptor antagonist on the prevention of recurrent asthma attacks after an emergency room visit

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Abstract

Background: The efficacy of montelukast, a specific cysteinyl leukotriene receptor antagonist, in preventing recurrent asthma attacks was evaluated for post-emergency management of acute asthma exacerbation.
Methods: Twenty-two patients with a history of chronic asthma whose symptoms were responsive to an inhaled β-adrenergic receptor agonist in an emergency room setting, were randomized into two groups, those with and those without montelukast (n = 11 for each group). Patients in the montelukast group received an oral dose of 10 mg montelukast before leaving the emergency room following rescue treatment with an inhaled β-adrenergic receptor agonist. Patients in both groups were instructed to use an inhaled β-adrenergic receptor agonist for shortness of breath or dyspnea in post-emergency management. Additional β-adrenergic receptor agonist use, subjective asthma symptoms, sleep impairment, additional emergency visits and/or hospitalization were monitored for 24 hours following the emergency room visit.
Results: In the montelukast group, the need for a rescue β-adrenergic receptor agonist was significantly decreased; 54.5% of patients in the montelukast group required use of β-adrenergic receptor agonist compared with 100% in the non-montelukast group ($P < 0.05$). The average number of uses of a β-adrenergic receptor agonist was 2.67 ± 3.58 times/24 h in the montelukast group compared with 11.95 ± 3.60 times/24 h in the non-montelukast group ($P < 0.01$). The average subjective asthma symptom scores were significantly decreased in the montelukast group, whereas no score change occurred in the non-montelukast group. The sleep impairment score was significantly lower in the montelukast group compared with that in the non-montelukast group ($P < 0.05$). No patients in either group had an emergency visit or hospitalization during this period.
Conclusions: The results demonstrate that montelukast can prevent recurrent asthma exacerbations in the home environment.

Key words: β_2-adrenergic receptor agonist, asthma exacerbation, leukotriene receptor antagonist, montelukast.

Introduction

In the management of asthma, the choice of drugs for controlling recurrent acute asthma exacerbations, especially in the home environment, is important for patients who have been released from hospital emergency care. Continuous use of inhaled β-adrenergic receptor agonists in combination with systemic administration of corticosteroids was recommended by the Global Initiative for Asthma (GINA) guidelines (2002) as a treatment for such conditions.[1] However, systemic corticosteroids

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are slow acting and it takes 4–6 h for the clinical effects of systemic corticosteroids to be manifested on acute asthma exacerbation.[2] In contrast, β-adrenergic receptor agonists are rapid and short acting, but they are effective only in a portion of acute asthmatic patients.[3] Thus, no adequate progress has been made in the drug treatment of acute asthma over the past 20 years,[4] despite the fact that the prevalence of emergency room visits following an acute asthma attack has increased substantially.

Leukotriene (LT) receptor antagonists have emerged as an important treatment for the long-term control of chronic asthma.[5,6] Evidence suggesting the clinical benefit of LT receptor antagonists has accumulated in acute asthmatic patients and their effectiveness is due to the rapid onset of their bronchodialating effect.[7,8] In the present study, we examine the effect of montelukast, a LT receptor antagonist, in the prevention of the recurrence of acute asthma exacerbations in patients who have been released after receiving rescue β-adrenergic receptor agonist treatment in an emergency room.

METHODS

The subjects of the present study were 22 patients with a 1 year or more history of asthma, whose mild to moderate asthma exacerbations responded to the use of inhaled β-adrenergic agonists in an emergency care visit. None of the study subjects had received systemic corticosteroid therapy. An improvement of acute asthma exacerbation with β-adrenergic receptor agonists was measured in terms of physical parameters, such as auscultatory findings, heart rate and respiratory rate, and symptoms of respiratory distress lasting for 1 h or more in an emergency room visit.

Subjects were randomized into two groups: those patient given montelukast and those not (n = 11 for each group). While still in the emergency room, patients in the montelukast group received a single oral dose of 10 mg montelukast just after rescue treatment with an inhaled β-adrenergic receptor agonist and were prescribed montelukast for 3 days. Patients in the non-montelukast group received no medication other than the initial rescue treatment. The study subjects excluded patients who needed further intensive treatment, such as in-patient care, those who had previously used LT receptor antagonists and those who had been using nebulized β-adrenergic receptor agonists in the home environment.

As post-emergency room management, both groups were instructed to use inhaled β-adrenergic receptor agonists with a metered-dose inhaler for recurrent asthma exacerbations as needed and to take a second dose of the β-adrenergic receptor agonist if the recurrent attack was not relieved within 30 min of the first dose. If the attack persisted after the second dose, patients were instructed to return to the emergency room.

The primary end-point for evaluating recurrence of asthma exacerbation in the home environment was the frequency of inhaled β-adrenergic receptor agonist use, which was monitored in the 24 h period between release from the emergency care visit and the out-patient visit of the following day, and was expressed as the calculated number of β-adrenergic receptor agonist uses per 24 h. The secondary end-points were subjective asthma symptom scores, nocturnal sleep impairment scores and number of emergency visits or hospitalizations. The scores of subjective asthma symptoms and nocturnal sleep impairment for the worst asthmatic attack before and after the emergency visit were determined according to the criteria of the Japanese Society of Allergology (Table 1) in patient interviews.[9]

Data are expressed as the mean ± SD. Differences between groups were analyzed by Student's t-tests and Fisher's exact test at a two-tailed significance of 5%.

RESULTS

Baseline patient characteristics of both groups are shown in Table 2. The treatment programs for asthma before the emergency care visit were similar in the two groups. Home management of chronic asthma in all patients was not adequately sustained, even with clinic visits. Both the average severity of asthma in the home environment measured with subjective asthma symptom scores prior to the emergency visit and mean room air S_pO_2 at the emergency visit were similar in both groups.

Frequency of inhaled β-adrenergic receptor agonist use

Subsequent to the emergency visit, all te patients in the non-montelukast group needed inhaled β-adrenergic receptor agonists, whereas only six patients (54.5%) in the montelukast group did ($P < 0.05$). The frequency of β-adrenergic receptor agonist use was significantly lower in the montelukast group compared with the non-montelukast group (2.67 ± 3.58 and 11.95 ± 3.60 times/24 h, respectively; $P < 0.01$; Fig. 1).

Table 1 Criteria of asthma symptoms and nocturnal sleep impairment scores prepared by the Japanese Society of Allergology[9]

	Score (points)
Asthma symptom scores	
Severe asthma exacerbation	9
Moderate asthma exacerbation	6
Mild asthma exacerbation	3
Wheeze	1
Severe cough	0.5
Mild cough	0.5
None	0
Nocturnal sleep impairment scores	
Not possible because of respiratory distress	9
Difficult because of respiratory distress	6
Fairly possible despite respiratory distress	3
Peaceful	0

Table 2 Characteristics of study subjects

Characteristics	Non-montelukast group (n = 11)	Montelukast group (n = 11)
Mean (± SD) ages (years)	41.2 ± 15.5	40.9 ± 16.9
Sex (no. males/females)	5/6	4/7
Mean (±SD) duration of asthma (years)	12.6 ± 15.3	9.8 ± 10.9
Smoking (no. smokers/non-smokers)	4/7	4/7
Severity (no. mild/moderate/severe)	7/4/0	6/5/0
Mean (± SD) attack score before emergency visit (points)	3.1 ± 1.2	3.1 ± 1.7
Treatment programs for asthma before the emergency visit (n)		
No regular treatment program	5	5
Oral β-adrenergic receptor agonists as needed	1	1
Inhaled β-adrenergic receptor agonists as needed	4	3
Irregular inhaled corticosteroids	1	2

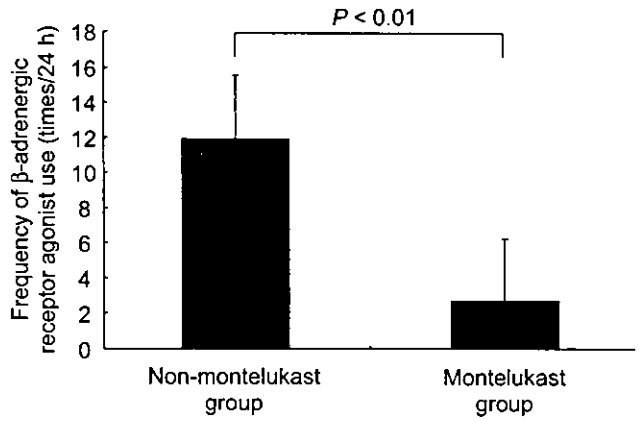

Fig. 1 Frequency of inhaled β-adrenergic receptor agonist use, monitored in the 24 h period between the release from emergency care visit and the out-patient visit of the following day, expressed as the calculated number of β-adrenergic receptor agonist uses per 24 h. Values are the mean ± SD for n = 11 subjects per group.

Subjective asthma symptom score

Changes in the average subjective asthma symptom score at the worst asthma attack before and after the emergency care visit were from 3.05 ± 1.23 to 2.64 ± 1.55 in the group without montelukast and from 3.14 ± 1.67 to 0.82 ± 0.78 in the montelukast group (Fig. 2). The decrease was significant in the montelukast group ($P < 0.01$), but not in the non-montelukast group ($P = 0.51$).

When the percentage change from baseline in the score of individual patients was calculated and then averaged, the average percentage reduction from baseline was significantly higher in the montelukast group than in the non-montelukast group (59.8 ± 39.6 and 6.1 ± 48.5%, respectively; $P < 0.05$).

Nocturnal sleep impairment score

The nocturnal sleep impairment score after an emergency care visit was significantly lower (2.72 ± 2.10) in the montelukast group compared with the non-montelukast group (5.45 ± 1.23), suggesting that nocturnal sleep was significantly improved with montelukast ($P < 0.01$; Fig. 3).

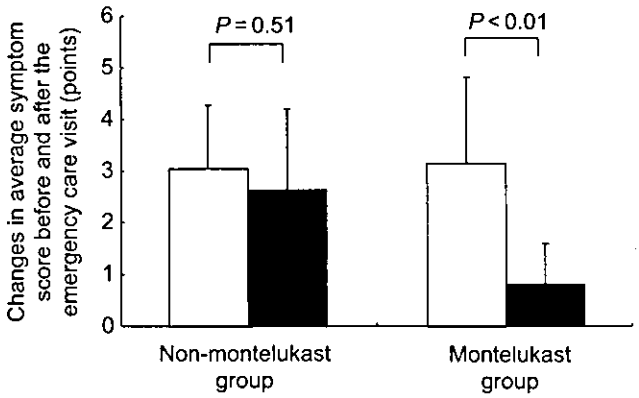

Fig. 2 Changes in the average subjective asthma symptom score at the worst asthma attack before (□) and after (■) the emergency care visit. The scores of subjective asthma symptoms were taken according to the criteria of the Japanese Society of Allergology[9] in patient interviews. Values are the mean ± SD for $n = 11$ subjects per group.

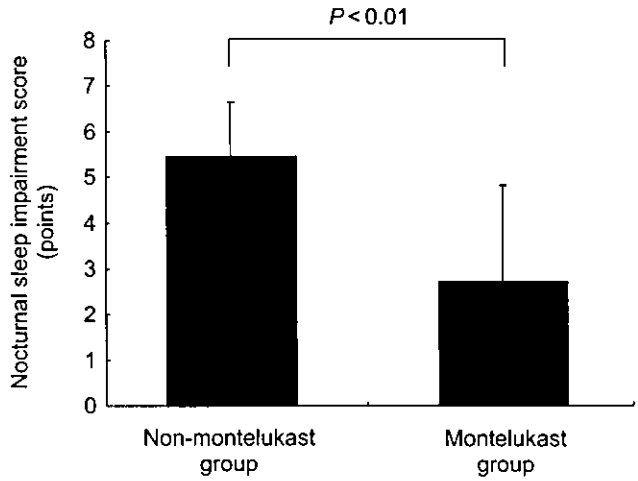

Fig. 3 Nocturnal sleep impairment scores after an emergency care visit. The scores of nocturnal sleep impairment were taken according to the criteria of the Japanese Society of Allergology[9] in patient interviews. Values are the mean ± SD for $n = 11$ subjects per group.

Number of emergency return visits and/or hospitalizations

No patient in either group returned to the emergency room or was hospitalized subsequent to the emergency care visit.

Discussion

In the present clinical study in emergency room asthmatic patients whose acute exacerbation responded to rescue β-adrenergic receptor agonists, a single oral dose of montelukast given before leaving the emergency room significantly reduced the subsequent use of β-adrenergic receptor agonists, as well as scores of subjective asthma symptoms and sleep disturbance. The results demonstrate the beneficial effect of montelukast in the home management of recurrent asthma exacerbations.

The pathophysiology of asthma has become increasingly more understood in recent years. The drugs of first choice for the treatment of an asthma attack in the emergency room have been short-acting β-adrenergic receptor agonists, according to the treatment guidelines for acute asthma.[1] When patients are relieved from an acute asthma attack by treatment, and the ameliorating effect continues, they are allowed to go home after an adequate home management program for recurrent attacks is given. In the GINA guidelines, the continual use of inhaled β-adrenergic receptor agonists in combination with systemic corticosteroids has been recommended for such post-emergency management of asthma exacerbations.[1] However, this treatment is inadequate as the management method for the following reasons: (i) approximately one-third of patients in an emergency setting poorly respond to short-acting β-adrenergic receptor agonists;[3] and (ii) corticosteroids have a delayed clinical effect, resulting in 4–6 h or even longer before patients have relief.[2] Furthermore, the use of systemic corticosteroids in patients with acute asthma does not improve pulmonary function within 6 h of their administration nor do systemic corticosteroids reduce hospitalizations of such patients, as revealed in a recent meta-analysis.[10] Although the alternative combination of an inhaled anticholinergic agent and an inhaled β-adrenergic receptor agonist produced a better bronchodilating effect and reduced the number of hospitalizations in patients with acute asthma,[11] anticholinergic agents themselves have been ineffective in the treatment of

β-adrenergic receptor agonist-resistant asthma exacerbations and, in the study of McFadden *et al.*, the presence of an anticholinergic agent in the β-adrenergic receptor agonist regimen did not influence the treatment effect.[12] The effects of intravenous injections of methylxanthine,[13] magnesium[14] and helium–oxygen therapy[15] have been investigated for the same clinical aspect, but there has been no conclusive consensus reached yet regarding their beneficial effects in the treatment of acute asthma. Thus, finding a drug that has fast action and a sustained effect for preventing recurrent asthma exacerbations is one of the important goals in the post-emergency management of acute asthma.

Cysteinyl LT are implicated in acute asthma, as evidenced by the elevated cysteinyl LT concentration in urine and induced sputum during an acute asthma attack.[16,17] The metabolites of arachidonic acid, produced by 5-lipoxygenase, mediate not only inflammatory cell chemotaxis of eosinophils and microvascular permeability, but also bronchial smooth muscle constriction and proliferation.[18,19]

Leukotriene receptor antagonists are considered effective drugs for the long-term control of chronic asthma according to the GINA guidelines.[1] Dockhorn *et al.* demonstrated that both oral and intravenous montelukast improved respiratory function in patients with chronic asthma.[20] The improvement in forced expiratory volume in 1 s (FEV_1) is much greater at 15 min after intravenous administration and the effect continued for 24 h with a single oral or intravenous dose of montelukast, suggesting the relatively fast and sustained bronchodilating effect of LT receptor antagonists. The effect of an LT receptor antagonist in the prevention of acute asthma was also indicated in a study in which administration of the drug significantly inhibited airway constriction in response to exercise,[21] the inhalation of cold air[22] or allergens[23] in patients with bronchial asthma. Clinical data for the use of LT receptor antagonists in acute asthmatic patients continue to accumulate. Camargo *et al.* compared the effect of standard therapy (placebo group) with that of a combination of standard therapy and intravenous montelukast (montelukast group) in patients with acute asthma who did not respond to an inhaled β-adrenergic receptor agonist.[7] Montelukast improved FEV_1 over 20 min after administration. The mean FEV_1 increased significantly from prerandomization baseline and the use of systemic corticosteroids or β-adrenergic receptor agonists was significantly less in patients in the montelukast group compared with the placebo group. In a study of acute asthmatic patients, peak respiratory flow increased more in the group treated with a combination of the systemic corticosteroid and oral montelukast compared with systemic corticosteroid alone, although the difference between the two groups was not significant.[8] Leukotriene receptor antagonists may be more effective in the management of acute asthma rather than in the long-term control of chronic asthma because the cysteinyl LT production pathway is more active in acute asthma than in the chronic form of the condition.[16,17] However, there is not enough evidence that LT receptor antagonists are more effective as relievers of acute asthma than as controllers of chronic asthma; thus, further investigation of the significance of inhibiting cysteinyl LT activity during asthma exacerbations is needed.

Although none of the subjects in the present study sustained home management of chronic asthma adequately, all subjects were responded to an inhaled β-adrenergic receptor agonist in emergency care. However, the effect of the β-adrenergic receptor agonist was transient, as evidenced by the need for additional doses of the inhaled β-adrenergic receptor agonist for recurrent exacerbation in both groups. Montelukast reduced the use of the β-arenergic receptor agonist, subjective asthma symptom scores and nocturnal sleep impairment scores, suggesting the effectiveness of LT receptor antagonists in the prevention of recurrent asthma attacks in patients with β-adrenergic receptor agonist-responsive acute asthma whose chronic asthma management is not adequately sustained. In fact, approximately half the patients in the montelukast group needed to use a β-adrenergic receptor agonist to some extent, but only one of them needed to use it as often as the patients in the non-montelukast group. In many previous studies, LT receptor antagonists have been shown to possess several anti-asthmatic effects, such as broncodilation and anti-inflammatory effects. The rapid onset of action obtained in the present clinical study suggests that the primary mechanism of action of LT receptor antagonists in the management of acute asthma is one of bronchodilation. Although the impact of LT receptor antagonists on respiratory function with time during asthma exacerbations was not investigated in the present study, this information is needed to clarify the precise mechanism of action of LT receptor antagonists.

There was a population of asthmatic patients who were responsive to LT receptor antagonists and one that was not: responders and non-responders found in the study of the long-term control of chronic asthma.[24–26]

Involvement of variants of the LTC_4 synthase gene and the 5-lipoxygenase gene in responsiveness to LT receptor antagonists has been suggested in some studies.[24-26] However, Camargo *et al.* reported that the bronchodialating effect of montelukast on acute asthma was observed in the majority of patients and their results did not confirm the obvious existence of responders or non-responders.[7]

The results of the present study demonstrate the beneficial effect of montelukast in the management of mild asthma exacerbations without the need for the administration of systemic corticosteroids. However, further investigation is needed to elucidate the role and importance of cysteinyl LT in the inflammation and constriction of the pulmonary pathway in acute asthma and the significance of inhibiting cysteinyl LT activity in acute asthma. Large-scale studies are needed to evaluate the therapeutic efficacy and usefulness of LT receptor antagonists in patients with acute asthma, including comparisons with anticholinergic agents and long-acting β-adrenergic receptor agonists. In addition, the aim of the present clinical study was not to compare the effectiveness directly between established systemic corticosteroids therapy and LT receptor antagonists in the management of asthma exacerbations. Either a comparative study with systemic corticosteroid therapy or an investigation of the add-on effect of LT receptor antagonists to systemic corticosteroid therapy is needed to prove the clinical usefulness of LT receptor antagonists in the management of acute asthma.

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ORIGINAL ARTICLE

COPD in Japan: the Nippon COPD Epidemiology study

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Chronic obstructive pulmonary disease in Japan: the Nippon COPD Epidemiology study
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Objectives: Despite high smoking rates, few prevalence studies of COPD have been performed in Asia. The Nippon COPD Epidemiology (NICE) Study used spirometry to measure prevalence of airflow limitation in Japanese adults.

Methodology: Clinical, spirometric, and risk factor exposure data were collected on 2343 subjects aged ≥ 40 years who were demographically similar to the Japanese population. Airflow limitation was defined according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (FEV_1/FVC < 70%).

Results: Prevalence of airflow limitation was 10.9%. Based upon GOLD severity criteria, 56% of these cases were found to be mild, 38% moderate, 5% severe, and 1% very severe. Airflow limitation was significantly more prevalent in males than females (16.4% vs. 5.0%; $P < 0.001$), in male ever-smokers than female ever-smokers (17.1% vs. 7.5%; $P < 0.001$), and in older subjects (3.5% in 40–49 years olds vs. 24.4% in those > 70 years; $P < 0.001$). Of note, airflow limitation was also found in 5.8% of non-smokers and 4.6% of those younger than age 60 years. Only 9.4% of cases with airflow limitation reported a previous diagnosis of COPD.

Conclusions: Prevalence of airflow limitation in Japan is higher than previously reported, suggesting a high degree of under-recognition of COPD. The high prevalence of smoking coupled with an aging population threatens to further increase the burden of COPD, highlighting the need for enhanced screening efforts and interventions of prevention and treatment.

Key words: airflow limitation, airway obstruction, chronic obstructive pulmonary disease, epidemiology, prevalence, smoking.

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Part of this material has been previously presented as a poster at the 11th Annual Congress of the European Respiratory Society (ERS) held in Berlin, Germany, in September 2001. This abstract was printed in the Supplement of the European Respiratory Journal (Volume 18, Supplement 33). Some of the information included in the poster was subsequently cited in a summary article on worldwide epidemiology of COPD in 'COPD Frontier', which is a Japanese-language newsletter for physicians in Japan. The poster presentation and article in 'COPD Frontier' represented preliminary study results. The information presented in this article represents the final analysis of study data. This article has not otherwise been published and is not being considered for publication elsewhere.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability throughout the world.[1] COPD ranks as the sixth leading cause of death in the world and the fifth leading cause of death in developed countries.[2] In addition, the burden of disease is expected to increase over the next 20 years.[2,3] However, the impact of COPD is under-appreciated in many parts of the world. The importance of the public health burden of COPD is highlighted in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Report, a collaborative effort of the World Health Organization and US National Heart, Lung, and Blood Institute.[4] This initiative strives to 'increase awareness of the medical community, public health officials, and the general public that COPD is a public health problem'.

The major risk factor for COPD is smoking, and Asian countries have some of the highest smoking prevalence rates in the world.[5] However, few COPD prevalence estimates derived from epidemiology studies are available for Asian countries, and there is a perception that COPD is not a common clinical problem in this region.[6] A survey of claims data from hospitals and clinics by the Japanese Ministry of Health and Welfare in 1996 reported only 220 000 diagnosed cases of COPD, which equates to a prevalence of 0.2%, a rate far lower than the prevalence rates of 4% to 10% reported in Western countries based upon epidemiological studies.[7,8] It has been hypothesised that one reason for this difference is that the Japanese are less susceptible to the deleterious effects of cigarette smoke than other ethnicities and have a different clinical presentation of COPD.[9] To address the paucity of COPD epidemiology data in Japan and to help assess possible prevalence differences with other developed countries, we undertook a study to measure and characterise the prevalence of airflow limitation in the adult Japanese population.

METHODS

Subject recruitment

The Nippon COPD Epidemiology (NICE) Study was an epidemiological study conducted in 18 (out of 47) Japanese prefectures that used spirometry to measure prevalence of airflow limitation. These 18 prefectures represented 49% of the Japanese population.[10] The study was conducted from September to December 2000. Ethics Committee approval was obtained from all study sites. Within each prefecture, we used the telephone directory to randomly identify households and attempted to contact these households by mail and telephone. A total of 42 029 households were identified across all 18 prefectures. One eligible individual was selected from each responding household based on the following criteria: age ≥ 40 years, able to undergo spirometry, able to visit the study site on predetermined dates, and willing to provide informed consent.

Diagnosis of chronic obstructive pulmonary disease

Study participants underwent spirometric evaluation and completed a self-reported questionnaire on clinical history, COPD risk factor exposure, respiratory symptoms, prior diagnoses, and treatment. Spirometry was performed under standardised conditions using a CHESTgraph 101 spirometer (Chest MI, Inc., Tokyo, Japan) that was calibrated daily. Up to four tests were used to obtain three satisfactory loop recordings. A panel of investigators reviewed all loop recordings retrospectively and excluded those without at least three satisfactory tests. From the three satisfactory loop recordings, the highest FEV_1 and FVC values were selected for analysis as recommended by the American Thoracic Society and the European Respiratory Society.[11,12] Reference values for FEV_1% predicted were derived from Japanese criteria.[13] Reversibility testing was not performed, as it was unacceptable to Institutional Review Boards to perform such testing in patients without a high suspicion of clinical disease. Study subjects with an FEV_1/FVC ratio < 70% were assigned a diagnosis of airflow limitation (airway obstruction). Severity of airflow limitation was based upon percent of predicted FEV_1 in accordance with GOLD criteria (FEV_1 ≥ 80% predicted, mild; FEV_1 = 50–79% predicted, moderate; FEV_1 = 30–49% predicted, severe; FEV_1 < 30% predicted, very severe).[4]

Patient stratification

The study population was stratified by age, gender, smoking status, duration of high-risk occupational exposure, and city size (population was used as a surrogate for air pollution since air quality data was not available: < 100 000, 100 000–500 000, and > 500 000 persons). The study population was also compared by age and gender to the Japanese population ≥ 40 years old.[10]

'Current smokers' were those who reported smoking within the past 30 days and who had smoked regularly for at least 1 year prior to that. 'Former smokers' were those who had smoked regularly but had quit and had not smoked within the past 30 days. 'Ever-smokers' included current and former smokers. Pack-years of smoking were calculated based on the number of cigarettes smoked per day and the number of years that the respondent had smoked. High-risk occupations identified from the literature and specifically queried in the questionnaire were: asbestos worker, beautician, building destroyer, carpenter, chemical worker, cotton ginner, dairy farmer, fry cook, grain or animal feed worker, mechanic, metal worker, miner, mushroom grower or processor, sand blaster, sawmill worker, stone worker, swine or poultry worker, weaver, welder, or wool presser.

Subjects with airflow limitation were stratified by age, gender, smoking status, duration of high-risk

occupational exposure, and city size. These subjects were also analysed based upon self-reported prior diagnosis of COPD (including chronic bronchitis or emphysema) and asthma.

Because we were unable to perform reversibility testing to rule out a diagnosis of asthma, we performed sensitivity testing to determine the proportion of airflow limitation cases that were potentially asthma and not COPD. Four questions on the questionnaire were related to asthma (see Table 5 for the list of questions). An affirmative response to any combination of these questions defined a subject as having possible asthma. The remainder of the subjects with airflow limitation was considered to have a diagnosis of COPD.

Statistical analysis

SAS 8.1 (SAS Institute Inc., Cary, NC, USA) and Stata 7.0 (StataCorp. College Station, TX, USA) statistical software were used to derive prevalence rates in various patient subgroups. Descriptive analyses were performed using frequency distributions. Comparison between continuous variables was made using the *t*-test and between proportions using the χ^2 test. In the bivariate analysis, the rate ratio for airflow limitation prevalence for each subgroup was calculated as the ratio between the prevalence in each subgroup compared to the lowest prevalence within each subgroup. Multivariate regression analysis was used to assess the relationship between risk factors and airflow limitation; odds ratios were converted to relative risk ratios.

RESULTS

Nippon COPD Epidemiology study population

Of 23 949 households successfully contacted, 19 637 were eligible to participate. Of these, 2711 (14%) contained an eligible respondent who enrolled in the study and completed the study protocol. Of these, 368 (13.6% of 2711) were excluded due to invalid spirometry results. Thus, the NICE study population was comprised of 2343 Japanese subjects aged ≥ 40 years.

Table 1 displays the characteristics of the NICE study population. The study population had a mean age of 58.0 years with slightly more males than females. The study population also consisted of slightly more ever-smokers than lifelong non-smokers. The majority of ever-smokers accumulated over 25 pack years. The proportion of current smokers was substantially higher among males (46.7%) than females (12.3%; $P < 0.001$). Only 10.9% of the study population reported working in a high-risk occupation for over 6 years.

Table 2 shows the characteristics of the study population compared with the general population of Japan in the study year (2000). The two populations were similar demographically, except for a slightly lower percentage of females in the study population compared to the general Japanese population.

Prevalence of airflow limitation

The unadjusted prevalence of airflow limitation in the study population was 10.9%. Spirometry values

Table 1 Characteristics of the NICE sample with valid spirometry, $n = 2343$

	No.	%	FEV_1 (L) (mean)	FVC (L) (mean)	FEV_1/FVC(%) (mean)
Age (years)					
40–49	660	28.2	3.17	3.89	81.7
50–59	675	28.8	2.82	3.53	80.1
60–69	599	25.6	2.44	3.21	76.5
70+	409	17.5	2.03	2.74	74.7
Gender					
Female	1125	48.0	2.28	2.84	80.2
Male	1218	52.0	3.05	3.94	77.3
Smoking status					
Never	1103	47.1	2.40	3.00	79.9
Current	707	30.2	2.97	3.83	77.5
Former	533	22.8	2.88	3.69	77.7
Pack-years					
0–24	1633	69.7	2.60	3.24	80.0
25–49	493	21.0	2.93	3.82	76.6
50+	217	9.3	2.76	3.73	73.5
High-risk job					
≤ 6 years	2087	89.1	2.67	3.38	79.0
> 6 years	256	10.9	2.78	3.63	76.2
City size					
Small (< 100 000)	721	30.8	2.58	3.24	79.7
Medium (100 000–500 000)	768	32.8	2.74	3.51	78.2
Large (> 500 000)	854	36.5	2.71	3.47	78.3
Total	2343	100.0	2.68	3.41	78.67

(mean ± SD) for those subjects with airflow limitation were: FEV_1, 2.16 ± 0.65 L; FVC, 3.39 ± 0.89 L; and FEV_1/FVC, 63.17 ± 7.36%. Severity of obstruction according to GOLD criteria was: 56% mild; 38% moderate; 5% severe; and 1% very severe.

Table 3 shows the unadjusted prevalence of airflow limitation and unadjusted and adjusted (for multivariate logistic regression analysis) rate ratios in various stratified subgroups. In the multivariate analysis, the risk of airflow limitation was significantly influenced by older age, male gender, and cumulative pack-years smoked. Bivariate analyses demonstrated the increased risk of airway limitation among various subgroups (Table 4).

Of the subjects with airflow limitation, 42.6% were current smokers and 42.6% had symptoms of cough and/or sputum. Only 9.4% of subjects with airflow limitation reported receiving a previous diagnosis of COPD, chronic bronchitis, or emphysema from their physician; 11.3% reported a prior diagnosis of asthma.

Table 2 Comparison between study population and Japanese population

Characteristic	Study sample No.	%	Japanese population† No.	%
Age (years)				
40–49	660	28.2	16 716 227	27.5
50–59	675	28.8	19 176 162	31.5
60–69	599	25.6	14 841 772	24.4
70+	409	17.5	10 051 176	16.5
Gender				
Female	1125	48.0	31 490 216	51.8
Male	1218	52.0	29 295 121	48.2

†Year 2000 Ages > 40.[33]

Sensitivity analysis

A sensitivity analysis was performed to assess the proportion of airflow limitation cases likely due to COPD or potentially due to asthma (Table 5). Using five different definitions of asthma, COPD prevalence estimates ranged from 8.6% to 10.9%.

DISCUSSION

This is the first spirometry-based study on prevalence of airflow limitation in Japan. The airflow limitation prevalence of 10.9% was substantially higher than previously reported in governmental statistics for COPD. While the contribution of asthma cannot be exactly determined, we conservatively estimate COPD prevalence to be at least 8.6%, which portends staggering future consequences for the health care delivery system in Japan, as the disease progresses in

Table 3 Characteristics of the population with airflow limitation ($n = 256$)

Characteristic	Prevalence (%)	Unadjusted (95% CI)	Unadjusted Rate ratio	Adjusted† Rate ratio	Adjusted† (95% CI)
Age (years)					
0–49	3.5	(2.1, 4.9)	1 (ref)	1 (ref)	
50–59	5.8	(4.0, 7.5)	1.56	1.30	(0.81, 1.99)
60–69	15.7	(12.8, 18.6)	3.72	3.36	(2.33, 4.59)
70+	24.4	(20.3, 28.6)	5.46	5.50	(4.03, 7.06)
Gender					
Female	5.0	(3.7, 6.3)	1 (ref)	1 (ref)	
Male	16.4	(14.3, 18.5)	3.30	1.97	(1.30, 2.92)
Smoking status					
Never	5.8	(4.4, 7.2)	1 (ref)	1 (ref)	
Current	15.4	(12.7, 18.1)	2.52	1.11	(0.66, 1.83)
Former	15.6	(12.5, 18.7)	2.52	1.02	(0.63, 1.61)
Pack-years (ever smokers, %)					
0–24	6.1	(5.0, 7.3)	1 (ref)	1 (ref)	
25–49	17.8	(14.5, 21.2)	2.75	1.92	(1.31, 2.75)
50+	31.3	(25.1, 37.6)	4.57	3.26	(2.22, 4.55)
High-risk job					
≤ 6 years	9.9	(8.6, 11.2)	1 (ref)	1 (ref)	
> 6 years	19.5	(14.6, 24.4)	1.98	1.38	(0.99, 1.89)
City size					
Small (< 100 000)	10.3	(8.0, 12.5)	1 (ref)	1 (ref)	
Medium (100 000–500 000)	11.6	(9.3, 13.9)	1.13	1.12	(0.81, 1.52)
Large (> 500 000)	10.9	(8.8, 13.0)	1.06	1.12	(0.81, 1.52)
Overall	10.9	[9.7, 12.2]			

†Adjusted for all factors listed. Pseudo $R^2 = 0.1585$; $n = 2343$.

Table 4 Relative rates[†] of airflow limitation in selected subpopulations

Characteristic 1	Prevalence	Characteristic 2	Prevalence	*P* value
Males	16.4%	Females	5.0%	$P<0.001$
40–59 years old	4.6%	60 years or older	19.2%	$P<0.001$
Ever-smoker and...		Ever-smoker and...		
Male	17.1%	Female	7.5%	$P<0.001$
> 6 years in high-risk occupation	22.1%	> 6 years in high-risk occupation	14.2%	$P<0.001$
Ever-smoker	15.0%	Never-smoker	5.8%	$P<0.001$
Ever-smoker and...		Never-smoker and...		
with prior COPD diagnosis	11.5	with prior COPD diagnosis	3.1%	$P<0.05$
with prior asthma diagnosis	8.9%	with prior asthma diagnosis	15.6%	NS
with allergy symptoms	44.3%	with allergy symptoms	40.6%	NS

[†]Unadjusted.

Table 5 Prevalence of airflow limitation by diagnostic category

Self-reported asthma diagnosis criteria[§]	Possible asthma *n* (%)[†]	COPD *n* (%)[†]	COPD prevalence in study population[‡] (%)
Any one of four asthma questions positive	55 (21.5%)	201 (78.5%)	8.6%
Any two of four asthma questions positive	24 (9.4%)	232 (90.6%)	9.9%
Any three of four asthma questions positive	10 (3.9%)	246 (96.1%)	10.5%
Any four of four asthma questions positive	0 (0.0%)	256 (100.0%)	10.9%
Self-reported prior diagnosis of asthma or paediatric asthma	29 (11.3%)	227 (88.7%)	9.7%

[†]% of 256 cases with airflow limitation; [‡]% of 2343 subjects in study population.

[§]Questions for asthma: 'During the past 12 months have you had more than one episode of waking up at night or early morning as a result of spasmodic breathlessness even when you didn't have a cold?'; 'During the past 12 months have you had more than one episode of waking up at night or early morning as a result of wheezing or whistling in the chest even when you did not have a cold?'; 'Have you ever been told by a doctor that you had bronchial asthma?'; 'Were you ever diagnosed as having asthma during your childhood?'.

severity. Moreover, Japan is likely to represent a bellwether to Asia, thus magnifying the importance and implications of these findings.

One finding with important implications for the burden of COPD on the Japanese health care system, is the degree of exposure of the population to risk factors for COPD. The prevalence of smoking was high, with over half of the study population having this major risk factor for COPD. Furthermore, the majority of smokers had high intensity smoking histories (i.e. greater than 25 pack years), which further increases the risk of developing COPD. Also, slightly over one-tenth of the population had long-term (> 6 years) exposure to high-risk occupations.

The patterns of prevalence for airflow limitation (increased prevalence with positive smoking history, age, and male gender) were similar to those of Western countries. In this study, we found a prevalence rate of 15% in ever-smokers, which is very similar to that shown in other studies.[7,14,15] Notably, the prevalence of airflow limitation was similar in current smokers and former smokers. This finding suggests a need for more effective smoking cessation programs that impact on individuals earlier in their smoking histories. Even for those who have already developed COPD, smoking cessation is clearly an intervention that has been demonstrated to have a favourable impact on the progression of disease.[16] It represents an essential intervention for COPD cases at any stage of the disease.

Another important finding is the substantial rate of airflow limitation and degree of underdiagnosis in subgroups that have been generally considered to be at low risk; non-smokers, women, and younger individuals. A diagnosis of COPD is often not considered for these low-risk groups even when relevant symptoms are present. Although COPD is a common condition in smokers, it is important to recognise that non-smokers may present with COPD as well. The 5.8% prevalence of airflow limitation for non-smokers in Japan is higher than rates of < 4% in other non-smoking populations reported in the literature.[17,18] A recent analysis of US data showed a 2.4% COPD prevalence in never-smokers in a working population, of which 31% was attributable to an occupational exposure.[19] This finding suggests a role of 'second-hand smoke' in contributing to this disease and highlights the need for further research regarding this aetiological factor for COPD in non-smokers.

Many individuals with COPD have symptoms that may be unrecognised. Although almost half of the cases with airflow limitation in our study were symptomatic, close to 90% of obstructed cases had not previously received a related diagnosis. This is substantially higher than in other studies such as IBERPOC in which 78% of COPD cases had no prior

diagnosis and NHANES (National Health and Nutrition Examination Survey) in which 63% of individuals with airway obstruction had no previous respiratory diagnosis.[7,20] Early COPD can be difficult to recognise, and often symptoms are not acted upon by physicians. This may be partly responsible for the markedly lower numbers reported earlier by the Japanese Ministry of Health and Welfare. Indeed, in this study, the majority of cases were of mild severity by GOLD criteria. However, it is at the early stages of the disease that effective interventions can provide the greatest opportunity to delay disease progression. The initiation of pharmacological therapy, such as bronchodilators as recommended by GOLD, also provides an opportunity to treat and reduce symptoms that can contribute to disability and impaired quality of life.

Our observations on under-diagnosis of COPD are consistent with reports from other countries. Analyses of population-based data from the US suggest that 24 million American adults demonstrate airway obstruction consistent with COPD, but only 10 million (41.7%) have received a physician diagnosis of COPD.[21] The under diagnosis of COPD in women is also consistent with previous reports. A survey of 192 primary care physicians from the United States and Canada using a hypothetical case presentation showed that physicians tend to underdiagnose COPD significantly more in women than in men.[22] The misdiagnosis of many cases of COPD as asthma also appears to follow a worldwide pattern.[23]

Finally, there is a belief among some Asian practitioners that COPD is less prevalent in Asia.[24] Prior studies have suggested that cigarette smoking may have a lesser impact on the decline in lung function in Asian populations compared to Western populations.[25,26] However, a recent report from Korea shows a 10.3% prevalence of airway obstruction (defined as $FEV_1/FVC < 75\%$) in those over age 18 years, and an 18% prevalence in those ≥ 45 years of age.[6] Our study corroborates the high prevalence of obstruction in another Asian population. Indeed, if we apply their definition of obstruction to our study population (over age 40), the crude prevalence of obstruction increases to 25%. The findings of these two studies cast considerable doubt on any 'protective effect' against COPD in Asian populations.

This study does have limitations. It has been observed that the prevalence of airway obstruction varies considerably depending on the criteria for airflow limitation.[27] The current study used GOLD criteria. If one uses different criteria in defining COPD in a population, for example FEV_1 predicted < 80% (as used by the British Thoracic Society) the prevalence is lower.[28] Of the 256 obstructed cases, 44% satisfied the British Thoracic Society criteria for COPD.

This study did not use reversibility testing to exclude asthma patients and we tried to account for this by defining a group of subjects with airflow limitation with possible asthma based on self-reported diagnosis and symptoms. However, it is possible that some patients identified as COPD-positive may have asthma. It is unlikely that this represents a substantial number of our study subjects since electively scheduled spirometric tests would not likely find obstruction of the level required for diagnosis (i.e. $FEV_1/FVC < 70\%$) in patients who do not have fixed obstruction. Our study design was consistent with that of others reported in the literature; there have been only two major prevalence studies in which reversibility testing was performed.[8] In a population-based study with similar subject inclusion criteria that did utilise reversibility testing, Pena *et al.* showed that only 5.2% of cases with spirometric obstruction demonstrated reversibility consistent with asthma.[20] The Global Initiative for Asthma estimates the prevalence of asthma in the general population of Japanst at 6.7%.[29] In our study, 21% of obstructed cases were characterised as having possible asthma, which is most likely an overrepresentation of asthma. Even if we exclude all of these cases, this still leaves a COPD prevalence of at least 8.6%, which is much higher than that indicated by previous reports from Japan.

Finally, there are other risk factors that contribute to COPD that were not addressed in the NICE study. For example, it has been proposed that dietary factors, childhood respiratory tract infections, and α-antitrypsin deficiency can contribute to a higher risk of developing COPD. While α-antitrypsin deficiency is extremely rare in Japanese, measurement of these other risk factors might help explain COPD rates in non-smokers.[30–32]

The measured prevalence of airflow limitation in Japan is dramatically higher than previous COPD prevalence estimates from the Ministry of Health and Welfare, suggesting a very high degree of underrecognition of this condition. Clearly, the degree to which COPD is unrecognised in symptomatic individuals represents a missed public health opportunity and limits initiation of effective prevention and treatment. Furthermore, in addition to this study, a high prevalence of airflow limitation was reported in a Korean community, suggesting that prevalence results similar to those seen in Western countries are likely to be reflected in other Asian countries as well. Given the prevalence of the major risk factor of smoking, the prevalence of COPD found in this study was not unexpected. High smoking rates coupled with non-smoking risk factors and a possible genetic heterogeneity could easily produce similar results in other Asian countries.[31] The surprisingly high prevalence in non-smokers, women, and younger adults, coupled with the startling rate of underdiagnosis, add to the importance of this study and its implications for health care policy in Japan.

COPD is a preventable and treatable disease. Our results corroborate the need to increase awareness of COPD as outlined in the objectives of the GOLD initiative. Our data also underscore the need for improving physician education regarding COPD and its diagnosis. While the presence of symptoms and risk factors for COPD should increase the index of suspicion for the disease, the absence of risk factors clearly does not exclude COPD as a diagnosis. These findings highlight the need for enhanced screening efforts in high-risk populations such as smokers, as well as in low-risk populations with symptoms of airway obstruction. Health policy makers must devise

process-efficient screening methods as well as preventive interventions in these low-risk subgroups. Without such policies, the global burden of the disease is likely to increase dramatically over the next decade, particularly as the population ages.

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