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Effect of Allerglobuline Injection on Serum Immunoglobulin Levels in ENT Patients

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SUMMARY **Allerglobuline is a human gammaglobulin preparation which has been reported to have a protective effect against Type I allergic diseases and chronic infection of the upper respiratory tract both in adults and children. This study included 64 patients suffering from perennial allergic rhinitis and/or chronic infection of the nose, paranasal sinuses and pharynx. All patients received Allerglobuline 10 ml intramuscular injection once a week for 5 times then once a month for another 3 times. Blood samples were taken before the first and after the last injections to assay for the levels of Igs G, A, M and E. The therapeutic responses were evaluated after the fifth injections by dividing into 5 grades (from Grade I = excellent to Grade V = no response). Statistical analysis revealed that there was no significant difference between the pre- and post-treatment levels of Igs, G, A and M. But the level of IgE decreased significantly after 8 injections ($p < 0.001$). There was no correlation between the level of immunoglobulins and grade of therapeutic responses. But the number of patients who respond satisfactorily to Allerglobuline treatment increased from 62.26% after 5 injections to 77.36% after 8 injections. This difference does not reach the statistically significant level but is noteworthy.**

Allerglobuline is a 10% human immunoglobulin preparation of placental blood. It was first introduced in France in 1960. The batches were selected on their capacity to protect guinea pigs against passively induced anaphylactic shock. This was first termed histamino protective activity and later proved to be due to its IgG content. After 1960, there was gradual progress in immunologic studies which helped to elucidate the mechanism of action of Allerglobuline against type I allergic reactions. Up to date, at least 3 possible mechanisms have been proposed. First IgG_4 antibodies inhibit IgE binding on an IgE F_c receptor of the mediator cells.[1] IgG_4 also competes with IgE to fix the allergens. Specific IgG to various allergens belonging to the IgG_1 subclass was also found in Allerglobuline and exhibits a strong inhibition of basophil degranulation.[2] This is the second explanation. Thirdly, it was demonstrated by several studies that placental IgG could inhibit IgE synthesis in vitro.[3,4] This activity was similar to activities found in colostrum and the molecule involved was called IgE binding factor.[5]

In Europe, the clinical efficacies of Allerglobuline have been reported in allergic asthma,[6] infantile asthma,[7] acute attacks of asthma in children,[8] allergic conjunctivitis[9] and atopic eczema.[10] Most interesting to us are the studies in children with chronic nasopharyngitis[11] and in hay fever patients[12] which also showed good results. In Thailand, Allerglobuline has been available since 1980, but its use is very limited because the effects on both clinical and laboratory findings in Thai patients are not known. At the Allergy Clinic, ENT Department, Siriraj Hospital, Bangkok, we have prescribed Allerglobuline injection for some of our patients and the results are varied. Therefore, the purpose of this study was to evaluate the therapeutic responses and to compare the serum immunoglobulin levels of these patients before and after Allerglobuline treatment and among those who express various responses to the treatment.

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MATERIALS AND METHODS

Inclusion criteria

Patients of either sex aged 13-60 years who were willing to participate in the study were included if they were suffering from perennial rhinitis, chronic sinusitis or chronic rhinopharyngitis for at least one year.

Sixty-four patients were included in this study. They were 31 males and 33 females, ages ranging from 13-60 years, average 31 years. The duration of their symptoms ranged from 1-45 years with the average of 8.66 ± 8.19 years. Every patient was diagnosed by careful history taking, ENT examinations, X-rays of the paranasal sinuses and routine allergy skin testing to common allergens. The detailed diagnoses of these patients are listed in Table 1. Most of the patients had a combination of allergy and infection together. Only 11 patients had allergic rhinitis, 2 had allergic asthma and one had chronic rhinopharyngitis alone.

Study design

Each patient received Allerglobuline 10 ml by intramuscular injection, one 5 ml vial on each buttock once a week for 5 weeks then once a month for 3 months. Altogether each patient received 8 sets of injections over a period of 4 months. There was one patient aged 13 years old who received only one vial of 5 ml Allerglobuline at a time. Each 5 ml vial of Allerglobuline contains 500 mg gammglobulin and other non-active ingredients in order to maintain pH and isotonic solution.

Blood samples were taken before start of treatment and again after the last injection. They were assayed for total IgE, IgG, IgA and IgM levels. The patients assessed the global symptom improvement at the time of the fifth and the last injection. The following scale was used for grading the symptom improvement: Grade I = excellent : virtually all symptoms have been eliminated; Grade II = good : most symptoms are improved, but some symptoms are still listed as mild; Grade III = fair : some responses, but most symptoms are still present; Grade IV = poor : minimal responses; Grade V = treatment failure : no response or worse than pretreatment baseline.

Some patients also recorded their nasal symptoms daily in the diary card. The severity of the symptoms were rated on a four-point scale ranging from 0 = absent to 3 = severe for itching, sneezing, blocked nose and runny nose throughout the treatment period.

Adverse effects were also ascertained from non-leading questions at each follow up visit. All adverse experiences were recorded with information about seriousness, date of onset, duration, action taken and outcome.

Statistical analysis of the results was done by Student's t test, Chi-square test, Wilcoxon and Mann-Whitney Match Pair test where applicable.

RESULTS

Of all 64 patients included, only 59 completed the 5th week injection. Four patients were lost follow-up for unknown reasons. One patient withdrew because of side effect which will be discussed later.

Table 1. Diagnosis of 64 patients participated in the study.

Diagnosis	
Allergic Rhinitis (AR)	61
Asthma	2
Chronic rhinopharyngitis	1
Total	64
AR combined with other diseases	
AR+asthma	11
AR+asthma+sinusitis	3
AR+asthma+food allergy	2
AR+asthma+drug allergy	2
AR+asthma+drug allergy+nasal polyp	2
AR+asthma+drug allergy+sinusitis	2
AR+sinusitis	9
AR+sinusitis+COMrt	1
AR+sinusitis+nasal polyp	1
AR+drug allergy	1
AR+drug allergy+food allergy	2
AR+drug allergy+ urticaria	1
AR+drug allergy+rhinopharyngitis	1
AR+chronic pharyngitis	7
AR+nasal polyp	2
AR+conjunctivitis	2
AR+food allergy+urticaria	1
Total	50

Fifty-three patients underwent the full course of 8 injections but only 48 patients had blood samples taken for analysis both pre- and post-treatment. Therefore, the result of serum immunoglobulin levels were studied in 48 patients.

Serum immunoglobulins G, A and M were assayed by a single radial immunodiffusion method using an immunodiffusion plate purchased from Behringwerke AG, Marburg, West Germany. The levels of IgG, A, M in sera of patients before and after treatment were compared and were not statistically significant different.

The total IgE level in serum was determined by fluorescence allergosorbent test (FAST) using the test kit purchased from 3M Diagnostic Systems, Santa Clara, California, USA. The serum levels of total IgE after treatment were found to be significantly lowered when compared with those before treatment ($p < 0.001$). The results of serum immunoglobulin levels were shown together in Table 2.

After weekly injections for 5 times, 59 patients evaluated the therapeutic responses of the treatment and after another monthly injection for 3 times, 53 patients assessed their symptom improvement. In order to compare the difference of the clinical result of Allerglobuline treatment between 5 and 8 injections we used the assessment made by the 53 patients who completed the 8 injection course. These are shown in Fig. 1.

If we considered Grades I, II and III together as a "satisfactory response" group and Grades IV and V as an "unsatisfactory response" group, it was demonstrated that after 8 injections the satisfactory response rate increased from 62.26% to 77.36%. However, by using the Chi-square test the increase was not statistically significant ($p = 0.2926$).

In an attempt to assess any difference of the immunologic background between the "satisfactory response" group and the "unsatisfactory response" group, we compared the serum levels of immunoglobulins before and after treatment in these two groups of patients. We found that there was no significant difference in the IgG, M and E levels, but the post treatment level of IgA in the "unsatisfactory response" group was lowered than in the other group ($p = 0.01$) (see Table 3). However, the number of patients in the "unsatisfactory response" group was relatively small (only 11 patients). Therefore, the significance of this difference has yet to be confirmed in a larger number of patients. Special attention has been paid to the level of IgE hence the correlation between the total IgE and the therapeutic responses were calculated and there was found to be no correlation both in pre- and post-treatment specimens ($p = 0.059$, $p = 0.099$ respectively). This implies that IgE level has no influence on the treatment outcome in this group of patients.

The diary card recorded throughout the study period by 15 patients were also analyzed. All four nasal symptoms i.e. itching, sneezing, rhinorrhea and obstruction were summed up and averaged at each visit. This was plotted and shown in Fig. 2. The decrease of the average nasal symptom scores was clearly in evidence at the 3rd injection. However, the rise of the symptom score at 7th injection was unexpected and could not be explained.

Adverse experiences reported in 64 patients are listed in Table 4. Pain and inflammation at the site of injection were the most common complaints. Fever, drowsiness and other side effects such as headahe, nausea, back pain and conjunctivitis were also mentioned but they were mild and did not occur after every injection therefore they were tolerable. Only one patient was withdrawn

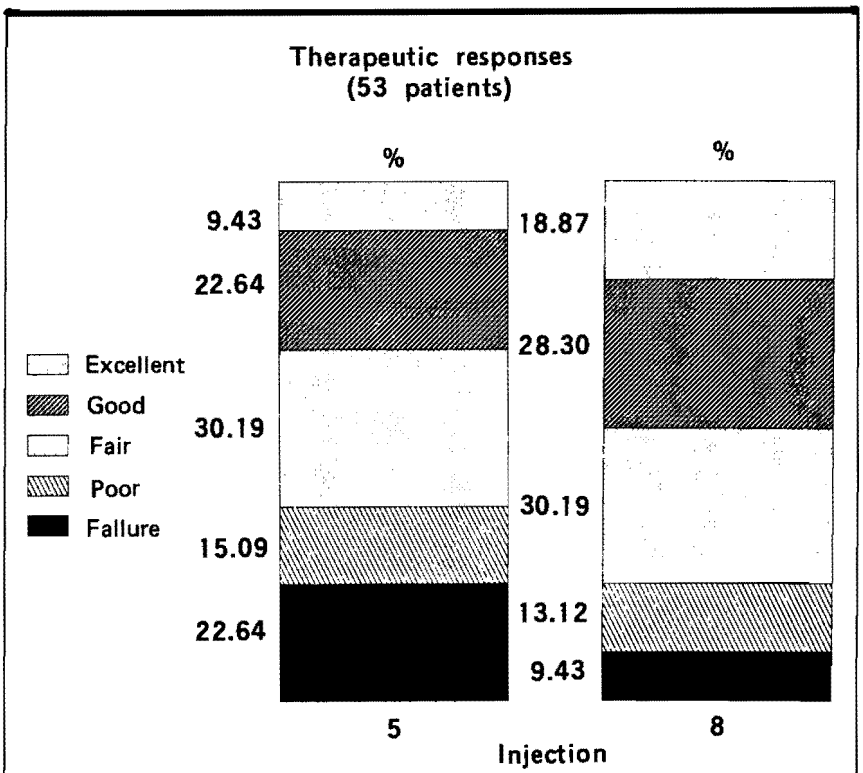

Fig. 1 Assessment global improvement after 5 and 8 injections.

Table 2. Serum levels of Igs G, A, M and E before and after Allerglobuline treatment.

	Serum Ig levels		
	Pre–treatment	Post–treatment	P
Ig G (92–207 IU/ml)	192.56 ± 47.43	201.56 ± 58.67	NS[1]
Ig A (54–268 IU/ml)	161.71 ± 68.18	159.65 ± 68.17	NS[1]
Ig M (99–322 IU/ml)	319.31 ± 133.87	282.81 ± 130.97	NS[1]
Ig E (14–26 IU/ml)	692.61 ± 934.32	340.40 ± 486.54	$< 0.001^{2}$,*

1 = Student's *t*–test, 2 = Wilcoxon and Mann–Whitney Match Pair test
* significant difference, NS–not significant difference.

Table 3. Comparison of the serum Ig Levels between the "satisfactory response" (grade I–III) and "unsatisfactory response" (Grade IV–V) groups.

Tharapeutic Responses	Ig G		Ig A		Ig M		Ig E	
	Pre Rx	Post Rx	Pre Rx	Post Rx	Pre Rx	Post Rx	Pre Rx	Post Rx
Grade I–III	188.51 ± 59.34	199.43 ± 59.34	165.81 ± 66.63	171.77 ± 71.43	310.70 ±131.02	278.51 ±135.63	571.40 ±818.13	275.79 ± 424.53
GradesIV–V	206.18 ± 61.37	208.73 ± 58.54	147.91 ± 74.77	118.91 ± 33.20	348.27 ± 145.73	297.27 ± 118.72	1100.36 ± 1206.67	556.81 ± 630.47
p[1]	NS	NS	NS	0.01	NS	NS	NS	NS

[1]Wilcoxon and Mann–Whitney Match Pair test
NS = Not significant difference

because of side effect. This patient was a female aged 34 years old, who used to have skin rashes occasionally before being included in this study and after the 3rd injection she developed a skin rash and myalgia for a few days. Since the event was mild and might be just co-incidental, the 4th injection was given; when the skin rash occurred again this case was withdrawn.

DISCUSSION

There are various schedules for giving Allerglobuline treatment, our study has demonstrated that the 8-time injection schedule gave more favorable results than the 5 time schedule.

By grading the therapeutic responses of the patients and classifying them into 2 groups, i.e. the "satisfactory response" group and "unsatisfactory response" group, we were unable to reveal any difference in the immunologic characteristics of the patients between these two groups. Therefore, we could not use the serum levels of any type of immunoglobulins as a criterion to select the patient who will be benefit from Allerglobuline treatment.

In Thailand, there have been another two studies concerning the effect of Allerglobuline injection.

Table 4. Adverse experiences reported in 64 patients.

Local pain : mild	22
: moderate	8
Local inflammation	7
Fever	7
Drowsiness	2
Others	4
(Rash, myalgia after 3rd and 4th injection---->withdrawal	1

(Dr. P. Phanuphak, personal communication), the second study was done cation), the second study was done in older children and adults.[13] Both

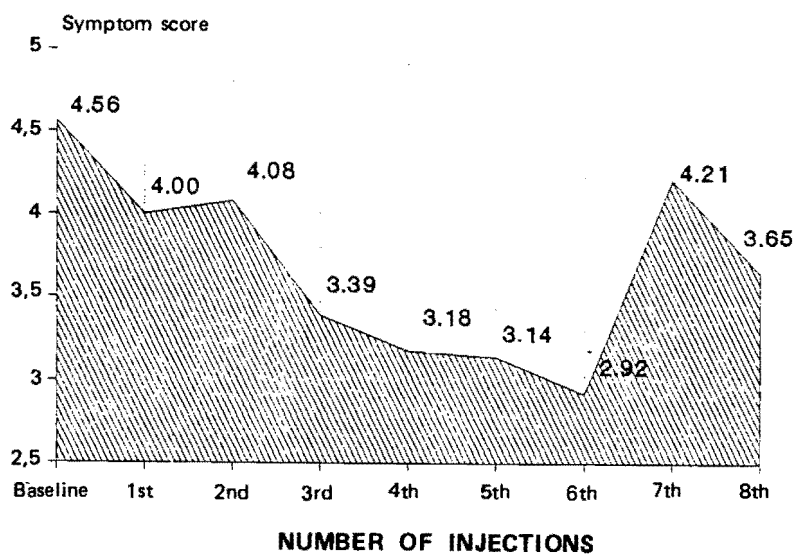

Fig. 2 Average nasal symptom scores at each follow up visit in 15 patients

studies included only allergic patients but the injection schedule was different. Summary and comparison of these two studies with our study is shown in Table 5. Regardless of the differences in many aspects of these three studies, surprisingly the therapeutic results were very similar.

Three possible mechanisms of action of Allerglobuline were already cited earlier. In this study we have demonstrated that the serum level of total IgE decreased significantly after treatment. Thus, at least one of the possible mechanisms of action of Allerglobulin which is associated with IgG_1 was confirmed. The level of IgG_4 blocking antibodies to some common allergens should also be measured in order to ascertain other mechanisms of action of Allerglobuline. Such assays are being planned in our laboratory and will be reported in the near future.

Table 5. Summary and comparison of three studies on Allerglobuline injection performed in Thai patients

	S. Wongsa–thuaytbong	P. Phanuphak et al	C. Bunnag et al
Age (yr)	9–60	2–11	13–60
Allergic rhinitis	10	31	61
Asthma	15	27	22
Chronic urticaria	4	–	2
Atopic eczema	1	9	–
Allergic conjunctivitis	–	11	2
Sinusitis	–	–	16
Rhinopharyngitis	–	–	8
Nasal polyp	–	–	5
Total patients	30	31	64
Dosage regimens			
Adults	10 ml IM q 5 d. x 4 then q 7 d. x 4		10 ml IM/wk x 5 then 10 ml IM/mo x 3
Children	5 ml IM	5 ml IM/wk x 5	5 ml (< 14 yr)
Effectiveness	AR 70% Asthma 53.3% Skin 100 %	69–70% (less for nasal symptoms)	5 times 62% 8 times 77%
Responder			
Pre–treatment		Low Ig G, High Ig E	
Post–treatment	Ig G↑	Low Ig G, Ig E ↓	Ig E ↓

Evidence supported by many reports from the Western hemisphere and also three reports in Thai patients are proposed as justification enough to conclude that Allerglobuline injection has therapeutic and immunologic effects in ENT patients suffering from both allergy and infection of the upper respiratory tract. The side effects are mild and tolerable. It could be regarded as an addition to the conventional medical treatment already given to the patient if satisfactory response is not achieved.

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