

# Comparison between nasal provocation tests and skin tests in patients treated with loratadine and cetirizine

Laurence Persi, MD,<sup>a</sup> Pascal Demoly, MD,<sup>a</sup> Alan G. Harris, MD,<sup>b</sup> Bernard Tisserand, MD,<sup>c</sup> François-B. Michel, MD,<sup>a</sup> and Jean Bousquet, MD<sup>a</sup> Montpellier and Verum, France, and Kenilworth, NJ

**Background:** The effect of H1-blockers may differ depending on the target organ.

**Objective:** A double-blind, placebo-controlled study was carried out to compare the effect of a 7-day treatment with loratadine (10 mg daily) or cetirizine (10 mg daily) on nasal challenge with grass pollen grains and skin tests with allergen or histamine.

**Methods:** Twenty-four patients were enrolled, but the analysis was carried out on 23. Nasal challenge was carried out by using 5-fold increasing numbers of pollen grains. Skin prick tests were done with serial concentrations of allergens and 1 concentration of histamine. Patients were tested in a cross-over design, with each treatment being administered for the previous 7 days and with a 2-week washout period.

**Results:** By comparison with placebo, loratadine and cetirizine increased significantly the threshold number of pollen grains required to induce a positive nasal challenge ( $P < .001$ ). There was no difference between loratadine and cetirizine. Skin test responses to allergen were significantly reduced by loratadine and cetirizine by comparison with placebo. Skin test responses to histamine were significantly decreased by the 2 H1-blockers, but they were more profoundly decreased by cetirizine than by loratadine.

**Conclusions:** Both H1-blockers reduced similarly allergen-induced skin test and nasal challenge responses. Cetirizine was more effective on histamine skin test responses. (*J Allergy Clin Immunol* 1999;103:591-4.)

**Key words:** Orchard grass, nasal provocation test, rhinitis, loratadine, cetirizine

H1-blockers represent one of the first lines of treatment for allergic rhinitis. New generation H1-blockers include astemizole, cetirizine, ebastine, fexofenadine, loratadine, and terfenadine.<sup>1</sup> Although these molecules vary widely in their structure, they have a similar efficacy in controlling the nasal and conjunctival symptoms of allergic rhinitis.<sup>2</sup>

H1-blockers block histamine at its H1-receptor level<sup>1</sup>; however, different molecules produce variable effects on

## Abbreviation used

IR: Index of reactivity

skin responses to histamine. Some molecules block almost completely the wheal and flare reaction, whereas others are less potent.<sup>3</sup> Cetirizine<sup>4-14</sup> blocks histamine-induced skin test responses or allergen-induced wheal and flare reactions<sup>15</sup> more completely than loratadine.<sup>16,17</sup> Despite these differences, loratadine and cetirizine have shown comparable effectiveness in the treatment of seasonal allergic rhinitis.<sup>18</sup> It is therefore possible that H1-blockers have different effects depending on the target organ and that the evolution of skin test responses during treatment does not predict the clinical efficacy of the drugs for nasal allergy.

A randomized, double-blind, placebo-controlled, cross-over study was carried out to compare the effects of 2 H1-blockers, cetirizine and loratadine (each in doses of 10 mg daily), on histamine- and allergen-induced wheal and flare reactions and nasal provocation test responses with allergens to examine whether the decrement in skin test reactivity is correlated with that of the nasal reactivity.

## METHODS

### Patients

Twenty-four patients (9 men and 15 women) ranging in age from 21 to 41 years (mean  $\pm$  SD,  $27.2 \pm 6.3$  years) were enrolled in the study after informed consent was obtained and the protocol was approved by the ethics committee. All patients fulfilled the following 3 criteria. (1) Patients had histories of seasonal allergic rhinitis for at least the past 2 years. (2) Skin prick test responses were positive with a standardized orchard grass pollen extract (Stallergènes SA, Fresnes, France).<sup>19</sup> The criteria of positivity of skin tests were set as previously published.<sup>20</sup> In addition, all patients had elevated titres of serum orchard grass pollen IgE (CAP System; Pharmacia Diagnostics, Uppsala, Sweden). (3) Patients had not received specific immunotherapy during the current year and had not been treated with antihistamines, corticosteroids, or ketotifene during the past 2 weeks. None of the patients had received astemizole for the past 2 months. Patients had not been seen with any rhinitis episode for at least 1 month before the study.

### Skin tests

The same investigator (LP) performed the entire study. Skin prick tests were done with orchard grass standardized extracts (Stallergènes Laboratories, Fresne, France)<sup>19</sup> by end-point titration with

From <sup>a</sup>Hôpital Arnaud de Villeneuve, Montpellier; <sup>b</sup>Integrated Therapeutic Group, Inc, Kenilworth; and <sup>c</sup>ITEM, Verum.

Received for publication Aug 11, 1997; revised Sept 3, 1998; accepted for publication Oct 6, 1998.

Reprint requests: Jean Bousquet, MD, Hôpital Arnaud de Villeneuve, 34295 Montpellier Cedex 5, France.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/1/95543

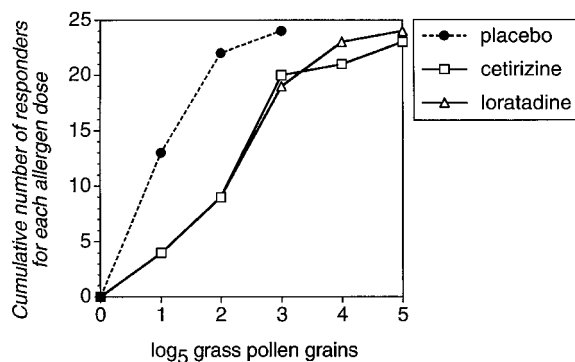


**FIG 1.** Results of nasal challenge with allergen. Placebo/loratadine:  $P < .003$ ; placebo/cetirizine:  $P < .005$ ; cetirizine/loratadine:  $P =$  not significant as determined by Wilcoxon  $W$  test.

five 3-fold increasing concentrations ranging from 0.12 to 100 index of reactivity (IR)/mL as previously described in detail.<sup>20</sup> The same batch of standardized and lyophilized extract was used throughout the study. A new vial was reconstituted every week. Skin prick tests with histamine dihydrochloride (10 mg/mL) were also done. The dose of histamine was chosen from the recommendations of the Nordic Guidelines for allergen standardization. Wheals and flares were recorded by the Scotch tape technique 15 minutes after the performance of the prick test. Mean wheal and flare sizes were recorded by using computed planimetry.

### Nasal challenge

Before inclusion in the study, patients were carefully evaluated for the absence of nasal symptoms (nasal discharge, sneezing, and itching). Capsules containing lactose or increasing concentrations of orchard grass pollens from 50 to 156,250 grains (5-fold increments) prepared by Stallergenes SA were insufflated into each nostril with a nasal Spinhaler (Fisons Laboratories, Loughborough, UK), with the patient refraining from breathing during the insufflation. For each concentration, the spinhaler was actuated 5 times. Each capsule was opened after insufflation to assess that it was completely empty. Lactose was initially insufflated, and eventual symptoms were recorded for 15 minutes. Then increasing numbers of grains were insufflated into the nostrils every 15 minutes until a symptom score of at least 5 was obtained from the sum of scores for 5 consecutive sneezes (score of 3), rhinorrhea (score of 1 to 3), and nasal blockage (score of 1 to 3). This threshold score was previously validated to correlate with the release of mediators in nasal secretions.<sup>21,22</sup>

### Study design

The study was done outside of the pollen season. The trial was a randomized, double-blind, placebo-controlled, cross-over study, with patients receiving loratadine (10 mg daily), cetirizine (10 mg daily), or placebo. All patients were investigated in the same manner, and nasal and skin tests were carried out simultaneously on the seventh day of each dosing period.

At the first experimental session, inclusion/exclusion criteria were assessed, vital signs were measured, and a first nasal allergen challenge was carried out before any treatment to confirm the nasal reactivity of the patients (baseline challenge).

The next 3 challenges were carried out at 2-week intervals, with patients being treated with cetirizine, loratadine, or placebo for 7 days, and nasal and skin challenges were carried out on the morning of the seventh day of treatment. Thirty minutes after administration of the last dose of the study treatment, the nasal provocation tests were started. To have a consistent blinding effect, placebo, cetirizine, and loratadine were given 30 minutes before the last chal-

lenge. It seems evident that when given at single doses these drugs may have different time courses of action. However, these drugs were shown in efficacy studies to be effective within 30 minutes. Moreover, for multiple doses, these 2 drugs are likely to have more than 24-hour efficacy. The histamine and allergen skin tests were performed 2 hours after taking the study drug.

Adverse events that occurred during drug administration were monitored during the study.

### Statistical analysis

The results of the skin and nasal challenges were analyzed by using cross-over ANOVA. Nonparametric tests were used to assess the nasal challenge results. The Wilcoxon  $W$  test was used for paired data. All statistical analyses were performed with the SAS computer package (version 6.10, SAS Institute). The skin test measurements were analyzed similarly. Results are expressed as medians and 25th to 75th percentiles. The study was not powered to find a significant difference between loratadine and cetirizine but was powered to find a difference between both H1-blockers and placebo.

## RESULTS

### Nasal challenge

Twenty-three patients were analyzed, and 1 patient was excluded because during the first session the cumulative score of 5 was not attained at any dose of pollen. All patients had a positive challenge response during the different test days. The median cumulative symptom score was similar and nonsignificantly different (placebo, 6.5; loratadine, 6.5; and cetirizine, 6.0).

The mean threshold number of pollen grains inducing a positive challenge was significantly greater for loratadine (range, 250 to 156,250; median and percentiles, 6250 and 1250 to 6250;  $P < .001$  as determined by Wilcoxon  $W$  test) and cetirizine (range, 250 to 156,250; median and percentiles, 6250 and 1250 to 6250;  $P < .001$ ) than for placebo (range, 250 to 6250; median and percentiles, 250 and 250 to 1250). There was no significant difference between loratadine and cetirizine (Fig 1).

### Skin tests to allergens

Cetirizine and loratadine significantly reduced the wheals induced by allergen by comparison with placebo (Fig 2). Cetirizine inhibited the wheal reaction similarly to loratadine. Cetirizine and loratadine significantly reduced the flares induced by allergen by comparison with placebo (Fig 2). Cetirizine inhibited the flare reaction similarly to loratadine.

### Skin tests to histamine

Cetirizine and loratadine were significantly more suppressive than placebo in the histamine-induced wheal (median and percentiles: placebo, 0.18 and 0.13 to 0.20 mm<sup>2</sup>; cetirizine, 0.08 and 0.06 to 0.10 mm<sup>2</sup>; loratadine, 0.12 and 0.09 to 0.15 mm<sup>2</sup>; placebo/cetirizine:  $P < .001$ ; placebo/loratadine:  $P < .02$ ; cetirizine/loratadine:  $P < .002$ ) and flare reactions (median and percentiles: placebo, 2.34 and 1.62 to 3.11 mm<sup>2</sup>; cetirizine, 0.10 and 0 to 0.25 mm<sup>2</sup>; loratadine, 1.0 and 0.07 to 1.73 mm<sup>2</sup>; placebo/cetirizine:  $P < .001$ ; placebo/loratadine:  $P < .001$ ; cetirizine/loratadine:  $P < .006$ ). Cetirizine was significantly more suppressive than loratadine.

## DISCUSSION

This study shows that 2 H1-blockers have the same clinical efficacy on nasal provocation test responses with allergen but behave differently in terms of skin test reactivity to histamine. However, both drugs were found to similarly reduce the allergen-induced skin test responses.

The methods used for nasal challenge and skin tests in this study have been widely validated.<sup>21-27</sup> Cetirizine and loratadine inhibited similarly the nasal reactivity to allergen. The results of this study are in accord with our previous experience with nasal challenge,<sup>21-24,27,28</sup> and all patients given placebo had a positive challenge response to allergen at a concentration of 6250 orchard grass pollen grains. Both H1-blockers were significantly superior to placebo, and there was no difference between these 2 drugs in the suppression of the nasal symptoms.

Several studies have been carried out on the skin test reactivity of cetirizine; however, double-blind, placebo-controlled, cross-over studies were done only with a single dose of H1-blocker in the histamine-induced skin test model.<sup>5,6,8,9,11-14</sup> Fewer nonplacebo-controlled studies were done with multiple doses of H1-blockers and histamine-induced skin tests.<sup>7,10,29</sup> Even fewer studies were carried out with allergen-induced skin tests. A controlled study compared a single dose of loratadine and cetirizine and showed a greater effect of cetirizine.<sup>4</sup> The present study is therefore original in that it examined the skin test reactivity to allergen in a double-blind, placebo-controlled study in which multiple doses of cetirizine and loratadine were used. Both the wheal and the flare induced by histamine were more profoundly decreased by cetirizine than by loratadine, confirming previous reports with single doses of H1-blockers<sup>6,13,14</sup> that showed that cetirizine has a greater activity on skin histamine reactivity than loratadine. It was observed as expected that cetirizine profoundly reduced the wheal reaction to allergen, but this effect was only slightly and nonsignificantly more potent than that of loratadine. However, the decrement by cetirizine on the flare component of the skin test reaction was more evident than that on the wheal and was more profound than that induced by loratadine. However, by using Bonferroni's correction, there was no significant difference between both drugs. The very potent activity of cetirizine on skin histamine receptors is involved in the flare response, whereas many proinflammatory mediators are involved in the wheal reaction.<sup>3</sup> These results are in accord with a recent study on histamine nasal challenge showing that cetirizine is more rapidly effective than loratadine.<sup>30</sup>

The results of the nasal challenge in the present study showed that there was no significant difference between cetirizine and loratadine, and the results obtained with loratadine are in accord with previous data from our group.<sup>24</sup> Although there may be no direct relationship between nasal allergen challenge results and symptoms during the pollen season, it was observed that the results of nasal challenge determined by using the method of the present study were significantly correlated with symp-

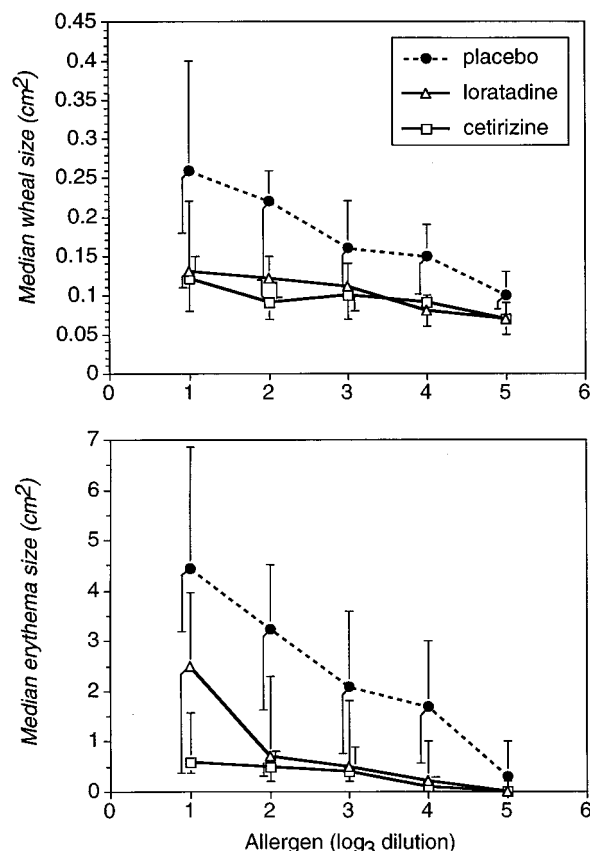


**FIG 2.** Results of skin tests with allergen. *Upper panel* shows effect of treatments on wheal size (statistical analysis by Wilcoxon *W* test). Dilution 1 (100 IR/mL): placebo (P)/loratadine (L),  $P = .02$ ; P/cetirizine (C),  $P = .0001$ ; C/L,  $P =$  not significant; dilution 2 (33 IR/mL): P/L,  $P = .0001$ ; P/C,  $P = .0001$ ; C/L,  $P =$  not significant; dilution 3 (11 IR/mL): P/L,  $P = .007$ ; P/C,  $P = .002$ ; C/L,  $P =$  not significant; dilution 4 (3.7 IR/mL): P/L,  $P = .0002$ ; P/C,  $P = .0001$ ; C/L,  $P =$  not significant; dilution 5 (1.2 IR/mL): P/L,  $P =$  not significant; P/C,  $P = .02$ ; C/L,  $P =$  not significant. *Lower panel* shows effect of treatments on erythema size (statistical analysis by Wilcoxon *W* test). Dilution 1 (100 IR/mL): P/L,  $P = .0001$ ; P/C,  $P = .0001$ ; C/L,  $P =$  not significant; dilution 2 (33 IR/mL): P/L,  $P = .0001$ ; P/C,  $P = .0001$ ; C/L,  $P =$  not significant; dilution 3 (11 IR/mL): P/L,  $P = .0001$ ; P/C,  $P = .0001$ ; C/L,  $P =$  not significant; dilution 4 (3.7 IR/mL): P/L,  $P = .0001$ ; P/C,  $P = .0001$ ; C/L,  $P =$  not significant; dilution 5 (1.2 IR/mL): P/L,  $P = .0008$ ; P/C,  $P = .0003$ ; C/L,  $P =$  not significant.

toms during the pollen season.<sup>23,27,28</sup>

Most studies that have compared the clinical efficacy of H1-blockers during the pollen season did not find a significant difference between drugs.<sup>2,31-34</sup> Recently, a park study found that a single dose of cetirizine was significantly superior to a single dose of loratadine in a capsule, but the differences between drugs and placebo were small in terms of global efficacy,<sup>35</sup> and the results seen with loratadine in that study were not consistent with the usually reported rates observed with this drug in other studies. Thus it appears that the new generation H1-blockers are usually similar in terms of clinical efficacy in the treatment of seasonal allergic rhinitis.

It has been proposed that the skin may be a relevant pharmacologic model to study the clinical effects of H1-

blockers,<sup>36</sup> but the results of the present study do not confirm that skin tests with histamine predict nasal challenge. Another conclusion is that results of allergen skin tests are not predicted by those of histamine skin tests. Moreover, it seems difficult to understand how skin tests to histamine may predict the efficacy of H1-blockers during the pollen season because histamine is only one of the mediators of the allergic reaction, and it has been observed that H1-blockers have so-called "anti-allergic" properties,<sup>37</sup> the clinical importance of which is not fully understood.

## REFERENCES

- Bousquet J, Campbell A, Canonica G. H1-receptor antagonists: structure and classification. In: Simons F, editor. Histamine and H1-receptor antagonists in allergic disease. New York: Marcel Dekker Inc; 1996. p. 91-116.
- Simons FE, Simons KJ. The pharmacology and use of H1-receptor-antagonist drugs. *N Engl J Med* 1994;330:1663-70.
- Bousquet J, Michel F. In vivo methods for study of allergy. Skin tests, techniques and interpretation. In: Middleton E, Reed C, Ellis E, Adkinson N, Yunginger J, Busse W, editors. Allergy: principles and practice. 4th ed. St Louis: Mosby Co; 1993. p. 573-94.
- Fadel R, Herpin-Richard N, Dufresne F, Rihoux JP. Pharmacological modulation by cetirizine and loratadine of antigen and histamine-induced skin weals and flares, and late accumulation of eosinophils. *J Int Med Res* 1990;18:366-71.
- Ghys L, Rihoux JP. Pharmacological modulation of cutaneous reactivity to histamine: a double-blind acute comparative study between cetirizine, terfenadine and astemizole. *J Int Med Res* 1989;17:24-7.
- Kontou-Fili K, Paleologos G, Herakleous M. Suppression of histamine-induced skin reactions by loratadine and cetirizine diHCl. *Eur J Clin Pharmacol* 1989;36:617-9.
- Levander S, Stahle-Backdahl M, Hagermark O. Peripheral antihistamine and central sedative effects of single and continuous oral doses of cetirizine and hydroxyzine. *Eur J Clin Pharmacol* 1991;41:435-9.
- Lever LR, Hill S, Marks R, Rosenberg R, Thompson D. Effects of cetirizine, loratadine and terfenadine on histamine weal and flare reactions. *Skin Pharmacol* 1992;5:29-33.
- Pechadre JC, Beudin P, Eschallier A, Trolese JF, Rihoux JP. A comparison of central and peripheral effects of cetirizine and loratadine. *J Int Med Res* 1991;19:289-95.
- Rihoux JP, Van-Neste DJ. Quantitative time course study of the skin response to histamine and the effect of H1 blockers. A 3-week crossover double-blind comparative trial of cetirizine and terfenadine. *Dermatologica* 1989;179:129-34.
- Rihoux JP, Dupont P. Comparative study of the peripheral and central effects of terfenadine and cetirizine 2 HCl. *Ann Allergy* 1987;59:235-8.
- Rihoux JP, Ghys L, Coulie P. Compared peripheral H1 inhibiting effects of cetirizine 2 HCl and loratadine. *Ann Allergy* 1990;65:139-42.
- Simons FE, McMillan JL, Simons KJ. A double-blind, single-dose, crossover comparison of cetirizine, terfenadine, loratadine, astemizole, and chlorpheniramine versus placebo: suppressive effects on histamine-induced wheals and flares during 24 hours in normal subjects. *J Allergy Clin Immunol* 1990;86:540-7.
- Van-Neste D, Rihoux JP. Dynamics of the skin blood flow response to histamine. Comparison of the effects of cetirizine and loratadine on the skin response to a histamine dry prick test monitored with laser-Doppler flowmetry. *Dermatology* 1993;186:281-3.
- Bousquet J, Chanal I, Skassa-Brociek W, Lemonier C, Michel FB. Lack of subsensitivity to loratadine during long-term dosing during 12 weeks. *J Allergy Clin Immunol* 1990;86:248-53.
- Roman IJ, Kassem N, Gural RP, Herron J. Suppression of histamine-induced wheal response by loratadine (SCH 29851) over 28 days in man. *Ann Allergy* 1986;57:253-6.
- Small P. Suppression of epicutaneous reactivity by terfenadine and loratadine. *Ann Allergy* 1992;68:30-4.
- Herman D, Arnaud A, Dry J, et al. Efficacite clinique et tolerance de la Loratadine versus Cetirizine dans le traitement de la rhinite allergique saisonniere. *Allerg Immunol Paris* 1992;24:270-4.
- Bousquet J, Djoukadar F, Hewitt B, Guerin B, Michel FB. Comparison of the stability of a mite and a pollen extract stored in normal conditions of use. *Clin Allergy* 1985;15:29-35.
- Bousquet J, Guerin B, Dotte A, et al. Comparison between rush immunotherapy with a standardized allergen and an alum adjuved pyridine extracted material in grass pollen allergy. *Clin Allergy* 1985;15:179-93.
- Lebel B, Bousquet J, Morel A, Chanal I, Godard P, Michel FB. Correlation between symptoms and the threshold for release of mediators in nasal secretions during nasal challenge with grass-pollen grains. *J Allergy Clin Immunol* 1988;82:869-77.
- Bousquet J, Becker WM, Hejjaoui A, et al. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species. II. Efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. *J Allergy Clin Immunol* 1991;88:43-53.
- Bousquet J, Maasch H, Martinot B, Hejjaoui A, Wahl R, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. II. Comparison between parameters assessing the efficacy of immunotherapy. *J Allergy Clin Immunol* 1988;82:439-46.
- Bousquet J, Lebel B, Chanal I, Morel A, Michel FB. Antiallergic activity of H1-receptor antagonists assessed by nasal challenge. *J Allergy Clin Immunol* 1988;82:881-7.
- Bousquet J, Calvayrac P, Guerin B, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. I. In vivo and in vitro parameters after a short course of treatment. *J Allergy Clin Immunol* 1985;76:734-44.
- Horst M, Hejjaoui A, Horst V, Michel FB, Bousquet J. Double-blind, placebo-controlled rush immunotherapy with a standardized *Alternaria* extract. *J Allergy Clin Immunol* 1990;85:460-72.
- Bousquet J, Maasch HJ, Hejjaoui A, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. III. Efficacy and safety of unfractionated and high-molecular-weight preparations in rhinoconjunctivitis and asthma. *J Allergy Clin Immunol* 1989;84:546-56.
- Bousquet J, Hejjaoui A, Soussana M, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. IV. Comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. *J Allergy Clin Immunol* 1990;85:490-7.
- Lobaton P, Moreno F, Coutie P. Comparison of cetirizine with astemizole in the treatment of perennial allergic rhinitis and study of the concomitant effect on histamine and allergen-induced wheal responses. *Ann Allergy* 1990;65:401-5.
- Frossard N, Lacronique J, Melac M, et al. Onset of action in the nasal antihistaminic effect of cetirizine and loratadine in patients with allergic rhinitis. *Allergy* 1997;52:205-9.
- Howarth PH, Emanuel MB, Holgate ST. Astemizole, a potent histamine H1-receptor antagonist: effect in allergic rhinoconjunctivitis, on antigen and histamine induced skin weal responses and relationship to serum levels. *Br J Clin Pharmacol* 1984;18:1-8.
- Haria M, Fitton A, Peters DH. Loratadine. A reappraisal of its pharmacological properties and therapeutic use in allergic disorders. *Drugs* 1994;48:617-37.
- Luria X, Bakke O. Ebastine (LAS W-090): overview of clinical trials. *Drugs Today* 1992;28(Suppl B):69-79.
- McTavish D, Goa KL, Ferrill M. Terfenadine. An updated review of its pharmacological properties and therapeutic efficacy. *Drugs* 1990;39:552-74.
- Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. *J Allergy Clin Immunol* 1996;97:617-26.
- Rihoux JP, Ghys L, Muhlethaler K, Wuthrich B. The skin as a target organ for the investigation of antiallergic drugs: comparison between cetirizine and terfenadine. *Dermatology* 1992;184:111-5.
- Bousquet J, Campbell A, Michel F. Antiallergic activities of antihistamines. In: Church M, Rihoux J, editors. Therapeutic index of antihistamines. Lewinston (NY): Hogrefe & Huber Publishers; 1992. p. 57-95.