

The New Role of Disodium Cromoglycate in the Treatment of Adults with Bronchial Asthma

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ABSTRACT

Background: Viral infection of the respiratory tract in patients with asthma is one of the most frequent causes of exacerbation of asthmatic symptoms. Disodium cromoglycate (DSCG) is a commonly used anti-asthmatic medicine with many beneficial biochemical and physiological effects. The purpose of this study was to investigate the efficacy of DSCG against colds when used in clinical practice.

Methods: A questionnaire survey to determine the efficacy of DSCG was undertaken in 220 adult patients with asthma (81 male, 139 female; mean age: 54.1 ± 13.7 years and 60.1 ± 12.7 years, respectively) from April to September 2004 at the Miyatake Asthma Clinic.

Results: The duration of DSCG inhalation therapy was not less than 5 years in more than half of the patients. The mean daily DSCG dose at the time of the questionnaire survey was 40 mg/day in over 50% of all patients. After DSCG was added to inhaled corticosteroid (ICS) combination therapy, 56.4% of the patients rated their condition as "improved", and 66.4% of the patients felt that the frequency of colds they had caught had decreased while DSCG was added to ICS.

Conclusions: DSCG inhalation therapy is a useful additional treatment following ICS to alleviate asthma symptoms, and to prevent colds in adult patients with asthma.

KEY WORDS

bronchial asthma, colds virus infection, disodium cromoglycate, questionnaire, visual analog scale

INTRODUCTION

Viral infection of the airway is an important risk factor for triggering an attack or exacerbation of bronchial asthma.¹⁻³ A significant issue in the management and treatment of patients with asthma is how to prevent infection from influenza and other viruses responsible for colds, especially during the winter season. DSCG is a drug that has been used for more than 35 years, not only for the control of bronchial asthma, but also for the management of various other allergy-based diseases. In addition to previously known actions, such as mast cell stabilization,^{4,5} and suppres-

sion of various inflammatory cells,⁶⁻¹¹ it has recently been suggested that DSCG exhibits anti-viral action. To date, however, no consensus has been reached on the possible anti-viral properties of DSCG, with some reports affirming this action¹²⁻¹⁴ and others contradicting it.^{15,16} In 2002, we identified and reported the anti-influenza activity of DSCG at *in vivo* and *in vitro* levels in experimental animals.¹⁷

According to the Global Initiative for Asthma (GINA, 2002 version), DSCG is listed as a Step 2 treatment.¹⁸ To date, however, the role of DSCG in the treatment of adults with bronchial asthma has not yet been clarified. The present study was undertaken

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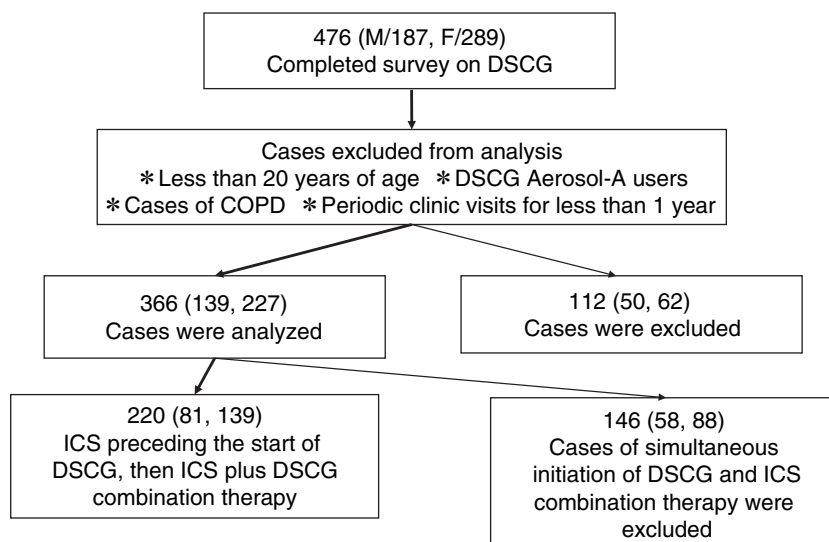


Fig. 1 The questionnaire survey was conducted from April 1 to September 30, 2004. Responses were collected from 476 patients with bronchial asthma who were treated with DSCG. As a result, in total, 220 patients were included in the analysis.

in an attempt to clarify the role of DSCG in the treatment of adult patients with asthma by a questionnaire survey of patients, focusing on the anti-asthmatic efficacy and anti-cold virus effects of DSCG.

METHODS

PATIENTS

A questionnaire survey was conducted for 6 months between April 1 and September 30, 2004. It involved outpatients with bronchial asthma who received DSCG inhalation therapy at the Miyatake Asthma Clinic in Osaka. Responses were collected from 476 patients (187 men, 289 women). The following patients were excluded from analysis: (1) patients who were less than 20 years of age, (2) patients who had visited the clinic regularly but for less than one year, (3) patients whose asthma was complicated by chronic obstructive pulmonary disease, which was classified more than Stage I by GOLD (the Global Initiative for Chronic Obstructive Lung Disease. NHLBI/WHO Workshop Report 2001),¹⁹ (4) patients receiving Intal[®] Aerosol A therapy, and (5) patients for whom combination therapy with DSCG and ICS had only just been initiated (Fig. 1).

The reasons for the exclusion of these patients from the analysis included the following: (1) many of the patients who were less than 20 years of age had received DSCG inhalation therapy for many years, beginning at their school age; if these patients were included in the analysis, their impressions of the therapeutic efficacy during childhood may have confounded the survey; (2) to clarify the anti-cold virus effects of DSCG, patients who had been infected with a cold viruses during at least one season needed to be

enrolled; (3) to clarify the anti-asthmatic efficacy of DSCG, only patients with bronchial asthma that satisfied the diagnostic standards prepared by the American Thoracic Society were enrolled;²⁰ (4) because a single inhaled dose of Intal[®] Aerosol A (1 mg/1 puff) differs greatly from that of the Intal[®] 20 mg capsules, we enrolled only patients treated with the capsule or with the Intal[®] nebulizer solution (20 mg/ampoule) for inhalation; and (5) to better illustrate the anti-asthmatic efficacy of DSCG, patients in whom ICS and DSCG treatments had been simultaneously initiated were excluded, because ICS has more potent anti-asthmatic effects than DSCG (Fig. 1).

In total, 220 patients (81 men and 139 women) were included in the analysis (mean age: 54.1 ± 13.7 years for men and 60.1 ± 12.7 years for women) (Fig. 1). Forty-nine percent of the patients had other atopic manifestations: allergic rhinitis, pollinosis, atopic dermatitis and food allergy were 34%, 23.2%, 6.8%, and 3.6%, respectively. One hundred and forty-three patients were investigated by a serum IgE-RAST test; positive results of house dust, mites, mold, Japanese cedar, rag-weed, timothy, cat, and dog were 40.6%, 42.0%, 8.4%, 45.5%, 12.6%, 22.4%, 18.2%, and 13.3%, respectively. Asthma severity was determined according to the 2002 GINA Guidelines,¹⁸ and were classified by Step 2, Step 3, and Step 4; these were 55.4%, 38.2%, and 6.4%, respectively. Some patients were concomitantly treated with anti-asthmatic medicines, such as inhaled beta₂-adrenoceptor agonists, theophylline, rescue oral glucocorticoids, and/or leukotriene receptor antagonist when necessary.

STUDY PROTOCOL

This study is a cross sectional questionnaire based survey, and thus the same patients serve as chronological controls. The duration of DSCG inhalation therapy was not less than 5 years in more than half of all patients. Therefore, the study was a comparison between two treatment periods in the same patients: patients treated with ICS monotherapy without DSCG and patients treated with ICS after an additional treatment with DSCG. The patients had been individually confirmed and re-educated with respect to their adherence to the inhalation method recommended and dosage schedule prescribed for the particular formulation by the physician (Dr. Miyatake) repetitively²¹ until the time of the questionnaire survey (Survey).

The study was approved by the Miyatake Asthma Clinic Ethics Committee. The objectives and significance of the questionnaire survey were explained by the physician (Dr. Miyatake) to each patient, and written informed consent was obtained from the patients. The questionnaire forms were collected and immediately checked for completeness and to ensure the entries were appropriate. This check was made first by the nurse and then by the same physician for each patient.

When making a final evaluation of the effectiveness of DSCG inhalation therapy, patients who answered "I find the therapy effective and want to continue receiving it" were assessed as to the degree of alleviation they had found for three symptoms (difficulty breathing, cough, and sputum) using a visual analog scale (VAS) in an attempt to objectively evaluate the patient's impression of effectiveness. The assessment using a VAS was repeated 6 months later and a comparison of the responses in each VAS was performed to ensure the accuracy of the assessment.

STATISTICAL ANALYSIS

All results are shown as means \pm SD. The two groups were compared using an unpaired Student's *t*-test or a paired *t*-test. The comparison of asthma status was performed with the chi-square test. Differences associated with $p < 0.05$ were considered statistically significant.

RESULTS

DURATION OF DSCG INHALATION THERAPY

The duration of DSCG inhalation therapy was more than 1 year but less than 3 years in 27.3% of all subjects, more than 3 years but less than 5 years in 20.0%, more than 5 years but less than 10 years in 26.4%, and more than 10 years in 26.4%.

TYPE OF DSCG INHALER USED AND FREQUENCY OF PEAK EXPIRATORY FLOW MEASUREMENTS

The Spinhaler[®] was used by 73.2% of all subjects, the E-haler[®] by 21.4%, a nebulizer by 4.1% and two or

more of these types of inhalers by 1.4%. Regular peak expiratory flow (PEF) monitoring was performed in 43.7% of the patients at the time of the start of DSCG inhalation therapy (Start) and was performed in 40.5% at the time of the questionnaire survey (Survey).

DAILY DSCG DOSE

The suggested daily DSCG dose at the Start was 80 mg/day in 34.5% of all subjects, 60 mg/day in 36.4%, 40 mg/day in 27.3%, and 20 mg/day in 1.8%. The self claimed daily DSCG dose reported by the patient at the time of the Survey was 80 mg/day in 7.3%, 60 mg/day in 11.4%, 40 mg/day in 56.4%, and 20 mg/day in 25.0%. The calculated daily DSCG dose in the medical record was 80 mg/day in 3.6%, 60 mg/day in 10.5%, 40 mg/day in 67.3%, and 20 mg/day in 18.6% of all subjects at the time of the Survey.

TYPE OF ICS USED WHEN DSCG THERAPY WAS STARTED

The type of ICS used before the start of DSCG therapy was chlorofluorocarbon beclomethasone dipropionate (CFC-BDP) in 48.6% of all cases, fluticasone propionate (FP) in 30.0%, budesonide (BUD) in 18.6%, and hydrofluoroalkane beclomethasone dipropionate (HFA-BDP) in 2.7%. The mean ICS dose at the Start was 1020.7 ± 481.0 mcg/day on a CFC-BDP basis.

THE EFFECTS OF COMBINATION THERAPY WITH DSCG AND ICS AFTER ICS MONOTHERAPY

After DSCG plus ICS combination therapy, 56.4% of all cases rated their condition as "improved", 33.2% as "I didn't notice a change", 5.9% as "DSCG inhalation therapy alone is preferable" and 4.5% as "ICS therapy alone is preferable" (Fig. 2). Reasons given for using combination DSCG plus ICS therapy in a multiple response questionnaire included the following; "using both makes me feel easier" (63.6%), "my physician recommended it" (45.0%), "throat discomfort and pain was alleviated following DSCG inhalation therapy" (10.0%), and "other" (10% or less) (Fig. 3).

THE FREQUENCY OF COLDS FOLLOWING DSCG PLUS ICS COMBINATION THERAPY

Answers to the question regarding the frequency of colds following DSCG plus ICS combination therapy included the following: "I feel the frequency of colds I have caught has decreased" (66.4%), "I don't notice a change" (13.6%) and "I don't feel the frequency of colds I have caught has decreased" (9.5%). Thus, 66.4% of the patients had the impression that periodical inhalation of DSCG was effective against colds (Fig. 4). When the anti-cold virus effects of DSCG was analyzed in relation to the duration of DSCG treatment, there was no association between the duration of DSCG treatment and the percentage of pa-

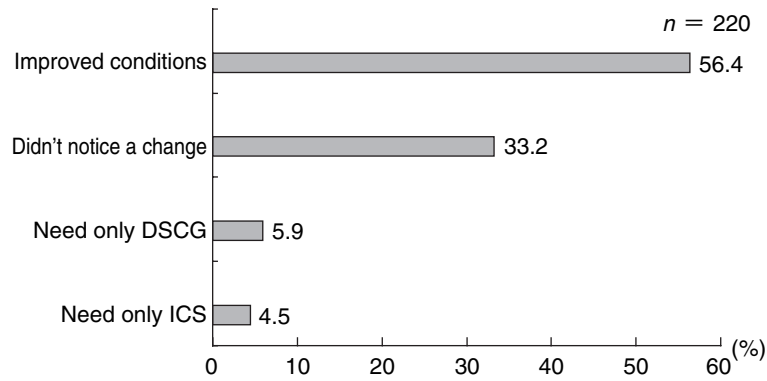


Fig. 2 The effects of adding DSCG to ICS were assessed in 220 patients with asthma.

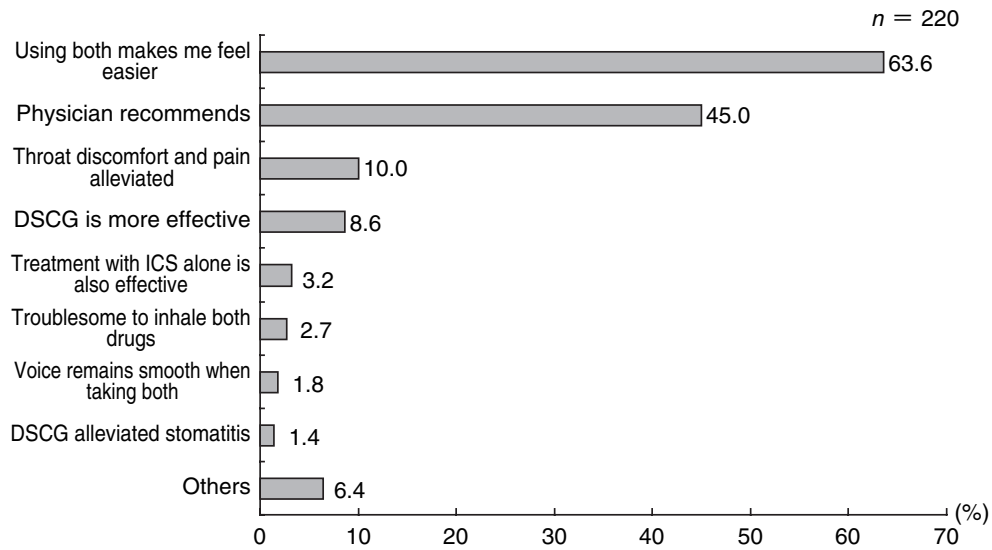


Fig. 3 Reasons given for using a combination DSCG plus ICS therapy were asked in a multiple response questionnaire.

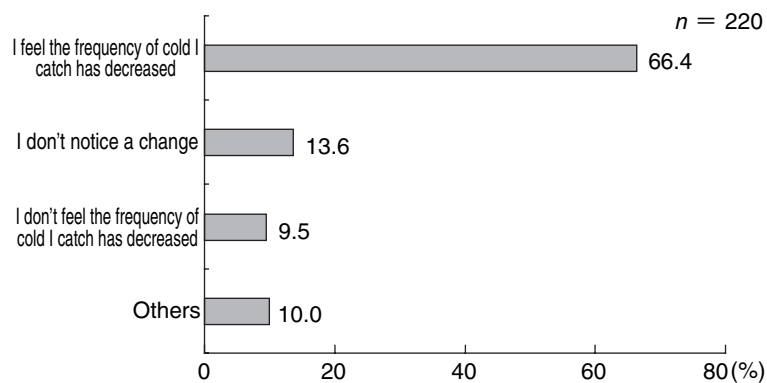


Fig. 4 The frequency of colds following DSCG plus ICS combination therapy was assessed by 220 patients with asthma.

tients who had the impression that there was a decrease in the frequency of colds they had caught

(Fig. 5).

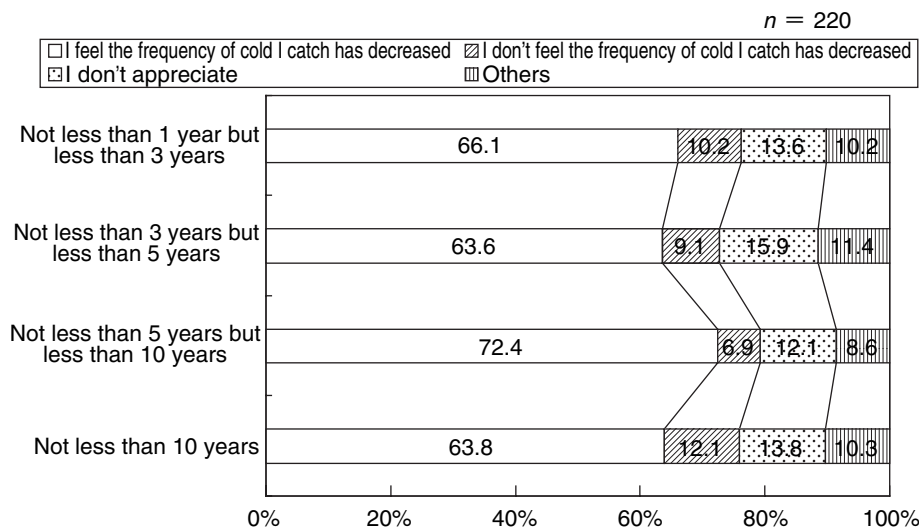


Fig. 5 The anti-cold viruses effects of DSCG were analyzed in relation to the duration of DSCG treatment.

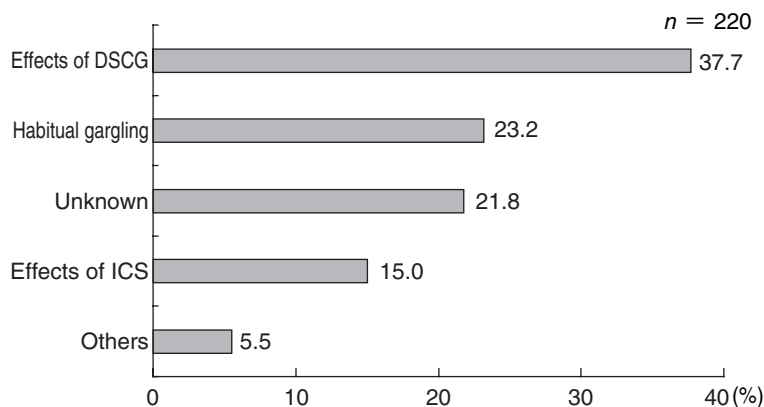


Fig. 6 Reasons for having the impression that there was a decrease in the frequency of colds caught given by 220 patients with asthma.

REASONS FOR HAVING THE IMPRESSION THAT THE FREQUENCY OF COLDS CAUGHT HAD DECREASED

The reasons for having the impression that there was a decrease in the frequency of colds caught given by the patients were as follows: “effects of DSCG” (37.7%), “habitual gargling” (23.2%), “unknown” (21.8%), “effects of ICS” (15.0%) and “other” (5.5%) (Fig. 6).

COMPARISON OF CLINICAL CHARACTERISTICS BETWEEN ASTHMATIC PATIENTS WHO HAD AN IMPRESSION OF A DECREASE IN THE FREQUENCY OF COLDS THEY CAUGHT (YES GROUP) AND PATIENTS WHO HAD NO SUCH IMPRESSION (NO GROUP)

One hundred and forty-seven patients (48 men, 99

women) were in the Yes group and 73 patients (33 men, 40 women) were in the No group. The mean age of patients at time of the Survey did not differ significantly between the Yes group (58.4 ± 13.1 years) and the No group (56.8 ± 13.9 years). The duration of asthma also did not differ significantly between the Yes group (17.0 ± 12.8 years) and the No group (15.5 ± 10.9 years). In addition, no significant intergroup difference was seen in the incidence of allergic complications, in the percentage of drug allergies, in the percentage of smokers or in the percentage of patients for whom PEF was recorded (Table 1). Laboratory findings such as serum IgE-RIST (IU/ml), peripheral eosinophil count (%), and indices of respiratory function, *i.e.*, FVC (L), FEV₁ (L), \dot{V} 50 (L/sec), and \dot{V} 25 (L/sec) at the time of the Survey did not differ significantly between the Yes group and the No

Table 1 Clinical characteristics between the Yes group and No group at the time of the questionnaire survey

	Yes group	No group	<i>p</i> -value
Number of patients	147	73	
Sex M/F	48/99	33/40	0.076
Age (yrs)	58.4 ± 13.1	56.8 ± 13.9	0.394
Asthma duration (yrs)	17.0 ± 12.8	15.5 ± 10.9	0.364
Allergic complications (%)	47.6	49.3	0.569
Drug allergy (%)	21.1	26.0	0.495
Smokers (%)	18.6	23.3	0.517
Monitoring PEF (%)	36.8	47.9	0.774

Yes group: Patients have an impression that the frequency of colds caught has decreased.

No group: Patients have no impression that the frequency of colds caught has decreased.

(Mean ± SD)

Table 2 Clinical characteristics of the Yes Group[†]

n = 147

	Start	Survey	<i>p</i> -value
IgE (IU/ml)	412.7 ± 694.4	584.1 ± 638.4	0.729
Eosinophil (%)	7.9 ± 6.6	6.2 ± 4.9	0.168
FVC (L)	2.36 ± 0.92	2.37 ± 0.83	0.917
FEV ₁ (L)*	1.59 ± 0.75	1.75 ± 0.68	0.001
Ṃ50 (L/sec)*	1.38 ± 0.98	1.74 ± 0.98	0.001
Ṃ25 (L/sec)*	0.54 ± 0.42	0.62 ± 0.35	0.037
ICS (mcg/day)*	1033.7 ± 490.4	786.4 ± 460.3	0.001

[†] Yes group: Patients have an impression that the frequency of colds caught has decreased.

Start: At the time of the start of DSCG. Survey: At the time of the questionnaire survey.

* Mean ± SD, statistically significant

Table 3 Clinical characteristics of the No Group[†]

n = 73

	Start	Survey	<i>p</i> -value
IgE (IU/ml)	458.6 ± 710.7	841.5 ± 1047.9	0.172
Eosinophil (%)*	8.9 ± 7.3	5.2 ± 4.9	0.018
FVC (L)*	2.65 ± 0.91	2.48 ± 0.86	0.011
FEV ₁ (L)	1.78 ± 0.73	1.79 ± 0.67	0.987
Ṃ50 (L/sec)	1.56 ± 1.01	1.72 ± 0.94	0.118
Ṃ25 (L/sec)	0.62 ± 0.46	0.63 ± 0.39	0.979
ICS (mcg/day)	944.5 ± 463.6	900.0 ± 386.9	0.171

[†] No group: Patients do not have an impression that the frequency of colds caught has decreased.

Start: At the time of the start of DSCG therapy. Survey: At the time of the questionnaire survey.

* Mean ± SD, statistically significant

group. And the ICS dose (mcg/day) also did not differ significantly in the two groups (Tables 2, 3). On the other hand, the above-mentioned laboratory findings and the ICS dose were compared at the Start of DSCG and at the time of the Survey in each group. The Yes group showed a significant increase from baseline in FEV₁, Ṃ50 and Ṃ25 levels at the time of the Survey while the mean ICS dose in this group was lower at the time of the Survey than at the Start (Table 2). In the No group, the peripheral eosinophil

count was significantly lower than baseline at the time of the Survey, but respiratory function and the mean ICS dose had not improved at the time of the Survey (Table 3).

ASSESSMENT OF ALLEVIATION OF ASTHMATIC SYMPTOMS (DIFFICULTY BREATHING, COUGH AND SPUTUM) USING A VAS IN PATIENTS WHO FOUND DSCG EFFECTIVE AND WANTED TO CONTINUE USE

The mean score of assessments at the time of the Survey was 76 for difficulty breathing, 70 for cough, and 67 for sputum. These scores appeared to reflect improvement in respiratory function. When reassessed 6 months later, the mean score remained almost unchanged at 72 for difficulty breathing, 72 for cough, and 70 for sputum. Thus, the anti-asthmatic effects of DSCG were stable.

PATIENTS' FINAL EVALUATION OF THE EFFECTIVENESS OF DSCG INHALATION THERAPY AS A MEANS OF TREATING ASTHMA

The answers of the patients to their final evaluation of the effectiveness of DSCG inhalation therapy as a means of treating asthma were as follows: "I find the therapy effective and want to continue to use it" (70.5%), "I find the therapy effective but want to discontinue its use" (6.4%), "I cannot make an assessment of the efficacy of the therapy but want to continue to use it" (21.0%), "I cannot make an assessment of the efficacy of the therapy and want to discontinue its use" (1.8%), and "I find the therapy ineffective and want to discontinue its use" (0.5%). Thus, more than 90% of the patients wished to continue DSCG therapy.

DISCUSSION

DSCG is an anti-asthmatic drug that was discovered in 1965 by Roger Altounyan.²² In Japan, DSCG has been used as an inhalational drug for bronchial asthma for more than thirty-five years. DSCG played an important role in the treatment of children with bronchial asthma since the time when the regular use of DSCG and salbutamol inhalation solution was initially recommended.²³ DSCG is listed as an alternative therapy in the GINA,¹⁸ in the British Guidelines on the Management of Asthma,²⁴ and in the Japanese guidelines on the management of asthma.²⁵ However, the clinical effects of DSCG on cold viruses have yet to be determined. We are managing large numbers of asthmatic patients in clinical practice, and have the impression that DSCG has anti-viral properties.^{13,14}

In the present study, 66.4% of the 220 adults with asthma stated that the frequency of colds they had caught had decreased (Fig. 4). Of these patients, 37.7% stated that the observed decrease in the frequency of colds caught was attributable to the effects of DSCG (Fig. 6). Furthermore, the study showed that DSCG exerted anti-cold virus effects which may last for 10 or more years (Fig. 5).

According to the findings obtained primarily *in vitro*, the anti-asthmatic effects of DSCG are known to be exerted through stabilization of the mast cell membrane,^{4,5} suppression of eosinophil activation,⁹

suppression of accumulation of T lymphocytes and eosinophils,^{7,10} suppression of the formation of IL-5 by peripheral mononuclear cells,²⁶ suppression of excitation of the sensory nerve C-fiber,^{27,28} suppression of the expression of adhesion molecules (ICAM-1, VCAM-1),¹⁰ and suppression of IgE formation.^{29,30} In addition, papers either endorsing¹²⁻¹⁴ or rejecting^{15,16} the anti-viral properties of DSCG have been published.

We previously reported that DSCG suppressed the infection of MDCK cells by the influenza virus (A/Aichi/2/68, H3N2; A/Memphis/1/71, H3N2) and markedly suppressed fatal infection by the mouse-adapted influenza virus (A/PR/8/34, H1N1).¹⁷ As for the mechanism of suppression of viral infection, DSCG has a symmetric chromone frame resembling the flavonoid frame, which is known to non-specifically adsorb viruses, and spectroscopic studies^{31,32} have shown that DSCG assumes a liquid crystal form under certain conditions. These findings suggest that *in vivo*, DSCG forms a thin membrane on the cell surface and enters the cells along with the invading virus. It then inhibits a series of virus events (denucleation, replication and budding) by reducing the pH and other conditions, such as phosphorylation, involved in virus proliferation. If DSCG exerts anti-viral effects via this mechanism, it is expected that DSCG inhibits viruses outside the cells and hence will exert effects not only against the influenza virus but also against other viruses.

In a recently reported study of the effects of DSCG on acute respiratory syncytial virus (RSV) infection in a mouse model, RSV proliferation in the lungs was suppressed and lung inflammation was less severe in mice transnasally pretreated with DSCG, compared with saline-treated mice.³³ Although a variety of possible means of anti-viral action have been suggested for DSCG, the exact mechanism has not yet been identified.

In the present questionnaire survey, 56.4% of patients who inhaled DSCG in addition to ICS stated that inhalation of both ICS and DSCG resulted in better control of asthma (Fig. 2). In the final assessment, 70.5% of asthmatic patients stated that the use of DSCG in combination with ICS was effective and that they wished to continue this therapy. There was a statistically significant improvement in respiratory function and a significant reduction in the mean required dose of ICS in the Yes group (Table 2). These findings may also endorse the anti-asthmatic efficacy of DSCG.

As the use of ICS in the management of bronchial asthma is increasing in Japan, the number of patients admitted to hospitals has decreased and the number of deaths from asthma has also decreased to less than 3,500 per year. However, control of asthma symptoms remains difficult in some patients, despite the use of ICS in combination with long-acting beta₂ stimulants

or the use of theophylline and leukotriene antagonists. When dealing with such cases, the addition of DSCG inhalation therapy is expected to alleviate asthma symptoms and respiratory dysfunction and to stabilize the QOL of patients.^{34,35}

In this study, we showed that DSCG inhalation therapy with ICS may prevent colds. However, this study is a questionnaire based and cross sectional survey. Thus our findings are preliminary and need to be confirmed by case controlled studies. As for the anti-viral effects of DSCG, we hope that basic and clinical studies *in vitro* and *in vivo* are resumed at multiple research facilities and that these studies yield sufficient data to prove the anti-viral effects of DSCG from the viewpoint of evidence-based medicine.

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