

Treatment of hay fever by Allerglobuline: a randomized double-blind study

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Summary

Eighty patients suffering from documented hay fever have been entered in a double-blind randomized study with the purpose of evaluating the efficacy of Allerglobuline®, a 10% human immunoglobulin preparation of placental origin, in the treatment of hay fever. The placebo was a 10% human albumin solution. The treatment started 6 weeks before the customary onset time of the clinical symptoms. It included a course of ten pre-seasonal intramuscular injections, with 1 vial (5 ml) given twice a week, and followed by a booster injection of 1 vial on 15 June and 30 June during the grass pollen season.

As the two groups of patients were similar, it was possible to demonstrate a significant symptomatic relief of rhinitis and conjunctivitis in the treated group, compared with the control group ($P < 0.0001$), and an improvement of the respiratory symptoms. Symptomatic improvement was already apparent at the onset of the pollen season and persisted during the following weeks. An appreciable reduction in the consumption of antihistamines could also be shown ($P < 0.0001$). Furthermore, a lesser increase in the total IgE level and in the specific cereal and grass pollen RAST could be demonstrated. This treatment can be seriously considered for the management of severe pollen allergy, particularly in those cases that show a poor response to immunotherapy.

Introduction

In 1961, Halpern and Frick's experimental work proved that immunoglobulin G (IgG) exhibits a competitive action with the sensitizing antibodies at the level of cell receptors [1]. At the same time, a 10% IgG preparation of human placental origin, Allerglobuline® (Institut Mérieux, Lyon, France), was launched for the treatment of the allergic condition. The batches were selected on their capacity to protect guinea-pigs against

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passively induced anaphylactic shock. Several mechanisms of action were suggested to account for this protective role. IgG could impede IgE binding on an IgE Fc receptor, as advocated by Halpern and Frick [1]. Another possible explanation was that IgG could act on released histamines, as reported by Parrot *et al.* [2]. IgG could eventually be partially aggregated and activate complement, and eventually reduce anaphylactic reactions [3].

Recently, allergen-specific IgG profiles were analysed from various batches of Allerglobuline, using an immunodot technique (unpublished data). It was concluded that samples contain a variety of specific IgGs that could act as 'blocking' antibodies against various allergens, in particular various pollens. The ratio between the amount of pollen-specific IgG in the preparation, at a 1/500 dilution, and a standard serum pool is about 3:1. The concentration of pollen-specific antibodies is about 25 µg IgG/ml in the non-diluted samples. Moreover, using a standardized basophil degranulation test [4], Allerglobuline exhibited a strong inhibition of cell degranulation, induced by cereal and grass pollens extract.

Previous clinical trials have demonstrated the therapeutic benefit of Allerglobuline injections in the treatment of children and young adults with asthma, allergic rhinopharyngitis, allergic conjunctivitis, hay fever and atopic eczema [5]. However, except in the latter, most of these studies were not controlled, and clearly warranted confirmation by prospective double-blind randomized trials. Considering the amount of pollen-specific antibodies and their blocking effect *in vitro*, we have conducted a double-blind, randomized trial to assess the clinical efficacy of Allerglobuline in the treatment of hay fever.

Subjects and methods

This study was conducted in Geneva between 3 May and 15 July 1986. According to pollen counts performed in the country, the cereal and grass pollen season was of middle to high severity. Although the season started rather late (6–8 June), there were three important peaks in June.

Eighty patients were included, forty men and forty women, aged 18–47 years (mean $\pm$ s.d. = 29.7 ± 8.96 years), who had all experienced hay fever for at least 2 years. The duration of their past history was 9.76 ± 5.44 seasons (mean $\pm$ s.d.). In all cases there was a family history of atopic disease. In fifty-four of them there were clinical signs of seasonal allergic rhinitis and conjunctivitis; the other twenty-six cases suffered from seasonal allergic rhinitis, conjunctivitis and mild asthma. Rhinitis was always middle to severe.

Total IgE was determined by PRIST, a non-competitive binding assay (IgE RIA, Pharmacia, Sweden) according to the manufacturer's instructions. All the subjects had high IgE levels. Skin-prick tests (using extracts from Stallergenes, Fresnes, France) and RASTs (Phadebas RAST, Pharmacia) were strongly positive for cereal and grass pollens. Sensitivity to other allergens (house dust mite, animal, tree pollen) did not exclude the patients.

Patients receiving immunotherapy and those showing associated serious asthma, infectious conditions or organic disease had been excluded, as well as subjects who had a history of allergic response to blood derivatives.

Each patient gave full informed consent before being assigned in a double-blind manner, with a randomized coding scheme, to receive one of the two following

preparations (Institut Mérieux, Lyon, France): (i) Allerglobuline, a 10% immunoglobulin preparation of placental origin, in 5-ml vials, or (ii) placebo, a 10% human albumin solution in 5-ml vials.

Treatment started 6 weeks before the customary time of onset of clinical signs. It included a series of ten injections of one vial: one injection twice a week in May, followed by a booster injection around 15 and 30 June. Forty patients received Allerglobuline and forty others the placebo. All were examined before entering the study and then in the course of each successive visit required for the different injections. At the end of May a daily diary was handed over to each of them to record the major symptoms observed, the medicine consumption [the additional symptomatic medication was exclusively antihistamines: Teldane® (Merrell, Zurich, Switzerland) and a collyrium Spersallerg® (Dispersa, Heltingen, Switzerland)] and the possible side-effects. A final medical visit was completed for each patient between 10 July and 15 July, in order to perform the scheduled check-up and to collect the daily diaries filled in by each participant.

Each observation was defined by means of a group of criteria in relation to ocular (irritation, tears, itching eyes), otorhinolaryngological (sneezing, runny nose, nasal obstruction) or respiratory (coughing, dyspnoea, expectoration) symptomatology with a severity index: no symptom = 1, discreet = 2, medium = 3, important = 4. Any trouble in daily life was also recorded as follows: no trouble = 1, mild = 2, medium = 3, serious = 4. All these data enabled the establishment of a set of weekly scores and a global profile for the illness in both its preseasonal phase and its pollinic phase.

Blood samples were collected at the end of the trial (15 July) to determine serum IgE levels and RAST for cereal and grass pollens. The samples collected before and after the study were tested together at the end, with the same reagents.

Statistical analysis

Student's *t*-test was used to compare quantitative data (score for each symptom for 4 weeks, number of antihistamine tablets and IgE levels). Analysis of variance allowed the comparison of time-related evolution between the two groups. The qualitative data related to the number of subjects with class 4 RAST were evaluated with the Chi-square test.

Results

The two groups of patients were initially similar, according to the duration of allergic history, severity of the rhinitis, IgE levels, RAST and skin tests (Table 1).

Since the onset of the pollinic phase, striking differences in clinical symptoms appeared between the two groups, especially during the sixth and seventh weeks of treatment. Nasal (Fig. 1a) and ocular (Fig. 1b) symptoms dramatically decreased in treated patients compared with controls and the difference was highly significant ($P < 0.0001$). An improvement in respiratory signs was also demonstrated (Fig. 1c) in the treated group, although it was less pronounced ($P < 0.04$).

Trouble in daily life was milder in the treated group compared with controls ($P < 0.0001$) (Fig. 2).

The clinical evaluation at the end of the study confirmed the preceding results. Data obtained from the daily diary showed favourable or highly favourable results in 85% of the treated group for rhinitis and 87% for conjunctivitis, *versus* 20% and 40%, respectively, in the placebo group ($P < 0.0001$). Concerning respiratory symptoms,

Table 1. Characteristics of the patients

	Allerglobuline (n=40)	Placebo (n=40)	Probability*
No. patients with allergy history in the family	40	40	
Duration of the past history (seasons) mean $\pm$ s.d.	8.75 $\pm$ 4.92	10.78 $\pm$ 5.80	P=0.09
No. patients			
With rhinitis and conjunctivitis	26	28	P=0.63
With rhinitis, conjunctivitis and asthma	14	12	P=0.63
IgE (IU/ml) mean $\pm$ s.d.	298 $\pm$ 189	239 $\pm$ 113	P=0.087
No. patients with RAST to pollen class 3	14	21	P=0.12
No. patients with RAST to pollen class 4	26	19	P=0.12
No. patients with strong positive cereal and grass pollen skin test	40	40	

* Quantitative results were analysed by Student's *t*-test. Qualitative results were compared by the Chi-square test. No significant results were found.

good or very good results were seen in 60% of the Allerglobuline group *versus* 22% with the placebo. Moreover, treated patients took less antihistamines during the pollen season than the controls: mean $\pm$ s.d. = 4.27 $\pm$ 4.21 *versus* 10.49 $\pm$ 4.15 tablets a week, respectively (Fig. 3). This difference is highly significant ($P < 0.0001$) and corresponds

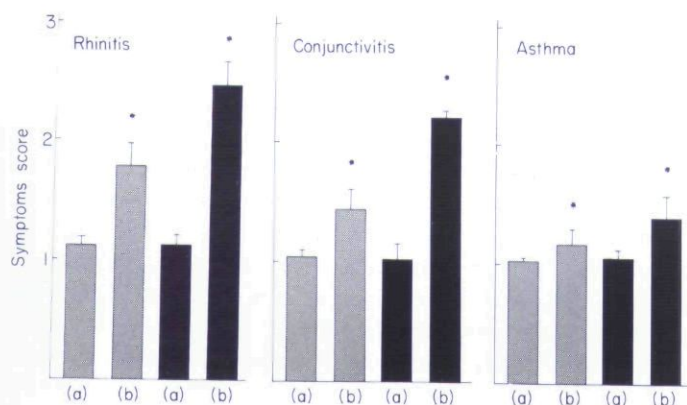


Fig. 1. Mean score of nasal ocular and respiratory symptoms in (■) Allerglobuline- and (■) placebo-treated patients. Data represent the mean $\pm$ 2 s.e.m. (a) Pre-season symptomatology (weeks 1,2,3,4), (b) pollen season (weeks 5,6,7,8). Results were analysed using Student's *t*-test: rhinitis, $P < 0.0001$; conjunctivitis, $P < 0.0001$; asthma, $P < 0.04$.

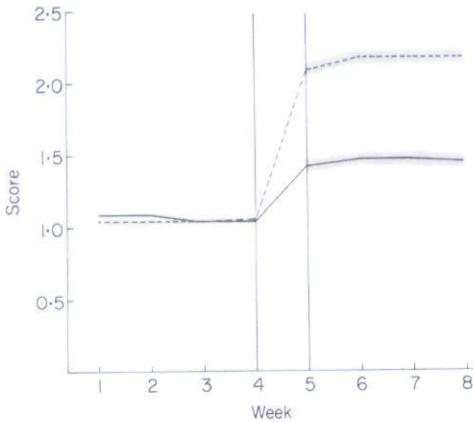


Fig. 2. Score of trouble in daily life before (fourth week) and during the pollen season in (—) Allerglobuline- and (---) placebo-treated patients. The shaded area represents ± 2 s.e.m. calculated from the residual variance. The analysis of variance was used to compare the two groups in the pre-season period and during the pollen season. The difference is very significant during the pollen season (weeks 5–8), $P < 0.0001$.

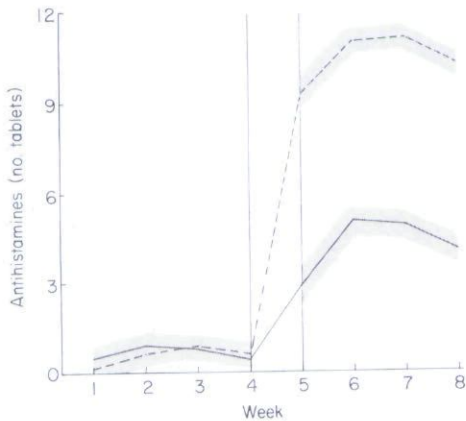


Fig. 3. Use of antihistamines as adjunctive therapy: an increase of antihistamines use is observed in both groups from the fifth week. Thirteen patients treated with (—) Allerglobuline (32%) have increased their daily consumption of tablets to five or more *versus* thirty-seven (92.5%) in the placebo group (---). The shaded area represents ± 2 s.e.m. calculated from the residual variance. The difference is assessed by analysis of variance on the two groups during the two periods, $P < 0.00001$.

to a 41% reduction in drug consumption. (The mean consumption in the two groups, in the pre-season period, was not significantly different.)

Concerning the biological parameters, the increase in serum IgE level after the pollen season was of 96 ± 63 IU/ml for the placebo group, compared with 35 ± 63 IU/ml for the treated group. The difference is statistically highly significant using Student's paired *t*-test ($P = 0.0002$). The comparative analysis of the specific RAST also showed some differences. The pre-season results in the placebo group showed nineteen subjects

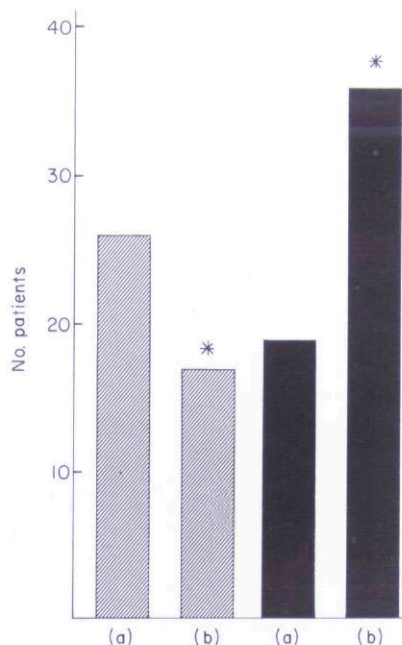


Fig. 4. Number of patients with a class 4 cereal and grass pollens RAST result. (a) Pre-season RAST (weeks 1,2,3,4), (b) pollen season RAST (weeks 5,6,7,8). (▨) Allerglobuline, (■) placebo. The comparison was carried out with the Chi-square test, $P < 0.0001$.

(47.5%) with a class 4 result, twenty-six (65%) in the treated group ($P = 0.11$). At the end of the pollen season, in the Allerglobuline group, only seventeen subjects were counted in class 4 (42.5%) *versus* twenty-six in the placebo group (90%) (Fig. 4). The difference is highly significant ($P < 0.0001$). Furthermore, following treatment, the change from class 3 to class 4, which is indicative of an increased sensitivity, was observed in three subjects from the Allerglobuline group (7.5%) and in seventeen from the placebo group (42.5%).

Discussion

Our report demonstrates the therapeutic effect of Allerglobuline in the treatment of hay fever. The injections were well tolerated although local pains were noticed in ten patients (*vs* two in the placebo group) and a minor general reaction in two patients (compared with one in the placebo group). The efficacy was assessed by the improvement in the daily life with a reduction of symptom scores by 50% for rhinitis, 66% for conjunctivitis and 56% for asthma. Moreover, during the pollinic season, treated subjects took 41% less antihistamines than controls.

This study confirms the results obtained by others in the treatment of seasonal allergic rhinitis [6].

Although the precise mechanism of action of Allerglobuline is not yet demonstrated, it could act by 'blocking' antibodies since it contains a wide range of grass and tree pollens antibodies as well as many allergen-specific IgGs, including house dust mite, epithelia and moulds. *In-vitro*, this product exhibits a 60–70% inhibition of allergen-induced basophil degranulation.

The blocking role of IgG is well documented in atopic patients undergoing immunotherapy to insect venom and pollen. The clinical improvement has been linked to a rise in IgG antibodies [7,8] or, according to Zeiss *et al.* [9], to a change of the ratio between blocking and IgE antibody. Because some allergen molecules are not intercepted and bound, some patient symptoms persist in varying degrees [10]. This could explain the partial reduction (50%) of symptom scores in our patients.

The passive supply of different IgG subclasses could also account for the clinical response: IgG4 antibodies may play an important role in the protection of an individual against allergy, especially when antigenic exposure is chronic [11]. IgG4 could interfere with IgE as a 'blocking' antibody or by inhibiting IgE binding to specific receptors on the cell surface. IgG4 may also function as a short-term anaphylactic antibody [12,13], in particular in patients with IgM antiglobulin [14].

Turning to the role of IgG1 antibodies, it has been reported that, in addition to their blocking effect [8], they may take part in suppression of the IgE antibody response [15]. Only IgG1 antibodies (not IgG4) have this capacity due to their cytophilic characteristics. Moreover, several studies have documented that long-term immunotherapy results in a blunting of the expected IgE antibody response [16,17]. Our results show that administration of Allergoglobuline also induces an inhibition of the expected rise in total and specific IgE, suggesting an immunoregulatory role of the IgG1 antibodies of the preparation. Although the amount of pollen-specific IgG1 antibodies is not known, it is probably high since IgG1 subclass represents 84% of the total IgG. However, whether the decrease of IgE levels, compared with controls, could explain the clinical improvement is still a controversial subject since the decrease in IgE levels is not always correlated with symptom relief, nor the IgE titre to symptom severity [18].

Another point to be noticed is that Allergoglobuline is produced from placental blood. Rigal and Babouin-Jobert [19] demonstrated that placental IgG could inhibit *in vitro* the IgE synthesis of lymphocytes from atopic patients, whereas plasmatic IgG could not. Moreover, Jarrett [20] showed that maternal antibodies could induce a rise of IgG responsiveness to the antigen and a profound IgE suppressive effect in the newborn, which persists into adult life. It could be suggested that the underlying mechanism of control could be linked to qualitative rather than quantitative characteristics of IgG related to specificity of antibody, presence of anti-idiotypic antibodies, or co-fractionated immunoregulatory factors similar to those found in colostrum [21].

References

- 1 Halpern BN, Frick OL. Protection against fatal anaphylactic shock with γ -globulins in guinea pigs and mice. *J Immunol* 1962; 88:683-9.
- 2 Parrot JL, Laborde C, Saindelle A. The allergic terrain. *Ann Allergy* 1964; 22:511-26.
- 3 Osler G, Hawrisiak MM, Ovary Z, Siqueira M, Bier OG. Studies on the mechanism of hypersensitivity phenomena. *J Exp Med* 1957; 106:811-34.
- 4 Sainte Laudy J. Standardization of basophil degranulation for pharmacological studies. *J Immunol Method* 1987; 98:279-82.
- 5 Pons-Guiraud A. Intérêt de l'Allergoglobuline® dans le traitement de la dermatite atopique de l'enfant et de l'adulte jeune. Etude randomisée en double aveugle. *Rev Med Interne* 1986; 7:537-42.
- 6 Grillat JP, Herman D. Effets cliniques d'immunoglobulines anti allergènes ayant un titre élevé en anticorps spécifiques IgG pour le traitement des allergies aux pollens de graminées. *Rev Fr Allergol* 1984; 24:121-5.

- 7 Golden DBK, Meyers DA, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Clinical relevance of the venom-specific immunoglobulin G antibody level during immunotherapy. *J Allergy Clin Immunol* 1982; 69:489-93.
- 8 Moss RB, Hsu YP, Kwasnicki JM, Sullivan MM, Reid MJ. Isotypic and antigenic restriction of the blocking antibody response to rye grass pollen: correlation of rye group I antigen-specific IgG1 with clinical response. *J Allergy Clin Immunol* 1987; 79:387-98.
- 9 Zeiss CR, Metzger WJ, Levitz D. Quantitative relationships between IgE antibody and blocking antibodies specific for antigen E in patients given immunotherapy with ragweed antigen E. *Clin Exp Immunol* 1977; 28:250-5.
- 10 Patterson R, Grammer LC, Shaughnessy MA. Immunotherapy: parameters of assessment. *J Allergy Clin Immunol* 1985; 76:394-7.
- 11 Aalberse RC, Van Der Gaag R, Van Leeuwen J. Serologic aspects of IgG4 antibodies. Prolonged immunisation results in an IgG4 restricted response. *J Immunol* 1983; 130:722-6.
- 12 Hindocha P, Wood CBS. Histamine release from human leucocytes by IgG4 subclass in the sera of allergic children. *Allergy* 1985; 40:523-8.
- 13 Gwynn CM, Almosawi T, Stanworth DR. Clinical associations with serum allergen-specific IgG4 antibodies. *Clin Allergy* 1982; 12:459-64.
- 14 Shakib F, Marrowbrown H, Phelps A, Redhead R. Detection of an IgM antiglobulin in the sera of atopic patients using insolubilized IgG4, and its capacity to release histamine from leucocytes. *Int Arch Allergy Appl Immunol* 1986; 79:349-56.
- 15 Djurup R. The subclass nature and clinical significance of the IgG antibody response in patients undergoing allergen specific immunotherapy. *Allergy* 1985; 40:469-86.
- 16 Ishizaka K, Ishizaka T. Mechanisms of reaginic hypersensitivity and IgE antibody response. *Immunol Rev* 1978; 41:109-48.
- 17 Creticos PS, Metre TE, Mardiney MR, Rosenborg GL, Norman PS, Aadkinson NF. Dose response of IgE and IgG antibodies during ragweed immunotherapy. *J Allergy Clin Immunol* 1984; 73:94-104.
- 18 Nickelsen JA, Georgitis JW, Reisman R. Lack of correlation between titers of serum allergen-specific IgE and symptoms in untreated patients with seasonal allergic rhinitis. *J. Allergy Clin Immunol* 1986; 77: 43-8.
- 19 Rigal D, Babouin-Jobert M. Immunomodulation induced by immunoglobulins. I. Action of placental immunoglobulin on in vitro spontaneous production of IgE in man. Poster. Joint Meeting Swiss Soc Allergology, French Soc Immunology, French Soc Allergology, Genève, 23-25 April 1987.
- 20 Jarrett EEE. Perinatal influence on IgE responses. *Lancet* 1984; ii:797-9.
- 21 Sarfati M, Vanderbeeken Y, Rubio-Trujillo M, Duncan D, Delespesse G. Presence of IgE suppressor factors in human colostrum. *Eur J Immunol* 1986; 16:1005-8.

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