ORIGINAL

Inhaled steroid therapy and hospitalization for bronchial asthma : trend in Tokushima University Hospital

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Abstract : With the recognition that airway inflammation is present even in patients with mild bronchial asthma, therapy with inhaled corticosteroids is now indicated in various stages of patients. In the present article, we retrospectively examined the prescriptions for inhaled corticosteroids and other drugs for the treatment of outpatients with bronchial asthma at Tokushima University Hospital. We also analyzed asthma control in these patients, in terms of the incidence of emergency consultations and hospitalizations due to asthma exacerbations. To analyze the recent trend, the patients observed from 1998 to 2000 (recent years) were included, and for control purpose, those in 1990 and 1991 (earlier years) were also included.

The percentage of patients treated with inhaled corticosteroids remarkably increased in recent years (mean ; 81.3%) compared to earlier years (mean ; 23.5%). In contrast, the usage of oral corticosteroids, oral xanthine derivatives, β_2-adrenergic receptor agonists and anti-allergic agents tended to decrease in the 10 years period. After the introduction in 1995, considerable patients up to 25% have been treated with anti-leukotrienes. Emergency consultations decreased in recent years (mean ; 0.18/patient/year) compared to earlier years (mean ; 0.79/patient/year). Emergency hospitalizations also decreased in recent years (mean ; 0.043/patient/year) compared to earlier years (mean ; 0.23/patient/year).

In the present study, spread of inhaled corticosteroid therapy and decline in incidence of emergency consultation and hospitalization were simultaneously observed at Tokushima University Hospital, and the former has, at least in part, a contribution to the latter.
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INTRODUCTION

Glucocorticoids are the most effective therapy in the long-term control of inflammatory and immune reactions within the airway especially in bronchial asthma (1). With the recognition that airway inflammation is present even in patients with mild asthma, therapy with inhaled corticosteroids is recom-

mended at an earlier stage of the disease. For example, the British Guidelines on Asthma Treatment, published in 1995 (2), and the Guidelines for the diagnosis and management of asthma, Expert Panel Report 2, published in 1997 by the National Institute of Health, emphasize the role of inhaled corticosteroids to obtain a long-term control (3). Moreover, several studies indicated that regular use of inhaled corticosteroids would prevent the major portion of asthma hospitalizations and deaths (4-6).

In Japan, after the introduction of beclomethasone dipropionate (BDP), an inhaled corticosteroid, to clinical practice in 1978, the prescription of BDP is reported to be increasing (7), and in addition, fluticasone propionate (FP) was introduced as another inhaled corticosteroid in 1998. Moreover, pranlukast, a leukotriene receptor antagonist, was introduced to clinical practice as early as 1995. In these situations, it is of interest to establish which drugs are commonly used for the control of bronchial asthma in a Japanese hospital and investigate the relationship of the trend in drug use and therapeutic outcome.

In the present study, we retrospectively examined the prescriptions for inhaled corticosteroids and other drugs for the treatment of outpatients with bronchial asthma at Tokushima University Hospital. We also analyzed asthma control in these patients, in terms of the incidence of emergency consultations and hospitalizations due to asthma exacerbations.

PATIENTS AND METHODS

Patients

We retrospectively examined the medical records of outpatients with bronchial asthma who were treated regularly at asthma clinic at Tokushima University hospital. To analyze the recent trend, the patients observed from 1998 to 2000 were included, and for control purpose, those from 1990 and 1991 were also included. The annual numbers of outpatients with bronchial asthma are shown in Table 1.

Medications

The annual number of patients with prescriptions for inhaled corticosteroids, oral corticosteroids, oral xanthine derivatives, inhaled β_2-adrenergic receptor (β_2-AR) agonists, oral β_2-AR agonists, anti-leukotrienes and other anti-allergic agents were established from medical records. To further examine the prescription of inhaled corticosteroids, those of beclomethasone dipropionate (BDP : Becotide® and Aldesin®) and fluticasone propionate (FP : Flutide®) were defined. Patients treated with each category of drugs are shown as percentage of all outpatients.

Emergency consultations

In general, pulmonary physicians at outpatient clinic follow patients with bronchial asthma regularly, such as every two weeks and every four weeks. In case of asthma exacerbations, patients are suggested to try inhaled β_2-AR agonists or other drugs indicated by the physician, and are also suggested to consult outpatient clinic (emergency consultations), if no relief was obtained by these treatment. Annual numbers of emergency consultations are, therefore, established to estimate asthma control. In addition, incidence of emergency consultation per patient (annual number of emergency consultation/ annual number of total patients) was calculated.

Hospitalizations

The annual numbers of hospitalizations due to asthma exacerbation were established from medical records to estimate asthma control. In addition, incidence of hospitalization per patient (annual number of hospitalization/ annual number of total patients) was calculated.

Table 1. Annual nunbers of outpatients with bronchial asthma at Tokushima University Hospital

	Annual numbers of outpatients with bronchial asthma				
	1990	1991	1998	1999	2000
Male	42	60	62	100	59
Female	50	86	132	127	104
Total	92	146	194	227	163

RESULTS

Medications of corticosteroids

The annual percentage of patients treated with inhaled corticosteroids and oral corticosteroids are shown in Figure 1. As shown, the percentage of patients treated with inhaled corticosteroids remarkably increased in 1998, 1999 and 2000 (71%, 87% and 86%, respectively) compared to 1990 and 1991 (24% and 23% respectively). Among the inhaled corticosteroids, increasing patients were treated with fluticasone propionate after the introduction of the drug in 1998. In contrast, the usage of oral corticosteroids tended to decrease in 10 years period.

Medications of xanthine derivatives and β_2-adrenergic receptor agonists

The annual percentage of patients treated with oral xanthine derivatives, inhaled β_2-AR agonists, oral β_2-AR agonists, and inhaled anti-cholinergic agents are shown in Figure 2. As shown, the usage of these drugs, except inhaled anti-cholinergic agents, tended to decrease in 10 years period. The usage of inhaled anti-cholinergic agents remained stable in 10 years.

Medications of anti-leukotrienes and other anti-allergic agents

The annual number and percentage of patients treated with anti-leukotrienes and other anti-allergic agents are shown in Table 2. After the introduction of anti-leukotrienes in 1995 in Japan, considerable patients up to 25% were treated with anti-leukotrienes. As shown, the usage of anti-allergic agents tended to decrease in 10 years period.

Annual number and incidence of emergency consultations

Annual numbers and incidences of emergency consultations are shown in Figure 3. As shown, emergency consultations remarkably decreased in 1998, 1999 and 2000 (0.15, 0.17 and 0.23 /patient/year, respectively) compared to 1990 and 1991 (0.78 and 0.80/patient/year, respectively).

Annual number and incidence of hospitalizations

Annual numbers and incidences of hospitaliza-

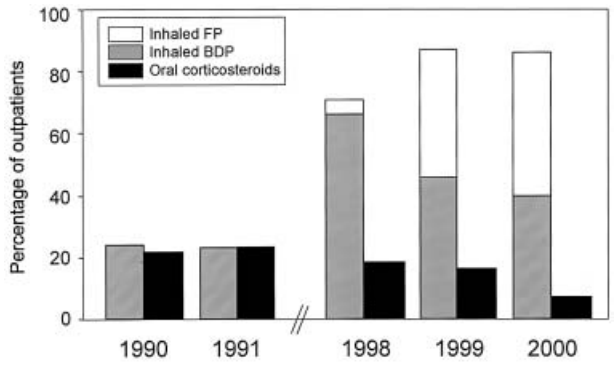

Figure 1. Annual percentage of outpatients with bronchial asthma treated with inhaled corticosteroids and oral corticosteroids in years of 1990, 1991, 1998, 1999 and 2000.
Open bars, hatched bars and closed bars indicate inhaled fluticasone propionate (FP) inhaled beclomethasone dipropionate (BDP) and oral corticosteroids, respectively.

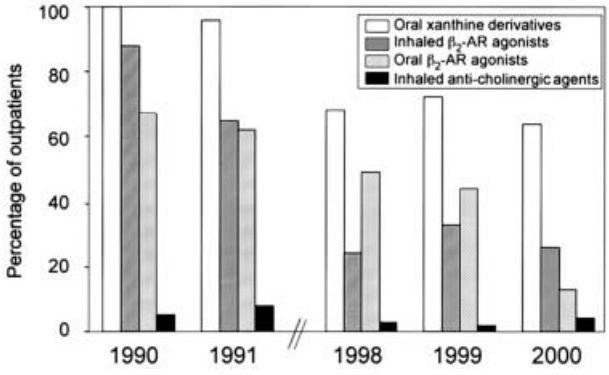

Figure 2. Annual percentage of outpatients with bronchial asthma treated with oral xanthine derivatives, inhaled β_2-adrenergic receptor (β_2-AR) agonists, oral β_2-AR agonists, and inhaled anti-cholinergic agents in years of 1990, 1991, 1998, 1999 and 2000.
Open bars, hatched bars, dotted bars and closed bars indicate oral xanthine derivatives, inhaled β_2-adrenergic receptor (β_2-AR) agonists, oral β_2-AR agonists, and inhaled anti-cholinergic agents, respectively.

Table 2. Annual nunbers of outpatients with bronchial asthma treated with anti-leukotrienes and other anti-allergic agents

	Annual numbers (% of total outpatients)				
Treatment	1990	1991	1998	1999	2000
Anti-leukotrienes	NA	NA	49 (25.5)	53 (23.3)	41 (25.2)
Anti-allergic agents	51 (55.4)	69 (47.3)	42 (21.9)	55 (19.1)	19 (11.7)

NA : not commercially available

tions are shown in Figure 4. As shown, hospitalizations remarkably decreased in 1998, 1999 and 2000 (0.05, 0.05 and 0.03 /patient/year, respectively) compared to 1990 and 1991 (0.18 and 0.28/patient/year, respectively).

DISCUSSION

Inhaled corticosteroid therapy was initially introduced to reduce the need for oral corticosteroids in patients with sever asthma (8). With the recognition that airway inflammation is present even in patients with mild asthma, inhaled corticosteroids began to be used for patients with milder asthma (1). In these circumstances, the usage of inhaled corticosteroids is increasing all over the world. As shown in Figure 1, the present study confirms the widespread use of inhaled corticosteroids.

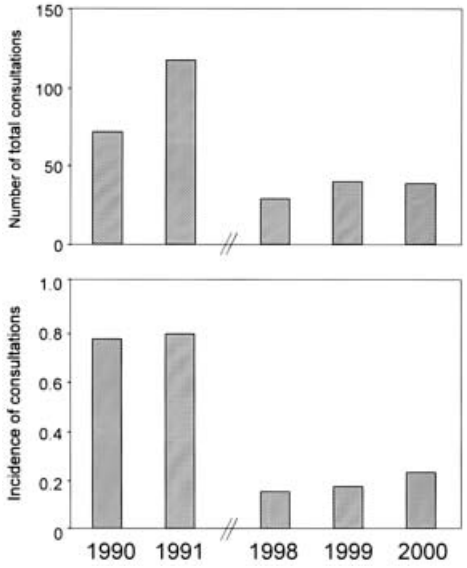

Figure 3. Annual number (*top*) and incidence (*bottom*) of emergency consultations due to asthma exacerbations in patients with bronchial asthma in years of 1990, 1991, 1998, 1999 and 2000.

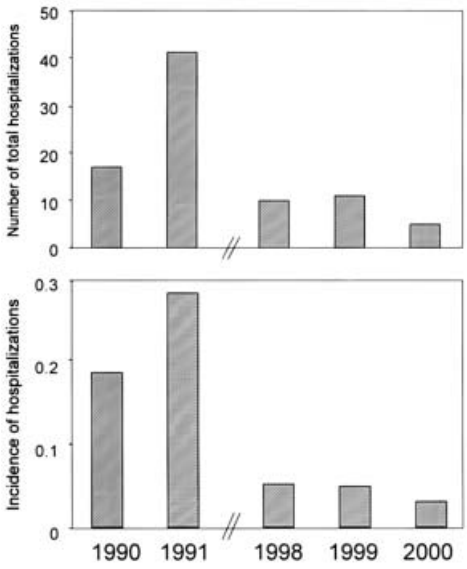

Figure 4. Annual number (*top*) and incidence (*bottom*) of hospitalizations due to asthma exacerbations in patients with bronchial asthma in years of 1990, 1991, 1998, 1999 and 2000.

Various reports revealed that the addition of long acting β_2-AR agonist is more effective on the improvements in symptoms and lung function than increasing dose of inhaled corticosteroids (9, 10). At present, inhaled long acting β_2-AR agonist is not yet available in Japan. Instead, oral xanthine derivatives, inhaled short-acting β_2-AR agonists and oral β_2-AR agonists are used for the control of asthma symptoms. Nevertheless, the present study revealed that the usage of these agents was decreasing in the 10 years period (Figure 2).

To estimate control of bronchial asthma, the risk of hospitalizations has been examined in various studies. In the study of 16941 children and adults with bronchial asthma in Massachusetts from 1991 to 1994, Donahue *et al.* (4) reported that the overall relative risk of hospitalization among those who received inhaled steroids was 0.5 and concluded that inhaled steroids conferred significant protection against exacerbations of asthma leading to hospitalizations. In the Saskatchewan study by Blais *et al.* (5) from 1977 to 1993, among 13563 children and adults with bronchial asthma, the first regular treatment with inhaled corticosteroids initiated in the year following the recognition of asthma could reduce the risk of admission to hospital for asthma by up to 80% compared with regular treatment with theophylline. The impact of inhaled corticosteroids on asthma control was also reported by Eisner *et al* (11) who examined life-threatening exacerbation in terms of the risk of intensive care unit admission. In addition, Suissa *et al.* (12) have recently reviewed several studies and concluded that regular use of inhaled corticosteroids would prevent the major portion of asthma hospitalizations. In addition to the risk of hospitalizations, we examined the incidence of emergency consultations to estimate asthma control, since Japanese patients are suggested to consult outpatient clinic in case of asthma exacerbations, if no relief was obtained by relievers indicated by the physicians at home first. As shown in Figures 3 and 4, lower incidence of emergency consultations, as well as hospitalizations, was observed in years of 1998, 1999 and 2000 than in years of 1990 and 1991.

In inhaled steroid therapy, a substantial gap between recommendation and actual practice has often been pointed out (13). It is reported that only about half of eligible patients with bronchial asthma received inhaled steroid therapy (14). In the study of elderly patients, forty percent of patients who experienced a recent acute exacerbation of bronchial asthma did not receive inhaled steroid therapy near discharge from their initial hospitalization for bronchial asthma (15). Further diffusion of inhaled steroid therapy into clinical practice is necessary, and more research must be conducted to examine the reason (s) for the barriers between recommendation and clinical practice.

Cysteinyl-leukotrienes are important pro-inflammatory mediators in bronchial asthma and several studies have already revealed clinical benefit of anti-leukotrienes in bronchial asthma(16-20). Much attention has, therefore, been recently paid to the role of anti-leukotrienes as a controller of bronchial asthma. As shown in Table 2, considerable patients were treated with anti-leukotrienes after the clinical introduction of pranlukast to Japan in 1995. In comparative study of inhaled corticosteroids and anti-leukotrienes, inhaled corticosteroids had a larger clinical benefit than anti-leukotrienes, although anti-leukotrienes seemed to have superior effects in certain group of patients (21-23). Therefore, it seems to be difficult to consider anti-leukotrienes as a major contributor of the better control of bronchial asthma in years of 1998, 1999 and 2000 in the present study. Further studies are warranted to establish the impact of anti-leukotrienes to reduce the risk of exacerbations in bronchial asthma.

In conclusion, spread of inhaled steroid therapy and decline in incidence of emergency consultation and hospitalization were simultaneously observed at Tokushima University Hospital, and the former has, at least in part, a contribution to the latter.

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