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ORIGINAL CONTRIBUTION

The effects of PG102, a water-soluble extract from *Actinidia arguta*, on serum total IgE levels: a double-blind, randomized, placebo-controlled exploratory clinical study

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Abstract
Background Recent studies have reported that blocking IgE has a potentially beneficial role in the treatment of various allergic diseases. Previously, we found that PG102, a water-soluble extract prepared from the edible fruits of *Actinidia arguta*, can effectively reduce IgE levels using murine models.
Aims To evaluate the efficacy of PG102 at lowering levels of total IgE in asymptomatic subjects with atopy.
Methods A total of 90 asymptomatic subjects with atopy were randomized equally to a PG102 group or a placebo control group and treated for 8 weeks in a double-blind manner. Total serum IgE, eosinophilic cation protein (ECP), eotaxin, thymus, and activation-regulated chemokine (TARC), IL-4, IL-5, and IL-13 levels were measured. Eosinophil counts were determined before and after treatment, and results were compared. In addition, possible adverse reactions were thoroughly checked in this first human trial.
Results Levels of total IgE significantly increased in the control group but showed no change in the PG102 group, and change differences between the control and PG102 groups were significant (+12.9%, vs.−5.7%, $p = 0.015$). Levels of ECP and eotaxin and eosinophil counts produced similar results. However, the other variables showed no significant changes after treatment.
Conclusion In this exploratory clinical trial, it was found that 8 weeks of treatment with PG102 effectively reduced the levels of total IgE in apparently asymptomatic subjects with atopy.

Keywords *Actinidia arguta* · Allergy · IgE · PG102

S.-H. Kim and S. Kim have equally contributed to this study.

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Introduction

Allergic reactions are initiated when an antigen crosslinks with immunoglobulin E (IgE) antibodies bound to their high-affinity Fc receptors on tissue mast cells or blood basophils [1]. Recently, it was suggested that a recombinant humanized monoclonal anti-IgE antibody (omalizumab) has a potential therapeutic role for the treatment of various allergic diseases, including bronchial asthma [2], allergic rhinitis [3], autoimmune urticaria [4], and atopic dermatitis [5]. These findings suggest the importance of IgE blockade in allergic diseases.

PG102 is a water-soluble extract prepared from the edible fruit of *Actinidia arguta*, commonly referred to as hardy kiwifruit. Using a murine model, we previously showed that PG102 effectively improved the symptoms of

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bronchial asthma [6, 7], atopic dermatitis [8], and food allergy [9], by decreasing serum total IgE levels. Furthermore, our unpublished experiments involving 4-week and 3-month repetitive toxicity experiments in rats and mice showed that PG102 is safe. Encouraged by these results, we carried out an exploratory clinical trial.

In the present study, we evaluated the efficacy of PG102 with respect to lowering serum total IgE levels in asymptomatic subjects with atopy and the effect of PG102 on allergy-related factors, such as eosinophilic cation protein (ECP), eotaxin, thymus, and activation-regulated chemokine (TARC), IL-4, IL-5, and IL-13.

Materials and methods

Patients

Subjects that responded to an advertisement were enrolled for screening at Seoul National University Hospital, Seoul, and also at Seoul National University Bundang Hospital, Kyunggi-do, South Korea. The inclusion criteria applied were as follows: adults (aged 18–65), currently no allergic symptoms, no history of hypersensitivity to *Actinidia arguta* or any other kiwifruit-derived foods, currently not on any anti-allergic medication, a positive skin test to one or more perennial allergen, and a serum total IgE level of >300 IU/mL. All subjects were provided written informed consent. The study protocol complied with the guidelines issued by the Korean Food and Drug Administration and was approved by the Institutional Review Boards at both hospitals. The study was carried out in accordance with the ethical principles of the Declaration of Helsinki and with the standards of Good Clinical Practice.

Preparation of the test product

PG102 was prepared from *Actinidia arguta* as described previously [6–9]. Each 500 mg tablet of PG102 contained 250 mg of powdered hot-water extract and 250 mg of microcrystalline cellulose. Placebo tablets contained microcrystalline cellulose and corn starch in the same ratio. The PG102 quality was controlled using bioassays, as described previously [8, 9].

Study design

This study was performed in randomized, double-blind, placebo-controlled manners. At visit 1 (week-2), enrolled subjects underwent physician's physical examination, blood test including complete blood cell count, liver function test, electrolyte and renal function test, coagulation test, urinalysis, stool examination for excluding parasitic infection, urine hCG test for indicated women, and serum IgE test for eligibility screening. At visit 2 (week 0), subjects satisfying the inclusion criteria were randomized to the PG102 or the control group and underwent skin prick tests with common inhalant allergens and blood tests to determine baseline serum IgE, ECP, eotaxin, TARC, IL-4, IL-5, and IL-13 levels. Subjects took two tablets of PG102 or placebo twice a day for 8 weeks. Treatment dose and duration were extrapolated from the results of animal experiments. At visit 3 (week 8), skin prick tests and blood tests were re-performed. Skin prick tests comprised 45 common inhalant allergens including *Dermatophagoides farinae*, *D. pteronyssinus*, two-spotted spider mite, Tyrophagus, cat dander, dog dander, cockroach, various pollens [tree pollens(alder, hazel, popular, elm, willow, birch, beech, oak, and plane tree), grass pollens (velvet, orchard, rye, timothy, Kentucky blue, and meadow grass) mugwort, and ragweed], and various fungi spores (Allergopharma, Reinbek, Germany), as previously described [10]. Serum level of total IgE and ECP was measured using immunoradiometric assay (DPA, USA). Serum concentrations of ECP (UniCAP ECP; Pharmacia Sweden), eotaxin, TARC, IL-4, IL-5, and IL-13 (ELISA-kit; R&D systems Inc, Minneapolis, Minesota, USA) were measured using ELISA-based method. Compliance with treatment was assessed using patients' self-reports and by counting remaining capsules, as proposed previously [11]. The first subject was screened on December 13, 2006 and enrolled as an eligible subject on December 27, 2006. The last visit made by a subject was on March 20, 2008. The primary efficacy variable was a change in serum total IgE levels, and the secondary efficacy variables were changes in the levels of eosinophils, ECP, eotaxin, TARC, IL-4, IL-5, and IL-13. To identify possible adverse events (AEs), subjects were thoroughly examined by an investigator at each visit, and urine analysis and blood tests were performed to determine complete blood counts (including differential counts), liver function, renal function, and serum levels of IgM, IgG, and IgA, before and after treatment.

Statistical analysis

The *t* test was used for continuous variables, and the X^2 test and Fisher's exact test were used for categorical variables in the analysis of demographic and clinical characteristics of study population. A one-tailed *t* test was performed to compare the improvement in efficacy variables between two groups. To minimize errors associated with the population distributions assumption, we used both the *t* test and Wilcoxon's rank sum tests for the analysis of skin test results. Comparison of efficacy variables between baseline and 8-week treatment in each group was made using paired

t test. Statistical analysis was performed using SPSS 12.0, and *p* values of less than 0.05 were considered significant.

This study was designed with sample size of 62 (31 for both groups) to have 85% power to detect the difference in serum IgE change between two groups. Mean change of IgE in the previous study by Yang et al. [12] showing significant decrease in total IgE was used for the sample size estimation. Target numbers of study subjects were calculated as 100 (50 for both groups) considering presumed dropout rate (35%).

Results

Group compositions and demographic characteristics

A total of 156 subjects were screened and 90 (57.7%) were randomized to the two study groups (45 subjects to the PG102 group and 45 to the control group). Baseline characteristics of the 90 study subjects are shown in Table 1. No demographic variable was found to be significantly different in the two groups. *Endolimax nana* was discovered in a stool examination of one subject in the control group. Because *Endolimax nana* is a commensal organism [13] and therefore is unlikely to affect total IgE levels, he was not excluded from the study. Thirty-two subjects in the PG102 group (71.1%) and 38 subjects in the control group (84.4%) completed the study; the dropout rate was not significantly different between the two groups (Fig. 1). Compliance with medication was not significantly different in the two groups (90.5% for the PG102 group and 89.2% for the control group, $p = 0.59$). Safety and efficacy assessments were made on an intention-to-treat (ITT) basis for the originally enrolled 90 study subjects.

Efficacy

The primary efficacy variable in this study was a change in serum total IgE level. As shown in Table 2, in the ITT population, the mean serum total IgE level increased significantly over the 8-week treatment course in the control group from 753.4 ± 522.5 IU/mL to 850.7 ± 732.3 IU/mL ($p = 0.029$), whereas in the PG102 group, mean total IgE decreased by 40.4 IU/mL, which was statistically insignificant. Interestingly, percentage changes in the levels of total IgE before and after treatment were −5.7% for the PG102 group and +12.9% for the control group; this difference was significant ($p = 0.015$).

To exclude the possible effect of seasonal environmental factors such as pollen, we performed subgroup analyses on

Table 1 Characteristics of the study subjects

	PG102 ($n = 45$) *N* (%)	Placebo ($n = 45$) *N* (%)	*p* value
Sex			
Male	26 (57.8)	26 (57.8)	1.000[a]
Female	19 (42.2)	19 (42.2)	
Age (years)			
Mean ± SD	36.3 ± 14.4	33.6 ± 12.6	0.343[b]
History of allergic diseases			
No	8 (17.8)	13 (28.9)	0.213[c]
Yes	37 (82.2)	32 (71.1)	
Bronchial asthma	3 (6.7)	2 (4.5)	
Allergic rhinitis	21 (46.7)	20 (45.5)	
Atopic dermatitis	4 (8.9)	8 (18.2)	
Drug allergy	2 (4.4)	4 (9.1)	
Hives	11 (24.4)	8 (18.2)	
Food allergy	2 (4.4)	2 (4.5)	
History of non-allergic diseases[d]			
Yes	7 (15.6)	9 (20.0)	0.581[c]
No	38 (84.4)	36 (80.0)	
History of other medications[e]			
Yes	15 (33.3)	17 (37.8)	0.659[c]
No	30 (66.7)	28 (62.2)	
Stool examination for parasite			
Negative	43 (100.0)	43 (97.3)	1.000[c]
Positive	0 (0.0)	1 (2.3)	

[a] *p* value by Chi-square test

[b] *p* value by *t* test

[c] *p* value by Fisher's exact test

[d] Non-allergic diseases include endocrine, musculoskeletal, neurological, digestive, dermatologic, urogenital, dental diseases

[e] History of non-allergic medications during 3 months before screening includes digestives, anticoagulants, antihypertensive drugs, oral hypoglycemic agents, analgesics, antipyretics, anti-anxiety drugs, topical steroids, quinolone antibiotics, minerals, vitamins, herbal products, cough and cold medications, etc

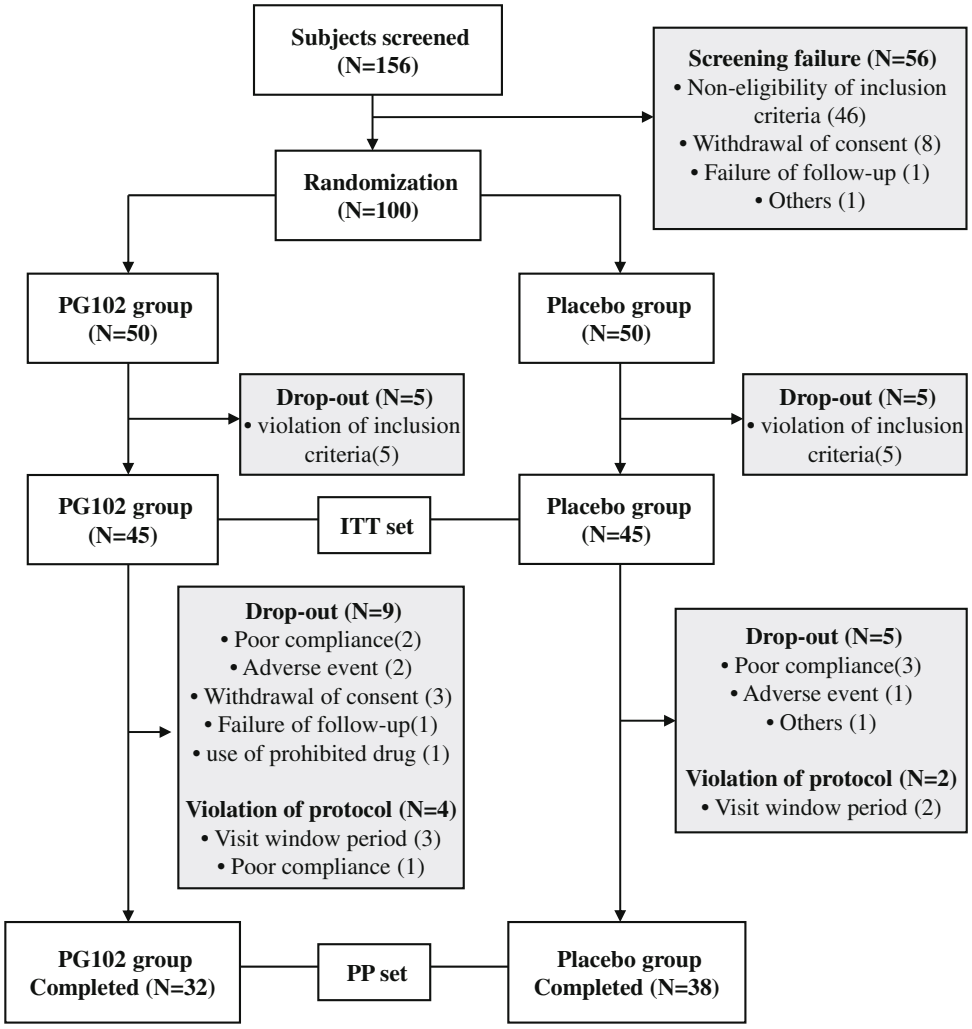

Fig. 1 Flow diagram of the study

Table 2 Effects of PG102 on total IgE level

Group	Baseline[a]	8-week treatment[a]	Difference[a]	*p* value[b]	Change (%)
PG102	710.2 ± 348.0	669.8 ± 309.5	−40.4 ± 238.6	0.262	−5.7
Placebo	753.4 ± 522.5	850.7 ± 732.3	97.2 ± 283.1	0.029	12.9
p value[c]			0.015		

[a] Mean ± SD (IU/mL)

[b] Compared between baseline values and 8-week treatment values by paired *t* test

[c] Compared between groups by *t* test

subjects who showed positive skin test results only to perennial allergens excluding subjects who showed positive skin responses to seasonal pollens. The distribution of the positive responders to perennial allergens was not much different between the two groups: 22 of the 45 subjects (48.9%) in the PG102 group and 23 of 45 subjects (51.1%) in the control group. The patterns of change in the serum level of IgE of these subgroups were also similar to those of total subject groups in both PG102 and control groups (data not shown).

Mean ECP serum level increased significantly by 7.7 μg/L (46.8%) over treatment in the control group ($p = 0.018$), whereas in the PG102 group, it decreased by 1.2 μg/L (6.9%) ($p = 0.694$). The difference in the change in ECP level between the two groups was significant ($p = 0.022$). A similar trend was observed for eotaxin. The mean serum level of eotaxin increased by 2.2 pg/mL (1.7%) from baseline during treatment ($p = 0.620$) in the control group, whereas in the PG102 group it decreased by 10.4 pg/mL (7.8%) ($p = 0.039$). This group difference was

Table 3 Effects of PG102 on ECP, eotaxin, and eosinophils

Parameter	Treatment	PG102[a]	Placebo[a]	p value[b]
ECP (μg/L)	Baseline	17.3 ± 19.8	16.5 ± 29.8	
	8-week treatment	16.1 ± 17.5	24.2 ± 30.9	
	Difference[c]	−1.2 ± 20.3	7.7 ± 21.1	0.022
	p value[d]	0.694	0.018	
	Change[e] (%)	−6.9	46.7	
Eotaxin (pg/mL)	Baseline	133.0 ± 36.3	129.7 ± 37.8	
	8-week treatment	122.7 ± 33.5	132.0 ± 34.8	
	Difference[c]	−10.4 ± 32.7	2.2 ± 30.1	0.030
	p value[d]	0.039	0.620	
	Change[e] (%)	−7.8	1.7	
Eosinophil count (/μL)	Baseline	244.6 ± 168.5	194.3 ± 153.3	
	8-week treatment	224.7 ± 163.6	224.5 ± 216.5	
	Difference[c]	−19.8 ± 97.4	30.2 ± 163.0	0.040
	p value[d]	0.178	0.220	
	Change[e] (%)	−8.1	15.5	

[a] Mean ± SD

[b] Compared between groups by t test

[c] Difference = mean value at visit 3—mean value at visit 2

[d] Compared between baseline values and 8-week treatment values by paired t test

[e] Change = (mean value at visit 3—mean value at visit 2)/ mean value at visit 2

also statistically significant ($p = 0.030$). In terms of numbers of eosinophils in peripheral blood, those in the PG102 group were 23.6% lower than in the control group after treatment ($p = 0.040$) (Table 3). However, group levels of IL-4, IL-5, IL-13, and TARC were similar (data not shown).

Regarding skin test results, no significant differences in positive rates to individual allergens or in skin test indices (defined as the number of positive results) were found after treatment (data not shown).

Safety

To determine whether the effect of PG102 on serum total IgE levels resulted from the inhibition of humoral immunity, serum levels of IgG, IgA, and IgM were measured before and after treatment. For serum IgG, levels significantly increased by 41.7 IU/mL in the PG102 group ($p = 0.044$) and by 42.8 IU/mL in the control group ($p = 0.065$) over the 8-week treatment period. However, this difference was not significant ($p = 0.486$). No inter-group or intra-group differences were found for IgA or IgM (data not shown).

During the study period, a total of 21 AEs were reported by 16 of the 90 ITT subjects (10 individuals in the PG102 group and 6 in the control group). The common AEs in the PG102 group were gastrointestinal (2 subjects), metabolic (2 subjects), and skin disorders (2 subjects). Detailed information is shown in Table 4. All AEs in the PG102 group were classified as 'mild'. The etiologies of most AE cases encountered during the study were 'definitely unrelated '(5 subjects) and 'probably unrelated' (3 subjects) in the PG102 group, while there were 6 'probably unrelated' and 3 'definitely unrelated' cases in the control group. There was no significant difference between the two groups. Three AEs, including urticaria and hyperlipidemia, were possibly related to the test product in the PG102 group.

Discussion

In this exploratory clinical trial, we observed that 8-week treatment with PG102 effectively reduced the levels of serum total IgE in apparently asymptomatic subjects. These effects were not due to the non-specific inhibition of humoral immunity, because serum levels of IgG, IgA, and IgM were unchanged. In addition, it was confirmed that PG102 treatment also significantly reduced the serum levels of ECP, eotaxin, and eosinophil counts in the peripheral blood, which are important mediators of allergic diseases.

In the present study, the baseline levels of serum total IgE in both the PG102 and control groups were relatively high. Assuming that the effect of PG102 might be more obvious in subjects with elevated levels of serum total IgE, we intentionally recruited asymptomatic subjects with a serum total IgE level of more than 300 IU/mL. All subjects enrolled in this study were atopic, and almost 70% of them had a history of allergic diseases, although they were asymptomatic at the time of recruitment. The possibility of parasite-associated increases in serum total IgE levels was excluded by performing stool examinations and by detailing consumption histories. Our data showed that PG102 could effectively reduce serum total IgE levels, especially in subjects with allergic diathesis.

It was notable that serum total IgE levels increased significantly in the control group. The placebo contained

Table 4 Characterization of adverse events

Body system	Preferred term	PG102, $N = 45$		Placebo, $N = 45$	
		Number of cases	(%)	Number of cases	(%)
Cardiovascular		0	0	1	2.2
	Edema	0	0	1	2.2
Gastrointestinal		2	4.4	2	4.4
	Constipation	0	0	1	2.2
	Gastritis	1	2.2	0	0.0
	Abdominal distension	0	0	1	2.2
	Gastroenteric disorder	1	2.2	0	0
General		1	2.2	0	0
	Back Pain	1	2.2	0	0
Liver		1	2.2	1	2.2
	Liver fatty	0	0	1	2.2
	LFT abnormality (SGPT, SGOT increased)	1	2.2	0	0
Metabolic		2	4.4	0	0
	Hyperlipidemia	1	2.2	0	0.0
	Hyperuricemia	1	2.2	0	0.0
Musculoskeletal		1	2.2	0	0
	Bone fracture-accidental	1	2.2	0	0
Psychiatric		1	2.2	0	0
	Insomnia	1	2.2	0	0
Respiratory		1	2.2	2	4.4
	Lymphadenitis	0	0	1	2.2
	Dyspnea	0	0	1	2.2
	Cold	1	2.2	0	0
Skin		2	4.4	4	8.9
	Urticaria	1	2.2	3	6.7
	Aquagenic urticaria	1	2.2	0	0
	Systemic erythema	0	0	1	2.2

only microcrystalline cellulose and corn starch, which are commonly used as supplements or additives in many drugs and food formulations. Therefore, it is unlikely that the placebo caused this increase in serum total IgE. It has been reported that serum total IgE levels in human blood are dependent on seasonal and environmental factors [14, 15]. For example, a twofold increase in serum total IgE level has been reported when pollen levels in air are high [16]. Subgroup analysis was performed on the subjects who showed positive skin tests only to seasonal pollens to exclude the possible effect of seasonal environmental factors such as pollen. The patterns of IgE change in the subgroup analysis were also similar to those in the total subject group analysis. This result means that seasonal environmental factors did not affect the IgE change of the specific group and the difference in IgE change between two groups was caused by the intervention of PG102 treatment. Taken together, our data clearly demonstrated that PG102 could reduce the level of serum total IgE in subjects with relatively high levels of serum IgE regardless of their specific allergen sensitization status.

IgE is a key player in the pathogenesis of allergies [17]. As mentioned earlier, non-specific blockade of IgE by anti-IgE antibody has produced promising results with respect to the treatment of various allergic diseases [2–5]. Therefore, the data showing that PG102 could lower the serum level of total IgE imply that PG102 has potential to be used in the individuals with allergic diseases. Another appealing characteristic of PG102 as an anti-allergic agent is that it reduces the levels of ECP, eotaxin, and eosinophil counts effectively, which are important players in the allergy pathogenesis. Results from this human trial are consistent with data from extensive in vivo animal and in vitro cell culture studies showing that PG102 downregulates the expression of IgE and several key cytokines involved in the pathogenesis of allergy. Overall, PG102 appears to have potential as an anti-allergic agent.

In the present study, changes in skin test results (skin test index and positive rates to individual allergens) after

treatment were not significant. According to our experience, however, any change in the skin test pattern requires relatively lengthy time to be detected, and the current protocol might not have allowed us to observe any meaningful level of change in the skin test.

PG102 is a water-soluble extract prepared from the edible fruit of *Actinidia arguta*. No serious allergic disease associated with kiwifruit has been reported, except for rare cases of acute hypersensitivity. In the present study, no serious AEs were encountered. Our findings suggest that PG102 provides an alternative means of regulating allergic response. Given its interesting biological activities as well as its high degree of safety, further scientific and clinical investigations are warranted.

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Conflict of interest The authors have no conflict of interest to declare.

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