Alleviation of seasonal allergic symptoms with superfine β-1,3-glucan: A randomized study

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Background: The incidence of allergic symptoms to cedar pollen has reached epidemic proportions in Japan. Intravenous injection of β-1,3-glucan in human subjects is known to induce a T_H1 response, whereas oral uptake does not.
Objective: It was examined whether orally ingested, superfine dispersed β-1,3-glucan (SDG), easily absorbed by intestinal mucosa, would alleviate allergic symptoms.
Methods: Allergic patients were orally administrated either SDG (n = 30) or nondispersed β-1,3-glucan (n = 30), and allergic symptoms were assessed clinically in a double-blind, placebo-controlled randomized study.
Results: SDG alleviated ongoing symptoms of Japanese cedar pollen–induced rhinorrhea, sneezing, nasal congestion, and itchy watery eyes, and its oral uptake before symptom onset exhibited preventive effects. Alleviation of allergic symptoms was evident not only for seasonal allergy to cedar pollen but also for perennial allergy. Oral ingestion of β-1,3-glucan in individuals with allergic tropism could reduce the spontaneous increase in both allergen-specific and total IgE titers. The clinical responses to treatment were well correlated with the capacity of monocytes to bind to β-1,3-glucan. Although SDG reduced allergic symptoms, the oral uptake of nondispersed β-1,3-glucan produced no clinical effects, despite the identical amount of β-1,3-glucan in both preparations.
Conclusion: We postulate that orally taken β-1,3-glucan prepared in a form easily absorbed by intestinal mucosa is able to alleviate cedar pollen–induced allergic symptoms.
Clinical implications: Orally effective SDG might greatly contribute to the resolution of epidemic medical problems of seasonal cedar pollen–induced allergy. (J Allergy Clin Immunol 2007;119:1119-26.)

Key words: *Allergic conjunctivitis, β-1,3-glucan, immunoregulation, macrophages*

Abbreviations used
NDG: Nondispersed β-1,3-glucan
PG: Prostaglandin
SDG: Superfine dispersed β-1,3-glucan
SSC: Synthesized symptom category

The incidence of allergic diseases, such as rhinitis and rhinoconjunctivitis, as of asthma, allergic eczema, and food allergies, has reached epidemic proportions in the industrialized world.[1-4] In Japan there has been a dramatic yearly increase in the number of persons with allergic symptoms, such as rhinorrhea, sneezing, nasal congestion, and itchy watery eyes, caused by the seasonal dispersal of Japanese cedar *(Cryptomeria japonica)* pollen, resulting in both social and economic problems. Crucial factors driving this trend are increased exposure to sensitizing allergens and unregulated disorders of the immune system during critical periods of disease development.[1] The regulation in the mucosa of allergic immune responses to airborne allergens is still poorly understood.[5] Allergic disease is characterized by the increase of allergen-specific IgE titers, the IgE-dependent activation of mast cells, and the recruitment of activated eosinophils and T cells to mucosal surfaces. These processes ultimately lead to inflammation and disease.[1,6,7]

Epidemiologic studies suggest an inverse correlation between infections and the development of allergy, atopy, or both.[2-4] Infection with *Mycobacteria tuberculosis* reduces the likelihood of atopy development in both human subjects[8] and mice.[9] Likewise, heat-killed *Listeria monocytogenes* successfully converted ongoing T_H2 responses to a T_H1-dominated response in mice[10,11] and reduced antigen-specific IgE production. This suggests that T_H1-type immune responses elicited by bacteria or their products might suppress allergic symptoms. There is increasing evidence that innate responses play a central role in immunity, and a new paradigm suggests the functional heterogeneity of macrophages and dendritic cells.[12-16] In the mucosal immune system the antigen-presenting activity of macrophages has been linked with the development of the T_H1 phenotype.[17]

β-1,3-Glucans are critical for the innate immune system; they are ubiquitously present in the cell walls of

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TABLE I. The study design of oral administration of β-1,3-glucan

Shiitake extract	β-1,3-Glucan particle size	β-1,3-Glucan contents	Oral administration	Periods
SDG (Micellapist)	0.08 μm	15 mg/100 mL	100 mL once a day	8 wk
NDG (control)	288 μm	15 mg/100 mL	100 mL once a day	8 wk

fungi.[18-21] Lentinan (LNT) is a β-1,3-D-glucan purified from the fruit body of the edible mushroom *Lentinus edodes* Berk (Sing).[22,23] We proposed elsewhere[15,16,24] that LNT-induced reductive macrophages skew toward T_H1 by producing IL-12 and that LPS-induced oxidative macrophages skew toward T_H2 by producing IL-6, IL-10, and prostaglandin (PG) E_2. In patients with inoperable recurrent gastric cancer undergoing chemotherapy, intravenously injected LNT, because of its T_H1-skewing potency through its action on macrophages, elicits a remarkable life-prolonging effect and is now widely used as an immunotherapeutic drug.[25]

However, why orally administered β-1,3-glucans are ineffective has been a long-standing puzzle. In aqueous solution the particulate size of β-1,3-glucans is approximately 100 to 200 μm; this impedes their absorption by the abdominal mucosa. As an orally effective form, superfine dispersed β-1,3-glucan (SDG) is now available. Therefore we designed a double-blind, placebo-controlled randomized study in which participants received a daily oral dose of SDG for 2 months and analyzed its effect on allergic rhinitis and rhinoconjunctivitis induced by the seasonal dispersal of Japanese cedar pollen.

METHODS

Human subjects

The protocols of this study were approved by the Ethics Committee of Meiji University of Oriental Medicine, Kyoto, Japan, and in accordance with the tenets of the Declaration of Helsinki, written informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study. This study was registered as a clinical trial at www.clinicaltrials.gov (identification number, NCT00276445). Patients ingested either SDG or nondispersed β-1,3-glucan (NDG) daily for the first 8-week period (January–April 2004); they were monitored throughout the second 8-week period.

We recruited 60 volunteer patients (28 male and 32 female patients) aged 21 to 61 years (31.3 ± 10.8 [SEM]) from the hospital of Meiji University of Oriental Medicine. Individuals who had undergone immunotherapy in the previous 5 years or had a history of immunologically or medically relevant diseases were not considered. For inclusion in this study, participants had to fulfill both of the following criteria: (1) annually recurring seasonal allergic conjunctivitis, with or without rhinitis, during springtime (Japanese cedar pollen season) and (2) a positive test result for allergen-specific IgE (>30 IU/mL) or a positive skin prick test response (wheal diameter, >3 mm) to Japanese cedar pollen or house dust mite extract. Study participants were sensitized to Japanese cedar pollen (88.1%) and house dust mites (67.8%); many responded to 2 or more allergens, suggesting that they were not monosensitized to Japanese cedar pollen.

Study design

The study was prospective, randomized, double-blind, and placebo-controlled. Allergic patients were randomly assigned to the SDG (n = 30) or placebo (NDG) group (n = 30). The distribution of age, sex, the date they started to participate, and total and specific IgE levels was similar in the 2 groups. The term of the clinical trial (16 weeks) consisted of an 8-week oral administration period, followed by an 8-week observation-only period. Once a day for the first 8 weeks, the participants took 15 mg of either SDG or NDG (Table I). During the 16-week course, they monitored their symptoms; they were not permitted to use nasal and topical corticosteroids, long-acting antihistamines, or any other antiallergic drugs. Blood samples were collected at the inception of the study and at the end of weeks 4 and 8.

To evaluate the clinical benefits of β-1,3-glucan, we asked the participants to record daily diary entries regarding their allergic symptoms. Participants made an overall assessment at the end of the first set of 8 weeks (treatment) and again at the end of the second 8-week period (no treatment) of the effect of the ingested substance on their allergic symptoms (Table II). To assess the subjective improvement, all patients used a 5-point score with which they rated the effect as "very improved," "improved," "slightly improved," "no change," or "worse." The symptom scores were synthesized and assigned to 5 synthesized symptom categories (SSCs) to assess the clinical effect in the defined pollen season, as shown in Table III.

Orally active β-1,3-glucan

A hot-water extract of fresh shiitake mushroom (*Lentinus edodes* Berk [Sing]) was used as a nondispersed shiitake extract (NDG, placebo control), and superfine dispersed shiitake extract (Micellapist) was used as the orally active SDG (both extracts donated by the Ajinomoto Co, Inc, Tokyo, Japan). The amount of β-1,3-glucan/LNT was 15 mg/100 mL in both extracts. According to the manufacturer's indications, the mean diameters of the particle-size distribution of β-1,3-glucans were 0.08 and 288 μm in SDG and NDG, respectively. The particle-size distribution was measured in solution (β-1,3-glucan concentration, 0.15 mg/mL). There was no change in the particle-size distribution after 3 months of storage at 4°C or at room temperature. Superfine dispersed LNT, but not nondispersed LNT, adhesion onto and uptake into Peyer's patches was confirmed, and electron microscopy showed that the former was present in the vacuoles of epithelial cells.[26] This indicates that β-1,3-glucan was not taken up into Peyer's patches unless particulates were superfine dispersed.

Blood samples

Total and specific IgE binding in response to exposure to pollen from Japanese cedar, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and house dust 1 and 2 was determined by using the ORITON IgE DiaPack2000 (Nippon Chemiphar Co, Ltd, Japan), according to the manufacturer's instructions. Blood cell populations were also assayed on a hematology workstation (SE-9000, Sysmex, Japan).

Binding activity of β-1,3-glucan/LNT to $CD14^+$ monocytes

Peripheral blood was incubated with fluorescein-labeled LNT at 37°C for 75 minutes. During the last 30 minutes, phycoerythrin-labeled anti-CD14 antibody was added. The fluorescein intensity on $CD14^+$ monocytes was measured with a fluorescence-activated cell sorter (FACSCalibur TMHG flow cytometry system, 4-color type analyzer; BD, Japan).

TABLE II. Daily entries with respect to rhinoconjunctivitis

Ocular symptoms	
Itchiness	0 = absent
	1 = intermittent tickling involving more than the corner of the eye
	2 = mild continuous itchiness that can be localized and does not encourage rubbing
	3 = severe itchiness tempting to be rubbed
Wateriness	0 = absent
	1 = not requiring wiping
	2 = requiring wiping
	3 = trickling down the cheeks
Discharge	0 = absent
	1 = slight discharge not requiring wiping
	2 = mild discharge requiring wiping
	3 = lids stuck together in the morning because of gumming
Nasal symptoms	
Sneezing	0 = absent
	1 = itchy without sneezing
	2 = sneezing a couple of times
	3 = sneezing many times
Rhinorrhea	0 = absent
	1 = rhinorrhea
	2 = rhinorrhea with significant nasal congestion
	3 = nasal congestion all day
Skin (atopic change) and chest (asthma) symptoms (ranging from 0 = absent to 3 = severe)	

0-3.0 points; intermediate assessments of 0.5, 1.5, and 2.5 were allowed.

Statistical analysis

For statistical analysis, we used the Wilcoxon test for intragroup comparisons and the Mann-Whitney *U* test for intergroup comparisons, parametric tests (Student *t* test), and the Pearson correlation test. *P* values of .05 or less were considered statistically significant.

RESULTS

Subjective evaluation of the effect of SDG

Of the 60 enrolled patients, 59 completed the study. None of the participants experienced anaphylactic or urticarial reactions, and no oral allergy syndrome was observed. First, subjective symptoms were analyzed as follows. Of the 29 participants who had ingested SDG, a score of ''very improved'' and ''improved'' was assigned to 4 (13.8%) and 14 (48.3%) patients, respectively, at the end of the administration period. In contrast, of the 30 patients who ingested NDG, only 1 (3.3%) each was assigned a rating of ''very improved'' or ''improved'' (Fig 1, *A-a*). The difference between the SDG and NDG groups was significant ($P < .0002$). Similarly, the difference was significant at the end of the second 8-week period ($P < .0001$; Fig 1, *A-b*). As to the 5 SSCs described in the legend for Fig 1, scores of 1E, 2E, and 3E were obtained in 20 (69%) of the 29 participants who had ingested SDG and in 7 (23.3%) of the 30 members of the NDG group ($P < .001$; Fig 1, *A-c*). These findings indicate that orally ingested SDG effectively reduces the clinical symptoms of allergic rhinoconjunctivitis and rhinitis and that this effect manifests only if the ingested substance derives from a superfine dispersion of β-1,3-glucan/LNT.

TABLE III. Assessment of symptom score improvement by synthesized symptom categories

First step: Each participant's weekly symptom score was defined as the sum of the scores of 7 days divided by 7.
Objective effectiveness was assessed in 3 criteria:
(1) ocular symptom improvement (+, ±, or −)*†
(2) nasal symptom improvement (+, ±, or −)*
(3) manifestation of allergy symptom after cessation of oral uptake (+ or −)‡

Second step: SSCs were assessed:
1E: ''+'' in 2-3 criteria
2E: ''+'' in 1 criteria and ''±'' in other criteria
3E: ''±'' in 2 criteria
4N: ''±'' in 1 criteria
5N: no improvement in all criteria

*A decrease of greater than 1.0 and greater than 0.5 in the weekly graded score after the first 8-week period was regarded as ''+'' and ''±,'' respectively.
†We considered the ocular itch score maintained at less than 0.5 points throughout the ingestion period as ''±'' because all volunteers experienced ocular itch every year.
‡Volunteers without symptoms during the first 8-week period accompanied by the increase of weekly symptom scores of greater than 1.0 during the second 8-week period were considered ''+.''

Alleviation of ongoing symptoms

All participants experienced recurrent annual seasonal allergic conjunctivitis and rhinitis in the spring; 52 (88.1%) of the 59 participants were sensitive to Japanese cedar pollen. During the course of this study,

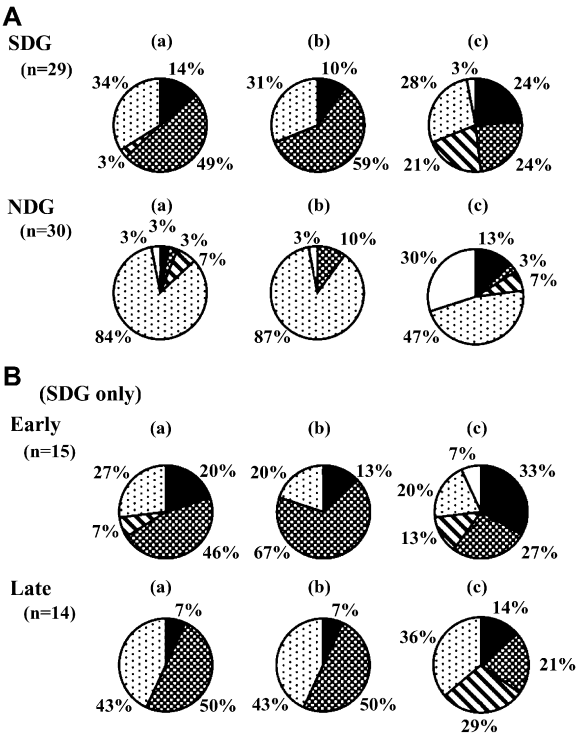

FIG 1. A, Comparison between SDG and NDG groups by subjectively judged efficacy *(a)* at the end of administration ($P < .0001$) and *(b)* 8 weeks thereafter ($P < .0002$). The efficacy assessment score was as follows: ■ 5, very improved; ▩ 4, improved; ▨ 3, slightly improved; ⬚ 2, no difference; and □ 1, worse. The symptom score improvement *(c)* was compared ($P < .0011$) by SSC criteria as follows: ■ 1E; ▩ 2E; ▨ 3E; ⬚ 4N; and □ 5N. **B**, The SDG group was divided into 2 groups at February 4th (early, n = 15; late, n = 14) and evaluated as in Fig 1, *A* (P = not significant).

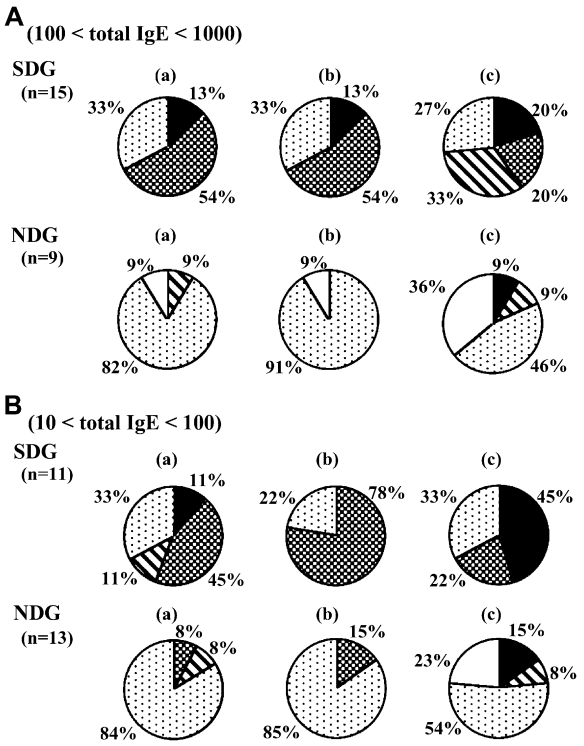

FIG 2. Subjectively judged efficacy (*a* and *b*) and symptom score improvement *(c)* and initial serum IgE titers. **A**, The participants with high IgE titers (100 < total IgE < 1000 IU; SDG, n = 15; NDG, n = 9) were compared *(a)* at the end of administration ($P < .0043$) and *(b)* 8 weeks thereafter ($P < .0028$) and *(c)* compared by the SSC ($P < .0064$). **B**, Those with low IgE titers (10 < total IgE < 100 IU; SDG, n = 11; NDG, n = 13) were compared: *a*, $P < .0300$; *b*, $P < .0148$; and *c*, $P < .0384$.

the seasonal dispersal of Japanese cedar pollen began on February 28th and continued to the middle of April in the living area of the study participants. Therefore to examine whether the preadministration of SDG resulted in a better improvement, the SDG (n = 29) and NDG (n = 30) groups were then subdivided into 2 groups each: early-start (before February 4th) and late-start (after February 4th) administration. Each group contained an approximately equal number of recipients (SDG group, 15 and 14, and NDG group, 15 and 15, respectively). Compared with the placebo recipients, both SDG groups manifested a significantly stronger decrease in their symptoms ($P < .05$ in each comparison, data not shown). Furthermore, at the end of both the first and second 8-week periods, the early-start and late-start groups did not differ significantly with respect to their assessment of the efficacy of SDG (Fig 1, *B-a* and *B-b*), and no difference in SSCs was observed between the 2 groups (Fig 1, *B-c*). By the division on February 12th to evaluate 2 weeks preadministration (the period thought necessary for SDG to manifest a pharmacologic effect) before pollen dispersal, the SDG group showed significant improvement in comparison with the NDG group in the early-start ($P < .0015$) and late-start ($P < .044$) groups. No significant difference between the 2 groups was evident in the efficacy and evaluation of synthesized categories (data not shown). The results suggest that oral SDG alleviated ongoing allergic symptoms and exhibited a preventive action on symptom manifestation.

Subjective scoring of allergic symptoms

Patterns reflecting the changes in subjectively assigned allergic symptom scores (ocular itch, sneezing, and rhinorrhea) are classified into 3 typical types. In 14 patients the oral ingestion of SDG resulted in a fast or gradual reduction in ocular itch, sneezing, and nasal rhinorrhea approximately 2 weeks after the start of uptake. In 9 patients no allergic symptoms, including ocular itch, were experienced during the ingestion. In 6 patients the oral ingestion of SDG did not elicit an improvement in any subjectively assigned symptom scores. It is of interest that in 10 of the 14 patients showing symptom score reduction, ocular itch reappeared when they ceased daily ingestion of SDG. In contrast, the NDG group reported no changes.

Clinical effects and serum IgE titers

We evaluated the correlation between the participants' initial serum IgE titers and their response to SDG by

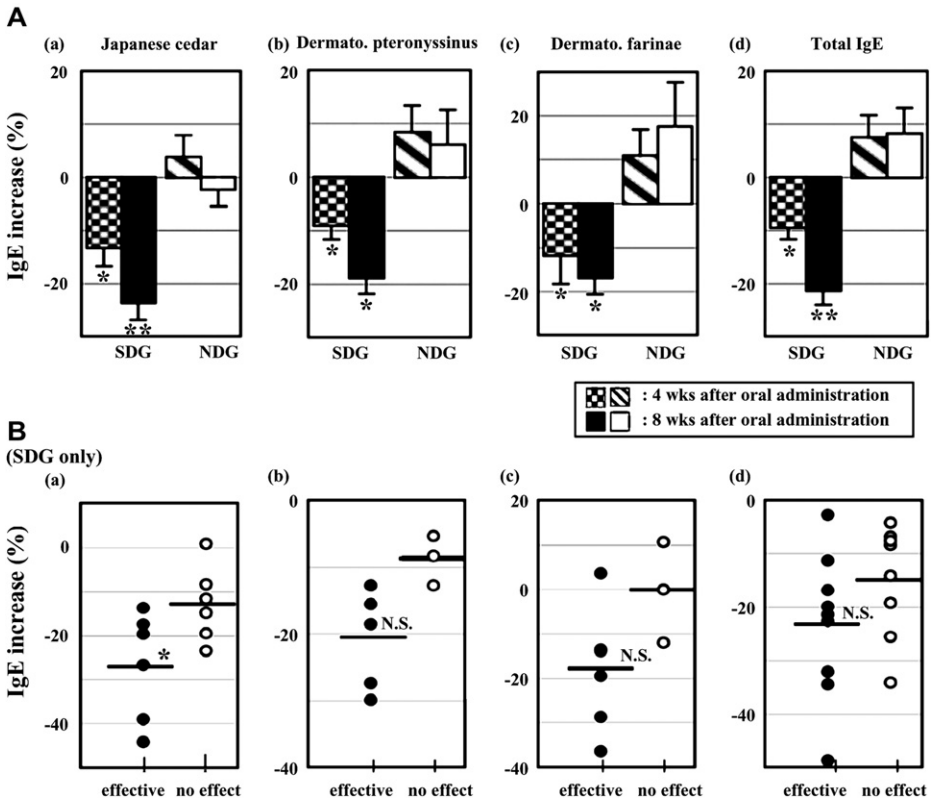

FIG 3. Correlation between the serum IgE titers and the clinical benefits. **A**, Allergen-specific and total serum IgE titers at 4 and 8 weeks after the start of SDG and NDG administration. *$P < .005$, **$P < .0001$. **B**, Symptom improvement by SDG and serum IgE titers. Patients with (SSC 1E and 2E) or without (4N and 5N) improvement are shown. *$P < .046$.

comparing the allergic symptoms of individuals with high (100 < total IgE < 1000 IU, n = 15) and low (30 < total IgE < 100 IU, n = 9) total serum IgE levels. Compared with the NDG group, the recipients of SDG experienced marked symptom relief in both groups (high initial IgE titer, $P < .0043$; low titer, $P < .030$). However, at the end of the 8-week SDG administration and at the end of the second 8-week period, there was no significant difference in the level of symptom relief between patients with initially high and low IgE titers. Similarly, they did not differ significantly when we analyzed their SSCs (Fig 2). These results suggest that the oral ingestion of SDG alleviates allergic symptoms irrespective of the preadministration IgE titer.

Correlation between the clinical effects and IgE titers

In the current study positive IgE was detected in Japanese cedar pollen (21/29 volunteers in the SDG group and 20/30 in the NDG group), *D pteronyssinus* (17 and 19, respectively), and *D farinae* (19 and 21, respectively). Next we examined whether SDG ingestion produced a decrease in the serum IgE levels of individuals whose preadministration level of allergen-specific and total IgE exceeded 30 and 3 IU/mL, respectively, using the following formula: [(*Postadministration titer*/*Preadministration titer*) − 1] × 100. As shown in Fig 3, *A*, the level of allergen-specific IgE was significantly decreased only in the SDG group. Patients allergic to Japanese cedar pollen who derived benefits from SDG exhibited a significant decrease in their allergen-specific IgE levels (Fig 3, *B-a*); the decrease was present but less pronounced in patients allergic to *Dermatophagoides* species (Fig 3, *B-b* and *B-c*). Total serum IgE was not significantly different between allergic patients who did or did not derive clinical benefits from the administration of SDG (Fig 3, *B-d*). The population with positive IgE to house dust mites displayed results similar to those with the other mite allergens (21 to house dust 1 and 21 to house dust 2, data not shown). Both house dusts are popularly examined allergens in Japan. The population with positive IgE levels to cypress, orchard grass, and cat dander in the current study, however, was insignificant.

Correlation between clinical effects and β-1,3-glucan binding to $CD14^+$ monocytes

LNT induces the T_H1-type response through its action on monocytes,[24] and theoretically, the binding ability of β-1,3-glucan/LNT to monocytes might directly influence its *in vivo* effect. Fig 4, *A*, shows the binding activity of β-1,3-glucan/LNT to $CD14^+$ monocytes; in the fluorescein-labeled dextran control, gating was set at greater

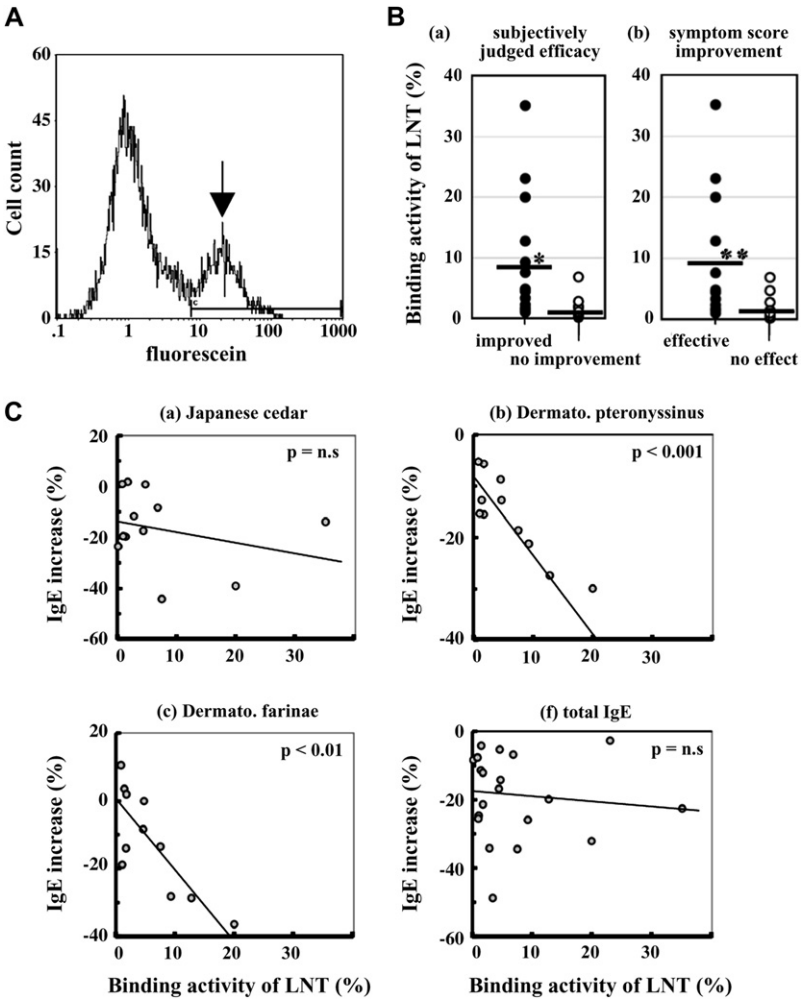

FIG 4. A, Number of fluorescein LNT–binding peripheral blood $CD14^+$ cells (*arrow*, control; the fluorescein-dextran). **B**, Correlation between LNT binding to monocytes and clinical benefits. *a*, Patients with (n = 17) and without (n = 8) subjective improvement. *b*, The symptom improvement score with (n = 12) and without (n = 8) improvement. $*P < .036$, $**P < .025$. **C**, Correlation between LNT binding to monocytes and IgE titers at the end of administration.

than 99.95%. The rate of their LNT binding–positive cells showed individual variations ranging from 0.16% to 35.04% among participants in this study. This reveals the marked heterogeneous ability of monocytes to bind to β-1,3-glucan/LNT and might predict the distinct pharmacologic role of β-1,3-glucan in the induction of T_H1 skewing among individuals. The rate of LNT-binding to $CD14^+$ monocytes was significantly higher in patients who did ($P < .036$) than in those who did not experience symptom alleviation (Fig 4, *B*).

We also studied the correlation between LNT binding to $CD14^+$ monocytes and the decrease in serum IgE titers (Fig 4, *C*) in patients receiving SDG. The ratio of LNT binding exhibited a good correlation with the decrease in allergen-specific IgE titers for *D pteronyssinus* ($P < .001$) and *D farinae* ($P < .01$). However, there was no correlation with serum total IgE titers and the decrease in Japanese cedar–specific IgE titers. These results suggest that the alleviation of rhinoconjunctivitis in allergic patients treated with oral SDG is at least partly attributable to the binding of β-1,3-glucan to their $CD14^+$ monocytes.

DISCUSSION

This study is the first demonstration that the oral ingestion of β-1,3-glucan alleviates ongoing symptoms of rhinoconjunctivitis and rhinitis. The oral administration of SDG, but not NDG, resulted in the alleviation of both seasonal and perennial allergic symptoms. We attribute the difference to the inefficient β-1,3-glucan uptake by the intestinal mucosa of patients receiving the placebo. The ingestion of SDG resulted in a reduction of both allergen-specific and total IgE titers, and there was a good correlation with the binding of LNT to $CD14^+$ monocytes. We also noted that the clinical response to treatment with SDG

was well correlated with a decrease in IgE titers and the binding of monocytes to β-1,3-glucan.

The inflammatory response in patients with allergy is comprised of a complex network of local and systemic immune interactions.[27] Classical mediators, such as histamine, cytokines, chemokines, adhesion molecules, cellular infiltration, and chronic nasal and conjunctival mucosal inflammation, play a role in the manifestation of allergic symptoms.[28] The symptomatic nasal congestion, sneezing, watery eyes, and ocular itch of some of our patients were alleviated as early as 1 or 2 weeks after the start of administration (data not shown). Oral SDG alleviated ongoing symptoms of rhinoconjunctivitis, indicating its therapeutic efficacy, although the prophylactic use seems more effective (Fig 1, *B*). Efforts are underway in our laboratory to determine the duration of the benefits derived from the oral administration of SDG. Although some patients continued to experience alleviation of their symptoms for as long as 6 months after the administration period, in others the symptoms returned immediately when they stopped ingesting SDG. The different responses were not correlated with the length of time of the ingestion that preceded their exposure to the seasonal allergen, their allergen-specific serum IgE titers, or the kind of allergen or allergens presensitized (data not shown). We postulate that reskewing of the T_H1/T_H2 balance toward T_H2 might occur after cessation of the daily ingestion of SDG because exposure to environmental allergens continues. In addition, allergic individuals might differ with respect to the allergen-induced local activation of T_H2 cells, inhibitory T_H1 cells, or regulatory T cells, and the observed differences might reflect variations in their pathologic allergic states (ie, acute or chronic allergies). In the face of increasing evidence that T_H1 and T_H2 cells are not always antagonistic, the downregulation of allergic inflammation might depend on cells other than T_H1 cells.[29]

Macrophages are thought to be capable of suppressing immune responses by secreting anti-inflammatory mediators, such as PGE_2, TGF-α, and IL-10.[13,30] By releasing IL-12, macrophages can specifically direct immune responses through T_H1 pathways.[31-36] IL-12 inhibits antigen-induced airway eosinophilia, even in the presence of circulating specific IgE.[37,38] Macrophage-mediated prevention of ongoing T_H2 responses[14,17,32,33,39,40] might explain the observed alleviation of ongoing rhinoconjunctivitis symptoms (Fig 1). Peritoneal macrophages elicited by LNT released lower levels of PGs, IL-10, and IL-6, whereas they produced more IL-12.[24] Given the selective effect of LNT on monocytes/macrophages,[22-24] it is possible that individuals whose $CD14^+$ monocytes have a high affinity for LNT experience a greater allergen-specific serum IgE reduction (Fig 4, *C*). We found that individuals reporting symptom alleviation manifested increased affinity of $CD14^+$ monocytes for β-1,3-glucan/LNT (Fig 4, *B*).

The elucidation of the relative role of perennial allergens versus seasonal cedar pollen in the observed improvement in allergic symptoms (Fig 1) is difficult. SDG-treated patients who experienced symptom alleviation manifested a statistically significant decrease in their IgE levels against Japanese cedar pollen and relatively lower serum IgE titers for *Dermatophagoides* species allergens than did patients who experienced no beneficial effects (Fig 3, *B*). Although the dispersion of specific pollen is seasonally circumscribed, the continual exposure to perennial allergens gives rise to chronic inflammation.[41,42] Although short-term clinical studies of specific immunotherapy for perennial allergens tended to yield poor results, in studies that covered periods exceeding 18 months, excellent results were obtained.[43,44]

Orally active SDG can be taken up easily without attendant side effects. It might alleviate T_H2-related allergies, including atopic IgE-mediated diseases and food allergies. Although the relatively small size of our study population and the short observation period prohibit definitive conclusions, our findings open a path toward the treatment of a variety of allergic, atopic, and asthmatic diseases.

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