

Anti-IgE- and anti-IgA-induced eosinophil migration in atopics and healthy volunteers

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Introduction

It is currently accepted that IgE plays a major role in allergy, and this is probably the reason why so many works are devoted to the regulation of synthesis of this antibody and to the Fc_ϵ receptors of different affinities present on a variety of cells possibly involved in allergic inflammation [1–9].

IgA is also suspected to play a role in allergy, although this role remains rather obscure. Nevertheless, high serum IgA antibodies were found in some subjects sensitive to ragweed or mite [10–12] and in patients presenting with an allergic bronchopulmonary aspergillosis [13–15]. The same immunoglobulin was demonstrated in the nasal secretions from ragweed and grass-pollen sensitive subjects as well as in the sputum from asthmatics [12,16,17]. Fc_α receptors were also shown on several cells playing a key role in allergic inflammation, such as T lymphocytes, monocytes and polymorphonuclear cells [7,18,19].

It has been demonstrated that IgA-containing immune complexes are able to stimulate neutrophils to produce O_2 -derived free radicals *in vitro* and can induce acute lung injury *in vivo* in the rat [21]. Moreover, it is possible to induce degranulation of human eosinophils with IgA challenge *in vitro* [21]; finally it has been shown that IL-5, which is known for its stimulating effect on the colony formation of eosinophils is able to enhance the production of IgA by stimulated B cells [23,24].

The triggering effect produced by an antigen on target cells such as mast cells and basophils has been studied extensively in the past 20 years and, since then, the allergic reaction has often been presented as a cascade of events starting from a well-defined cell, the mast cell, which is considered to be an obligatory first step in the sequence.

In the past few years, more attention has been paid to the late and delayed reactions and, more especially, to the cells and mediators that could play a specific role in the development of such late phenomena. The description by de Monchy *et al.* [25] of a close correlation between the presence of eosinophils and eosinophil cationic protein (ECP) in the bronchoalveolar lavage (BAL) fluid of asthmatic patients presenting a dual reaction after antigen

challenge, drew the attention to this polymorphonuclear cell the mediators of which are numerous and possibly toxic [25–30].

The recruitment of eosinophils after antigen challenge in atopic subjects was described by Eidinger *et al.* [31] some 30 years ago on the dermis. Since then, the phenomenon has been confirmed several times in different sites using different techniques [32–37].

It was also demonstrated that formyl methionyl phenylalanine (fMLP) and platelet activating factor (PAF) could induce a similar recruitment of eosinophils in atopic skin *in vivo* and, interestingly, Henocq and Vargaftig [38] showed that the stimulus (PAF and fMLP) was followed by the recruitment of eosinophils only in atopic subjects when compared to healthy subjects. This fact suggests that allergic eosinophils present an abnormally high sensitivity to the chemotactic factors.

This fact prompted us to investigate the effect of a skin challenge carried out with either anti-IgE or anti-IgA in both healthy and atopic subjects. The questions were: do these two different challenges induce similar immediate weal-and-flare reactions, and are these two challenges followed by similar recruitment of eosinophils? In the case of significant eosinophil migration, is the phenomenon inhibited by H_1 blockade?

Materials and methods

Ten healthy volunteers, nine males and one female, aged 18–36 years (mean $\pm$ s.d.: 25.2 ± 5.5) and ten atopic volunteers, nine males and one female, aged 21–34 (mean $\pm$ s.d.: 29.9 ± 3.8) agreed to enter the anti-IgE study. They were duly informed about the experimental design and the materials and drugs used and gave their written consent.

Ten healthy volunteers, eight males and two females, aged 19–26 years (mean $\pm$ s.d.: 23.1 ± 2) and ten atopic subjects, five males and five females, aged 18–31 years (mean $\pm$ s.d.: 23.9 ± 3.3) entered the anti-IgA study. They were also informed about the experimental conditions and the drugs used and gave their written consent. The study was approved by the Ethical Committee of Braine-l'Alleud, Waterloo Hospital, Belgium.

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The healthy subjects had no history of allergy and their grass pollen skin tests were negative. The atopic subjects were grass-pollen sensitive with a typical history of allergic rhinitis during the pollen season and a positive weal response 15 min after a prick test with pollen extract (100 i.r.).

Reagents

The following solutions were used for the skin challenge:

(i) anti-IgE: goat anti-human IgE (G.A.H.U., Nordic Immunology, Tilburg, The Netherlands), solution of 0.0002 mg/ml, and (ii) anti-IgA: rabbit anti-human IgA (Cappel, Organon Teknika Corporation, West Chester, U.S.A.), solution of 0.01 mg/ml.

Drugs

Cetirizine dihydrochloride 10 mg, presented as opaque gelatin capsules, and terfenadine 60 mg presented in identical capsules, were given b.d. for 4 days under double-blind, cross-over, randomized conditions.

In order to verify whether the bioavailability of encapsulated, pulverized terfenadine was similar to that of the marketed form, a preliminary clinical pharmacology study was performed in 10 healthy volunteers, which demonstrated that capsules and tablets were

equally effective in inhibiting the skin reactivity to histamine (prick method with two concentrations of histamine: 10 and 100 mg/ml) at 2, 4, 6 and 8 hr after a single oral administration of the two presentations, and at 24 and 120 hr after a more prolonged administration of the recommended dose (Fig. 1).

Cetirizine dihydrochloride 10 mg was given b.d. for 4 days in tablet form. The placebo, presented as identical tablets, was given in the same way under double-blind, cross-over, randomized conditions.

The cutaneous challenge tests took place on the third day of drug administration. An interval of at least 2 weeks was arranged between each experimental day.

Cutaneous tests

Small amounts of anti-IgE and anti-IgA solutions were injected into the skin of the forearm of the volunteers (approximately 20 μ l, i.e. an amount just sufficient to induce the appearance of a limited dermal button).

Weals and erythemas were outlined on the skin 15 min after intradermal (i.d.) injections and transferred onto transparencies. The area of each reaction was measured by a computerized planimetry system described earlier [39].

The migration of the eosinophils, neutrophils and monocytes 24 h after anti-IgE and anti-IgA challenge was evaluated by the modified skin window technique already described [54]. Results were expressed as percentages of cells.

Statistical analysis

Mean percentages of neutrophils, monocytes and eosinophils and standard deviations were calculated, as well as mean weal and flare areas $\pm$ s.d.

Multivariate analyses of variance for repeated measurements were performed. The replications were, respectively, the data obtained under control conditions, under cetirizine and terfenadine, or under placebo. Pairwise contrasts were used to establish differences between control and treatment conditions. Values were accepted as statistically significant at $P < 0.05$.

Results

Weals and erythema

Anti-IgE. Under control conditions, the size of the anti-IgE-induced weals and erythemas were very similar in both healthy and atopic subjects (Table 1). Cetirizine was better than terfenadine in inhibiting these reactions.

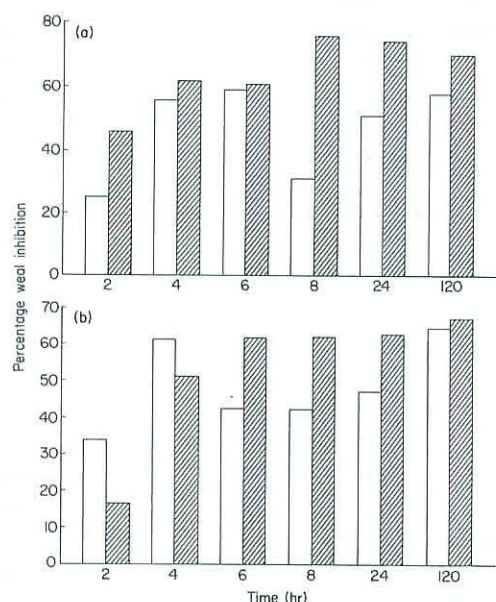


Fig. 1. Inhibition by terfenadine 60 mg tablets (□) and capsules (▨) of the skin reactivity to histamine ((a) 10 mg/ml; (b) 100 mg/ml) in 10 healthy subjects. Results expressed as percentage of pre-treatment values. Measurements were performed 2, 4, 6 and 8 hr after single intake of 60 mg and at 24 and 120 hr during chronic administration.

Table 1. Mean weal-and-flare areas 15 min after anti-IgE challenge, under control conditions and after a 4-day treatment with cetirizine and terfenadine, in healthy subjects and atopic subjects

				Statistical significance*		
	Control	Cetirizine (C)	Terfenadine (T)	C vs. control	T vs. control	C vs. T
Healthy subjects						
Weals	97.4 ± 51.1	51.2 ± 27.8	70.3 ± 41	0.03	0.23	0.9
Flares	1063 ± 552	205 ± 114	469 ± 509	0.0006	0.03	0.09
Atopic subjects						
Weals	106.3 ± 56	49.9 ± 30.7	77.5 ± 26.4	0.02	0.07	0.07
Flares	914 ± 526	194 ± 144	228 ± 173	0.003	0.002	0.64

Results expressed in mm²: means ± s.d.

* Orthogonal contrasts following the analysis of variance.

P > 0.1 = not significant. Trend: P < 0.01 > 0.05.

Anti-IgA. The weals induced by anti-IgA were similar in both healthy volunteers and atopic subjects. The erythema induced by anti-IgA was not as large as that induced by anti-IgE and differed from one subject to another. H₁ blockade by cetirizine did not modify the anti-IgA-induced weals. The erythematous area was much smaller after cetirizine, but the difference compared to the controls under placebo was not significant due to the marked inter-individual differences (Table 2).

Leucocyte migration

Anti-IgE. The cellular response was studied 24 hr after challenge under control conditions and on the fourth day of treatment with cetirizine and terfenadine.

This response in healthy subjects consisted of mainly neutrophils and monocytes, with very few eosinophils. This pattern of cells was not significantly affected by either cetirizine or terfenadine (Table 3).

In atopic subjects, there was a significant accumulation of eosinophils, with a concomitant decrease in neutrophils (Table 3). Cetirizine significantly inhibited the accumulation of eosinophils while terfenadine induced a non-significant decrease of these cells.

Anti-IgA. In the healthy subjects, the cellular response 24 hr after anti-IgA challenge mainly consisted of neutrophils and monocytes while the percentage of eosinophils was low throughout, especially in the controls (Table 4).

In the atopic subjects, the cellular response at 24 hr was very similar to that of healthy subjects as regards neutrophils and monocytes. The percentage of eosino-

Table 2. Mean weal-and-flare areas 15 min after anti-IgA challenge under control conditions and after a 4-day treatment with cetirizine and placebo in healthy subjects and in atopics

	Control	Placebo	Cetirizine
Healthy subjects			
Weals	68.3 ± 30.8	79.3 ± 39.6	86.5 ± 26.9
Flares	404.5 ± 312.5	443.2 ± 611.8	82.8 ± 97.6
Atopic subjects			
Weals	97.6 ± 65.8	89.4 ± 41	72.5 ± 30.9
Flares	346.5 ± 341.4	373 ± 365	85.6 ± 113

Results expressed in mm²: mean ± s.d.

No statistical difference between the three groups.

phils was significantly higher in the controls and under placebo when the atopic subjects were compared to healthy volunteers ($P=0.0001$ and $P=0.001$, respectively) (Table 5).

H₁ blockade by cetirizine did not influence the mean percentages of eosinophils, neutrophils and monocytes.

Late phase reactions (LCRs)

Anti-IgE study. Most of the atopic and non-atopic volunteers presented similar LCRs at 6–24 hr after challenge. These reactions, which were above all erythematous, were limited to the area of the immediate

Table 3. Mean % ($\pm$ s.d.) of neutrophils (N), eosinophils (EO) and monocytes (M) 24 hr after anti-IgE challenge of healthy volunteers and atopic subjects under control conditions and during a 4-day treatment with cetirizine and terfenadine

	Control	Cetirizine	Terfenadine	P-value (control vs. treatment)
Healthy subjects				
N	66.1 $\pm$ 11.2	61.9 $\pm$ 20.8	55.8 $\pm$ 19.6	0.19
EO	2 $\pm$ 4	3.2 $\pm$ 4.1	1.7 $\pm$ 1.9	0.71
M	31.8 $\pm$ 9.9	34.8 $\pm$ 21.8	42.1 $\pm$ 19.7	0.22
Atopic subjects				
N	34.2 $\pm$ 15	39.7 $\pm$ 14.2	45.8 $\pm$ 18.1	0.41
EO	19.9 $\pm$ 8.1	10.8 $\pm$ 6.4*	14.5 $\pm$ 12.1	0.08
M	44.8 $\pm$ 10.1	49.4 $\pm$ 15.3	39.5 $\pm$ 14	0.49

* $P=0.03$: difference between cetirizine and control value: orthogonal contrast following the analysis of variance.

† Global difference between means.

$P>0.1$ = not significant. Trend = $P<0.1>0.05$.

Table 4. Mean % ($\pm$ s.d.) of neutrophils (N), eosinophils (EO) and monocytes (M) 24 hr after anti-IgA challenge of healthy volunteers and atopics under control conditions and during a 4-day treatment with cetirizine and a placebo

	Control	Placebo	Cetirizine	P-value (control vs. treatment)
Healthy subjects				
N	30.1 $\pm$ 27.5	27.9 $\pm$ 22.6	27.4 $\pm$ 16.9	0.97
EO	0.8 $\pm$ 1.5	3.2 $\pm$ 6.1	3.6 $\pm$ 2.0*	0.04
M	69.1 $\pm$ 27.4	69.0 $\pm$ 20.9	69.0 $\pm$ 16.5	1.0
Atopic subjects				
N	34.2 $\pm$ 20.5	30.7 $\pm$ 16.3	35.2 $\pm$ 14.8	0.73
EO	4.7 $\pm$ 5.4	6.3 $\pm$ 6.4	6.6 $\pm$ 7.8	0.29
M	61.9 $\pm$ 20.3	62.9 $\pm$ 17.7	58.1 $\pm$ 13.0	0.80

* $P=0.01$ difference between cetirizine and control conditions.

† Global difference between means.

No statistical difference between cetirizine and placebo conditions.

erythema, and were not significantly different under either placebo or cetirizine.

Anti-IgA study. Most of the atopic and non-atopic volunteers presented similar LCRs at 6–24 hours after challenge. These reactions were characterized by an

Table 5. Percentage of eosinophils after anti-IgA challenge in atopic subjects

Subjects	Control	Placebo	Cetirizine
1	<u>12.2</u>	6	0
2	0	0	0
3	3	0	0
4	2	6	3.6
5	<u>15</u>	<u>22.8</u>	<u>15.0</u>
6	4	<u>7.5</u>	<u>23.0</u>
7	0	5.8	0
8	2	8	5.3
9	0	3	10.0
10	0	4	<u>10.0</u>
$\bar{x}$	4.7	6.3	6.6
s.d.	± 5.4	± 6.4	± 7.8

Individual data. The abnormally high values are underlined.

erythema and a more or less marked oedema. These LCRs were not significantly modified by H_1 blockade. There was no correlation between the severity of the LCR and the percentage of eosinophils observed with the skin window test.

Discussion

These two clinical pharmacology studies carried out with healthy volunteers and atopic subjects where the skin was challenged with anti-IgE and anti-IgA showed marked differences between these two immunoglobulins especially when cellular recruitment is considered.

The anti-IgE challenge in atopic subjects was very similar to an antigen challenge since it was followed by an immediate weal-and-flare reaction, a slight late cutaneous reaction (LCR) 6–24 hr after challenge, and a significant recruitment of eosinophils as demonstrated by a modified skin window technique (between 7.5 and 35%, mean 19.9%). Interestingly, the healthy volunteers who presented very similar immediate reactions and LCRs did not show any significant recruitment of eosinophils (mean 3.4%).

Such an observation is in favour of an abnormally high activation state of the atopic eosinophils responding more easily to a given stimulus, and this is in accordance with several works which demonstrate the existence of eosinophil activation in allergic diseases both *in vitro* and *in vivo* [40–47].

It is possible that we could have induced a significant accumulation of eosinophils in healthy subjects by

increasing the amount of anti-IgE injected, but this remains to be investigated objectively. We have to take into consideration the fact that our volunteers presented only discreet LCRs probably because the challenge was rather weak. Nevertheless, it is possible that an anti-IgE-induced skin reaction in a healthy subject does not closely mimic a real allergic reaction induced by antigen challenge in atopic subjects, depending upon the experimental conditions. The possibility of provoking LCRs corresponding to different cell patterns is an interesting point that demonstrates that an organ (here the skin) has a limited morphological language for expressing different physiopathological conditions.

As can be seen from Table 2, H_1 blockade by cetirizine significantly inhibited this anti-IgE-induced migration of eosinophils, a result which is in accordance with previous studies performed with the same or with different techniques [48–50]. Terfenadine induced a less pronounced inhibition that was not statistically significant.

The immediate weals induced by anti-IgA challenge were very similar in healthy volunteers compared to those in atopic subjects. These reactions were also similar to those induced by an antigen or by anti-IgE challenge. In contrast, the anti-IgA-induced erythemas were significantly smaller and varied regularly from one volunteer to another, being absent in some cases.

While these anti-IgA-induced erythemas were obviously inhibited by cetirizine pre-treatment, the weals in both atopic and healthy volunteers were not affected at all by this potent H_1 blocker. Yet it may be observed from the data of the first study that the anti-IgE-induced weals were 50% inhibited in the two groups of volunteers taking the same H_1 antihistamine. Such a fact is surprising and it automatically raises the following questions: what is the target cell involved in an immediate weal reaction induced by anti-IgA challenge, and what are the mediators?

In all the experiments we have performed with cetirizine, we could show that the drug was markedly able to block the skin reactions (and especially the oedema) induced by histamine, methacholine, *Staphylococcus aureus* protein A, vasoactive intestinal polypeptide (VIP), kallikrein and PAF [39, 51–55]. Only the substance-P induced oedema was poorly affected by cetirizine and we wonder if an anti-IgA challenge could be followed by a local release of such a neuromediator.

Another possibility is the release of mediators from the eosinophils which are known to bear Fc_ϵ receptors [7]. Nevertheless, there are very few eosinophils in the normal skin and it is perhaps not wise to propose that the challenge of a few cells is sufficient to induce the rapid development of a local oedema. Furthermore, other cells, the T cells and the macrophages which might be more numerous in the skin, also bear Fc_ϵ receptors. It is thus

possible to imagine that the anti-IgA acute reaction involves on the one hand several cell types and, on the other, several mediators, the activities of which are not influenced by H_1 blockade.

Finally, interference with the complement system cannot be excluded, even if it is a subject of controversy. One must recall that several reports showed that IgA does not fix complement [56,57] but, on the other hand, some workers also showed that S IgA has the potential sites needed for interaction with complement, depending upon the experimental conditions [58,59].

We must not forget that some results obtained in the past could have been influenced by contamination of IgA with other classes of immunoglobulins. Using a purified mouse myeloma IgA protein with specific antigen-antibody capacity, Pfaffenback *et al.* [60] demonstrated that IgA immune complexes were not able to activate C3–9 in human serum.

Moreover, it has even been proposed that IgA might act as a modulator of the complement system because it is able to block its activation regardless of the pathway of activation [61].

However, if we hypothesize that some complement activation could have taken place in the present experiment, such an activation should have induced the appearance of anaphylatoxins with probable, subsequent mast cell degranulation [62–65]; i.e. the expression of this phenomenon should have been significantly blocked by cetirizine.

The existence of a dermal oedema induced by complement activation and resistant to H_1 blockade has also been described in experimental animals [66], but this kind of oedema is of slow onset (30 min) and of long duration (up to 240 min), i.e. very different from the anti-IgA-induced oedema we observed in our volunteers.

The pattern of cells observed after anti-IgA challenge was definitely different from the one after anti-IgE challenge.

All but one healthy volunteer presented with a very low percentage of eosinophils (<5%). In the atopic subjects, the mean percentage of these cells was also low regardless of the experimental conditions (control or placebo or cetirizine treatment), but we observed five subjects presenting with, at least during one session, a rather high percentage of eosinophils (>7.5%). According to the randomization list, this erratic response could not be correlated with a hypothetical sequence effect of the successive challenges.

The present data suggest that the cellular response to anti-IgA challenge could be different in atopic subjects when compared with healthy subjects, and also that there might be profound inter-individual differences and time-dependent variations.

Nevertheless, the number of volunteers tested in the present study is too low to reach a definite conclusion, and for this reason we might conclude that further investigations are needed in order to demonstrate accurately the possible role of IgA in the development of allergic inflammation in some allergic individuals. Moreover, we are not sure about the stability and the biological activity of the injected material. Additional data are necessary to show a possible inhibiting effect of cetirizine on this IgA-induced migration of eosinophils.

An additional reason for considering these studies as preliminary ones is that we used animal antibodies for the skin challenges, the specificity of which might be questionable. Nevertheless, these two kinds of challenges allowed us to demonstrate differences in the immediate oedema, as well as in the cellular pattern at 24 hr, and this is also a reason to believe that the two antibodies actually did elicit specific responses by touching different targets in the challenged tissue.

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