

Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: A prospective, randomized, placebo-controlled trial

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Background: Some clinical studies suggest that a combination of an H₁- and H₂-antagonist may be effective in the prophylaxis of allergic reactions.

Objective: The efficacy of pretreatment with an H₁/H₂-antagonist combination, H₁-antagonist alone, or placebo in the prophylaxis of local and systemic adverse reactions to specific immunotherapy with Hymenoptera venom was compared.

Methods: In a prospective, randomized, double-blind, placebo-controlled study, 121 patients with Hymenoptera venom allergy were treated with rush immunotherapy and pretreatment with one of the following: 120 mg of terfenadine plus 300 mg of ranitidine, 120 mg of terfenadine alone, or placebo. The incidence of unwanted systemic adverse and local reactions was recorded for up to 50 weeks.

Results: In seven patients (6%), six in the placebo group and one in the terfenadine group, systemic side effects required cessation of therapy ($p = 0.005$). Subjective symptoms occurred in four patients (10%) in the terfenadine plus ranitidine group and in three patients (7%) in the terfenadine group. Regarding local reactions, significantly fewer patients treated with a combination of terfenadine and ranitidine and with terfenadine alone as compared with placebo had severe local symptoms of erythema (29%, 29%, and 49%), edema (24%, 18%, and 41%), and pruritus (13%, 11%, and 31%) at week 1 ($p < 0.05$). This therapeutic benefit was limited to the first 4 weeks of treatment. Treatment with a combination of terfenadine and ranitidine was not superior to treatment with terfenadine alone.

Conclusions: Pretreatment with H₁-antihistamines with or without H₂-antihistamines significantly reduced local and systemic adverse reactions to immunotherapy with Hymenoptera venom and may therefore be helpful in the management of immunotherapy. (*J Allergy Clin Immunol* 1997;100:458-63.)

Key words: Hymenoptera venom allergy, immunotherapy, adverse reactions, pretreatment, prophylaxis, terfenadine, ranitidine, antihistamines, H₁/H₂-antagonists

Anaphylactic reactions to insect stings are not uncommon in the general population. The frequency of Hymenoptera venom allergy in the medical literature varies from 0.4% to 26.5%.¹ After critical evaluation of the studies, a prevalence of about 1% in normal subjects can be estimated with much higher rates for sensitization (e.g., positive RAST results).^{1, 2} Specific immunotherapy (hyposensitization) with Hymenoptera venoms is considered to be a safe and effective treatment for properly selected patients.^{1, 3, 4} However, adverse reactions to immunotherapy are not infrequent.^{5, 6} They consist of either local reactions (pain, erythema, or edema), occurring mostly during the first weeks of therapy, or systemic anaphylaxis.⁷ This complication is reported in a variable number of patients (about 1% to 30%).⁶

Antihistamines are widely used for the treatment of mild reactions to Hymenoptera venom injection. The clinical benefit of H₁-receptor antagonists in the treatment of immediate-type hypersensitivity is well established. Terfenadine, a nonsedating H₁-antagonist, is effective in the treatment of a variety of disorders including anaphylactoid reactions and chronic urticaria.^{8, 9} It has been shown to suppress immediate and late-phase allergic responses.¹⁰ On the other hand, the role of H₂-receptors in allergic diseases is still controversial. Despite sporadic case reports describing a beneficial effect of H₂-antagonists alone in the treatment of anaphylactoid reactions, most studies focus on the combined effect of H₂-antagonists and H₁-antihistamines.¹¹ Many clinical trials suggest that a combination of H₁- and H₂-antagonists is more effective in prophylaxis and treatment of anaphylactoid reactions than use of an H₁-antagonist alone. Prophylaxis of anaphylactoid reactions caused by colloid volume substitutes, general anesthetics, and radiographic contrast media, as well as the treatment of chronic urticaria, may be provided more efficiently by a combined H₁/H₂-antagonist regimen.¹²⁻¹⁴

Pretreatment with antihistamines has been claimed to increase the safety of immunotherapy.³ However, there may be the danger of masking a beginning allergic reaction by premedication with antihistamines. So far, no convincing study on the safety and prophylactic efficacy of H₁- and H₂-antagonists in specific immunotherapy has been published. The aim of this placebo-controlled study was to evaluate whether prophylactic

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TABLE I. Demographic characteristics of different study groups of patients allergic to Hymenoptera venom undergoing specific hyposensitization

	Terfenadine	Terfenadine plus ranitidine	Placebo
Patients (n)	41	41	39
Age (yr)			
Mean	42.3	43.3	43.0
Range	19-66	18-70	21-59
Sex (%)			
Male	49	44	36
Female	51	56	64
Mean weight (kg)	74	71.6	73.3
Mean height (cm)	171	169	172
Type of insect (n)			
Honeybee	7	2	3
Yellow jacket	35	39	36
Severity of anaphylactoid reaction in history (n)			
Grade I	3	4	4
Grade II	15	16	17
Grade III	21	19	17
Grade IV	2	2	1
Insect venom-specific IgE (mean CAP RAST class)	2.14	2.30	2.46

oral therapy with terfenadine or a combination of terfenadine and ranitidine is a safe and effective approach with which to reduce adverse reactions to Hymenoptera venom hyposensitization.

METHODS

Patients

One hundred twenty-one patients (52 men and 69 women), aged 18 to 70 years undergoing Hymenoptera venom hyposensitization, were enrolled in the study. The clinical data of the 121 patients are given in Table I. Inclusion criteria were a documented systemic anaphylaxis to honeybee (*Apis mellifera*) or yellow jacket (*Vespula* spp.) stings (grade I, II, III, or IV according to Ring and Messmer¹⁵) and demonstration of a sensitization (positive intracutaneous skin test response to bee or yellow jacket venom at a concentration of 10^{-1} µg/ml or less and demonstration of specific IgE antibodies by RAST). Of the 121 patients, 11 had honeybee venom allergy, 109 had yellow jacket venom allergy, and one had honeybee and yellow jacket venom allergy. Criteria for exclusion from the study were the classic contraindications for immunotherapy and presence of diseases that might interfere with the immunotherapy or treatment evaluation.³ Patients were asked to withhold drugs that could interfere with the study. Drugs such as antihistamines, sedatives, and hypnotics were withheld for 1 week before the study; and astemizole, systemic corticosteroids, β-blocking agents, and nonsteroidal antiinflammatory drugs were withheld for 4 weeks before the study. The study protocol and the statement of informed consent were approved by the ethical committee of the Hamburg Medical Association, and a signed informed consent document was obtained from each patient before the study.

Treatment protocol

Specific hyposensitization was initiated by an in-patient rush immunotherapy protocol with three subcutaneous injections given daily over 5 days. After reaching a maintenance dose of 100 µg, the treatment was continued on an outpatient basis according to a standardized hyposensitization protocol in pre-

determined intervals (7, 14, and 21 days), followed by monthly injections. Patients were under supervision for at least 30 minutes after each injection. Patients were randomized to one of three oral pretreatment groups: group I, 120 mg of terfenadine plus 300 mg of ranitidine ($n = 41$); group II, 120 mg of terfenadine alone ($n = 41$); and group III, placebo ($n = 39$). The pretreatment medications terfenadine and ranitidine, terfenadine and placebo, or double placebo were administered in double-blind fashion once daily in the morning 1 to 1½ hours before injections.

Assessment of local and systemic reactions

The evaluation of efficacy was based on the physician's assessment of local and systemic reactions at each visit. Immediate local symptoms erythema, edema (swelling), and pruritus were measured 30 minutes after injection. The severity of each symptom was rated and scored as follows: 1 = none, 2 = mild, 3 = moderate, and 4 = severe. The individual symptom scores were added to a total local symptom score. Thus a score of 3 corresponds to no local reactions, and the maximal score was 12.

Systemic allergic reactions were recorded and classified as cardiovascular, respiratory, gastrointestinal, skin and mucosal reactions, subjective symptoms, and additional symptoms. At the end of the study a global evaluation was completed by the treating physician on a 4-point scale (1 = excellent to 4 = poor) for both the efficacy and compatibility of the treatment. For evaluation of immunologic changes, serum-specific IgE and IgG to honeybee or yellow jacket venom was measured at weeks 11, 26, and 50 by the commercially available IgE RAST (Phadebas RAST) and IgG RAST kits in accordance with the recommendations of the manufacturer (Pharmacia, Uppsala, Sweden). IgE values are expressed in classes from 0 to 4; specific IgG is expressed as percentage of the reference values.

Statistics

Statistical analysis was performed on the pooled efficacy data and was based on the distribution of side effects caused by immunotherapy injections in the different pretreatment groups.

TABLE II. Patients discontinuing the study because of systemic adverse reactions to immunotherapy

Patient No.	Age (yr)	Sex (M/F)	Insect venom	Cessation of therapy	Symptoms	Study group
1	46	F	Yellow jacket	Week 1	Dyspnea, urticaria, large local reaction	Placebo
2	34	M	Honeybee	Week 1	Dyspnea, rhinitis, conjunctivitis, fever	Placebo
3	52	F	Yellow jacket	Week 1	Rhinitis, conjunctivitis	Placebo
4	26	M	Honeybee	Week 5	Tachycardia, hypotension	Placebo
5	58	M	Honeybee	Week 1	Dyspnea, large local reaction	Placebo
6	55	F	Yellow jacket	Week 1	Generalized pruritus, rhinitis, conjunctivitis, large local reaction	Placebo
7	35	F	Yellow jacket	Week 1	Dyspnea, hypotension, nausea, large local reaction	Terfenadine

Frequency distributions were analyzed by the chi square test. The Jonckheere-Terpstra test was performed for evaluation of the local reactions; for continuous data, the Kruskal-Wallis test between groups and the Wilcoxon test within a group were used. Intention-to-treat analysis was performed for small samples. Statistical significance was declared by a *p* value of less than 0.05.

RESULTS

Of the 121 patients who participated in the study, 41 were randomized to terfenadine plus ranitidine treatment, 41 to terfenadine treatment, and 39 to placebo treatment. With respect to demographic data, there were no statistically significant differences between the groups (Table I). The number of patients completing the study was greater in the terfenadine plus ranitidine group (36 patients, 88%) and the terfenadine group (33 patients, 81%) than in the placebo group (28 patients, 72%).

Systemic adverse reactions

Objective systemic adverse reactions to immunotherapy required cessation of the study in seven patients (6%). Of these, six patients were in the placebo group, and one was in the terfenadine group (Table II). Six reactions were recorded during the first week and one in the fifth week of immunotherapy. The difference between treatment and placebo groups was statistically significant (*p* = 0.005). No severe or life-threatening symptoms (grade III or IV) were observed in either group.¹⁵ Objective symptoms in response to immunotherapy ranged from large local, pruritic, and urticarial cutaneous reactions to respiratory symptoms of rhinitis and conjunctivitis to circulatory symptoms of mild tachycardia (110 beats/min) and hypotension (100/60 mm Hg). In patient 7, who reacted during terfenadine pretreatment, psychologic aggravation caused by anxiety cannot be ruled out. Subjective symptoms including vertigo, unease, and headache were observed after a dose of 0.001 µg. Immunotherapy was stopped after the development of dyspnea, nausea, and hypotension (90/60 mm Hg) after a dose of 30 µg.

Mild and moderate subjective symptoms that did not require cessation of the therapy were recorded in the terfenadine plus ranitidine group in four patients (10%) after week 1 (burning face, headache, palpitations, and nausea) and in one of these patients in week 22 (heat sensation and nausea) and in the terfenadine group in three patients (7%), two in week 1 (headache, nausea) and one in week 42 (palpitations).

All but one of the patients with objective systemic adverse reactions reacted within 30 minutes after injection. Patient 1 experienced urticaria after 2 hours. They reacted to doses ranging from 10 to 100 µg of Hymenoptera venom.

Local reactions

Local reactions during immunotherapy showed significantly higher symptom scores for erythema, edema, and pruritus in the placebo group as compared with both treatment groups at the end of the first week (Fig. 1). There was significantly increased proportion of patients with severe symptoms of erythema (49%), edema (41%), and pruritus (31%) in the placebo group as compared with the terfenadine plus ranitidine group (29%, 24%, and 13%) and the terfenadine group (29%, 18%, and 11%), respectively (*p* = 0.041, 0.01, 0.025). Local reaction scores were lower in the terfenadine group than in the terfenadine plus ranitidine group (*p* = 0.202, 0.131, 0.331); however, the differences were not significant. The local reaction scores and the differences between the groups decreased with duration of immunotherapy (Fig. 2). After the fourth week of therapy, there was no significant difference between the groups. After the eighth week of therapy, more than 90% of the edema and pruritus reactions and more than 65% of the erythema reactions were classified as absent or mild only. The proportion of patients with the maximal total reaction score of 12 for all local symptoms after 1 week of treatment was significantly increased (*p* < 0.01) in patients receiving placebo (23%) as compared with patients receiving a terfenadine-ranitidine combination (8%) or terfenadine alone (11%) at the end of the first week. Afterwards, the score decreased in all groups, and

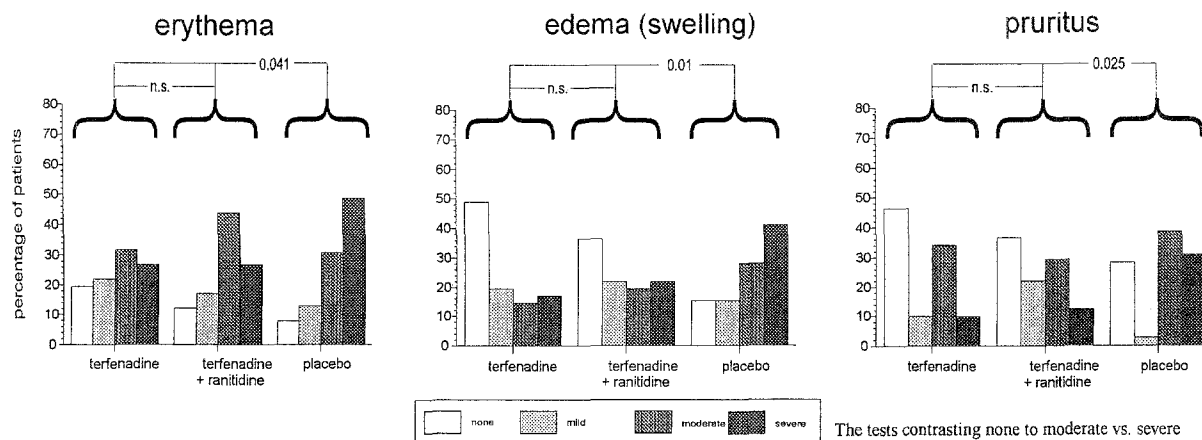


FIG. 1. Frequency distribution of local symptoms (erythema, edema, and pruritus) after 1 week of immunotherapy for each treatment group. Local scores are significantly lower in patients treated with terfenadine and terfenadine plus ranitidine than in patients treated with placebo. *n.s.*, Not significant.

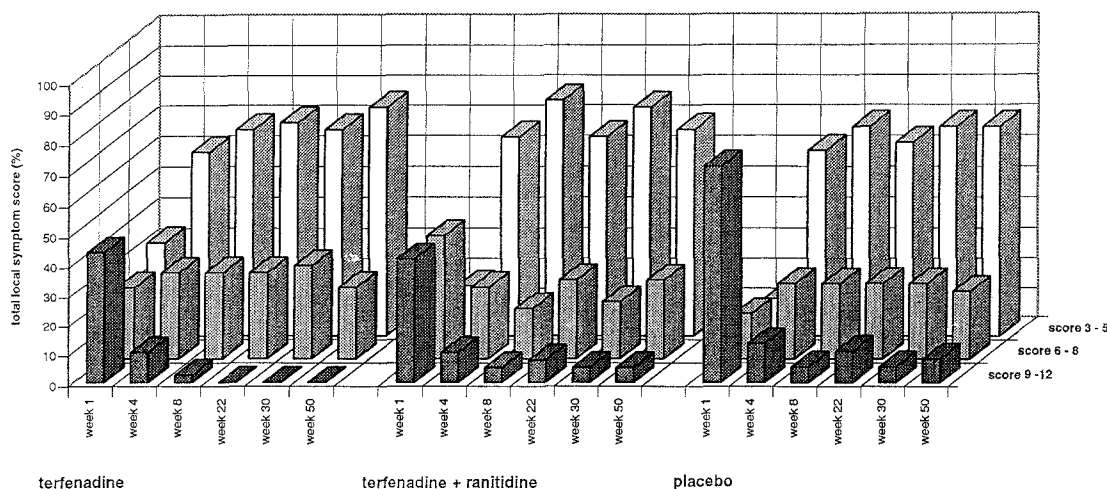


FIG. 2. Total local symptom scores for each treatment group during 50 weeks of study. Significant differences for terfenadine and terfenadine plus ranitidine treatment versus placebo were found after 1 week of therapy. Alleviation of local symptoms caused by immunotherapy is significantly better with terfenadine and terfenadine plus ranitidine than with placebo ($p < 0.05$). However, there was a reduction in local symptoms in all groups during immunotherapy; no significant differences were seen from week 4 onward.

in week 50 only one patient in the placebo group had a score of 12; in more than 84% of patients, low scores between 3 and 6 were recorded (Fig. 2).

Laboratory changes

There was no significant change in insect venom-specific IgE values during immunotherapy (Fig. 3), nor were significant differences noted between groups. Insect venom-specific IgG increased significantly in all groups from before immunotherapy to week 11 ($p < 0.01$) (Fig. 4). The median increased from 20.0%, 15.0%, and 22.5% before treatment to 84.0%, 47.5%, and 87.0% in week 11 for terfenadine plus ranitidine, terfenadine alone, and placebo treatment. In weeks 26

and 50 the values decreased again to 63.0%, 36.0%, and 78.0%, respectively. There was a trend toward higher IgG levels in the placebo group, although significant differences were only seen in week 50 in patients pretreated with terfenadine versus placebo ($p < 0.05$).

Global evaluation

In the global evaluation of efficacy by the physician, terfenadine plus ranitidine and terfenadine alone were rated better than placebo. The efficacy of the treatment was excellent or good in 98%, 90%, and 77% of patients, respectively ($p = 0.79$). The tolerance of the medication was excellent in 95%, 97%, and 97% of patients, respectively ($p = 0.99$).

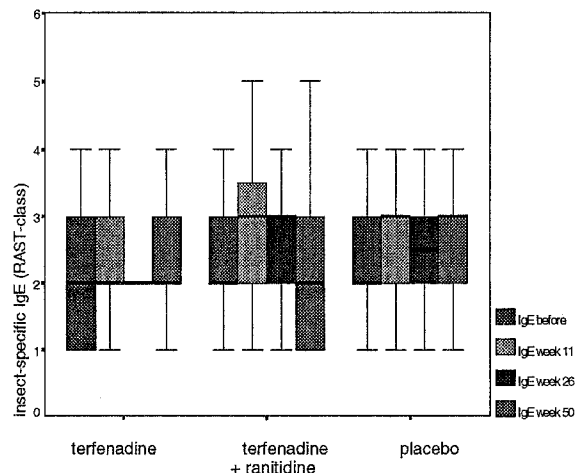


FIG. 3. Insect-specific IgE to Hymenoptera venom during immunotherapy. There was no significant difference between patients treated with terfenadine, terfenadine plus ranitidine, and placebo.

Safety

In four patients mild adverse reactions in relation to the premedication were observed by the physician. In the terfenadine group two patients (5%) discontinued the study, one because of nausea and another because of transient headache; in the terfenadine plus ranitidine group one patient (2%) experienced headache and was dismissed from the study after compliance problems, and one patient in the placebo group (3%) experienced transient fatigue.

DISCUSSION

The prospective, placebo-controlled study in 121 subjects undergoing specific hyposensitization with insect venom over 50 weeks showed that local and systemic reactions during immunotherapy can be significantly reduced by pretreatment with terfenadine or terfenadine and ranitidine in combination. Regarding local reactions, we found a significant reduction in severity of erythema, edema, and pruritus after venom injections in the initial phase of immunotherapy. Local swelling at the injection site is often associated with discomfort and pain and may last for up to 5 days. Nonallergic small local reactions caused by a toxic response to venom constituents are seen in almost all patients. However, there is evidence that large local reactions may be allergic in origin.⁷ The clinical picture of these reactions resembles an IgE-mediated late-phase reaction.¹⁶ The development of large local reactions can be effectively reduced by pretreatment with antihistamines, consistent with a histamine-related pathologic mechanism. Similar findings were also made by Berchtold et al.,¹⁷ who observed a significant reduction of local and generalized cutaneous symptoms after pretreatment with terfenadine during rush immunotherapy. No additional benefit on local symptoms was found by adding the H₂-antago-

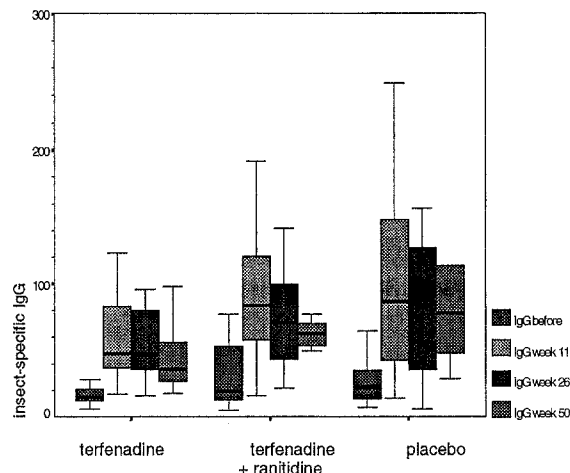


FIG. 4. Median (horizontal bars), 25 and 75 percentiles (boxes), and range (vertical bars) of insect-specific IgG to Hymenoptera venom during immunotherapy. IgG increased significantly from before immunotherapy to week 11 of immunotherapy in all groups. Afterwards, a plateau appeared to be reached with only minor decrease of values. There is a trend toward higher IgG values in the placebo group. However, differences between groups are not significant, with the exception of patients treated with terfenadine versus placebo in week 50.

nist to the H₁-antagonist terfenadine. The use of H₂-antagonists alone seems to be ineffective in late-phase reactions, as well as in histamine-induced skin reactions.¹⁸ Large local reactions seem to be a self-limiting process for many patients during immunotherapy. After 50 weeks of treatment, the incidence of local reactions was very low in all groups.

A significantly lower proportion of systemic adverse reactions was found after pretreatment with terfenadine plus ranitidine and terfenadine. In contrast to the six patients in the placebo group, only one patient pretreated with terfenadine discontinued the study because of anaphylactoid reactions. Thus in contrast to others, we found a possible benefit of pretreatment with antihistamines in the prevention of systemic adverse reactions to immunotherapy.^{17, 19} However, in the study by Berchtold et al.¹⁷ a smaller number of patients was evaluated, and in this placebo group treatment with clemastine and prednisone was allowed, which may have concealed significant differences. Our results are supported by a study that demonstrated a reduction of systemic reactions to immunotherapy with birch or grass pollen extracts.²⁰ The question of whether the use of H₁- or H₂-antagonists carries the risk of masking a beginning mild allergic reaction (e.g., cutaneous symptoms), which could be a warning signal for the subsequent development of a serious allergic reaction, is one of the major arguments against general antihistamine pretreatment. We cannot support this reservation on the basis of our data. All systemic adverse reactions during premedication with antihistamines began within 30 minutes, and no

prolonged reactions were noted. During immunotherapy no serious systemic adverse reactions were observed in any of the groups. More patients had to discontinue the study because of systemic adverse reactions in the placebo group than those in the active treatment groups. Whether the addition of an H₂-antagonist to the H₁-antagonist provides a further benefit in the reduction of systemic reactions cannot be determined, because the lack of power may have concealed significant differences. There is evidence from animal and in vitro experiments that a combination of H₁- and H₂-antagonists may be helpful in the suppression of anaphylactoid reactions.^{21, 22} The mechanism of action of this kind of treatment has not been established. H₂-receptors have been found on antigen-specific T suppressor cells induced by immunotherapy.²³ H₂-antagonists may be able to modulate the IgE response through these receptors.

Although there was a trend toward higher venom-specific IgG levels in the placebo group, changes in IgE and IgG responses during immunotherapy did not differ between groups with the exception of week 50, when patients treated with terfenadine showed lower absolute IgG levels than patients treated with placebo. The relevance of this finding is unclear, because this difference does not affect the terfenadine plus ranitidine group and the protective role of specific IgG is doubtful. A significant rise in IgG levels was observed in all groups. No sting provocation was done; therefore, no statement on efficacy can be made. Before this pretreatment regimen can be recommended for general practice, it should be shown that the reduction of side effects is not associated with loss of efficacy of immunotherapy.

Both active treatments were generally efficient and well tolerated by the patients. The tolerance was excellent or good in more than 95% of patients in all groups. No unusual or unexpected side effects were observed. As expected, the incidence of headache and nausea occurred more often in patients treated with terfenadine with or without ranitidine than in patients treated with placebo. Because less than 1% of patients discontinued the study because of adverse events, overall the treatment was well tolerated.

In conclusion, our study provides evidence that pretreatment with the H₁-antagonist terfenadine is effective in the prevention of systemic and local adverse reactions to immunotherapy with Hymenoptera venom. The effect on local reactions is limited to the initiation phase of immunotherapy. The addition of ranitidine, an H₂-antagonist, does not provide a further benefit for the suppression of local reactions. Its value for the prophylaxis of systemic reactions must be evaluated in a greater number of patients.

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