

RESEARCH ARTICLE

Hyposensitization in the treatment of resistant cases of vernal keratoconjunctivitis

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Abstract

Purpose: The study evaluated the treatment of resistant cases of vernal keratoconjunctivitis by hyposensitization resulting from intradermal skin reactions of different allergens. **Methods:** This prospective study was carried out in the Department of Ophthalmology and the Department of Microbiology and Immunology, Zagazig University, and included 36 patients with bilateral vernal keratoconjunctivitis that was resistant to topical corticosteroids and antihistaminic drugs. Patients were subjected to intradermal skin reactions to different allergens after stoppage of the medication. Subcutaneous injections of different allergens were administered in addition to topical vasoconstrictor and antihistaminic eye drops for different durations of 12, 18, and 24 months.

Results: The study revealed that most of the patients were sensitive to pollens (65%), house dust (55%), and tobacco smoke (40%). Among 36 total patients who received different doses of allergens, 10 of 20 patients showed marked improvement following a 24-month treatment period, with a 50% success rate. Another 3 of 9 patients showed marked improvement following an 18-month treatment period, with a 33.3% success rate.

Conclusion: The use of intradermal skin reactions to determine the sensitivity for different stimulating allergens in resistant cases of vernal keratoconjunctivitis was conclusive. Treatment by hyposensitization using prepared vaccines had an acceptable success rate especially in patients treated for 24 months. Future studies will be needed to determine how effective this treatment is with other allergens and for longer durations of hyposensitization. Additional immunologic studies will be essential for developing a strategy of management of resistance in such cases of resistant vernal keratoconjunctivitis.

Keywords: Hyposensitization; resistant cases; vernal keratoconjunctivitis

Introduction

Vernal keratoconjunctivitis is a common clinical entity that causes considerable ocular morbidity. Resistant cases of vernal keratoconjunctivitis that do not respond to topical treatment, especially corticosteroids and sodium cromoglycate preparations, represent a challenge. The long-term use of corticosteroid drops and ointments is associated with complications such as increased intraocular tension as well as cataract formation (1).

Immunotherapy is a process that gradually desensitizes the body to the allergen via injection of tiny amounts of the allergen under the skin over the

course of the disease for certain durations. During immunotherapy, the body will begin to develop a normal immune response to the allergen, and will not experience symptoms such as severe itching, burning sensation, redness, and watery eyes every time the body is exposed to the allergen (2). Although immunotherapy may take several months or even years to produce acceptable results, it can eventually diminish the need for eye drops or other medications that may have serious ocular complications (3,4).

The use of allergen-specific immunotherapy in the treatment of allergic diseases was first described by Noon in 1911 (5). A number of successful studies have encouraged development of allergen-specific

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immunotherapy. The practice of subcutaneous allergen-specific immunotherapy (SCIT) was developed by Bousquet et al. (6) and involves injection of increasing quantities of allergen extract (7).

Werfel (8) encouraged the use of SCIT because he considered it one of the safest methods for desensitization. However, other authors such as Burastero et al. (9) and Malling et al. (10) expressed a preference for the use of sublingual immunotherapy in the treatment of allergic diseases.

The role of immunotherapy (hyposensitization) in the treatment of allergic ocular conditions with specific antigens requires more study (4,8). Therefore, the present study was planned to evaluate these immunologic aspects in the diagnosis and treatment of resistant cases of vernal keratoconjunctivitis. The participating patients suffered from refractory symptoms and serious ocular side effects from their medication.

Patients and methods

The protocol for this research project was approved by the ethics committee of the institution in which the work was undertaken, and it conformed to the provisions of the Declaration of Helsinki of 1995 as revised in Tokyo in 2004. The patients gave informed consent, and patient anonymity was preserved.

The study was a prospective randomized study and was carried out in the Department of Ophthalmology and the Department of Microbiology and Immunology of Zagazig University in Egypt. The study included 36 patients with bilateral vernal keratoconjunctivitis that was resistant to topical corticosteroids and antihistaminic drugs following 3 months of treatment. There was no history of previous immunotherapy treatment.

Criteria for resistance (inclusion in the study) were based on the following:

- Marked eye discomfort, including itching and redness.
- Use of topical corticosteroids for more than 1 month.
- Use of topical or systemic antihistamines for more than 3 months.
- Use of topical sodium cromoglycate for more than 3 months.
- Stable environmental living conditions (i.e., patients changing their environmental living conditions were excluded from the study).

Patients underwent the procedures described below.

Ophthalmic history

The ophthalmic history included the following:

- Age, gender, occupation, and its relation to different allergens such as dust, heat, and pollens.
- History of the disease, including onset, course, duration, and medications.
- History of the characteristic symptoms, such as eye redness, itching, lacrimation, photophobia, eye discomfort, and "ropy" eye discharge.

Ophthalmologic examination

Ophthalmologic examination was performed with special consideration to conjunctival examination for the presence of conjunctival injection, limbal vernal masses, palpebral cobblestone papillae, corneal epithelial plaques, and ulcer. In addition, intraocular tension was measured using the applanation tonometer.

Intradermal skin test

Intradermal skin testing was carried out using 26-gauge syringes of 0.1 mL injected intradermally into the inner side of the forearm at 10 separated areas (4-cm distance separating each site) using 9 prepared allergens—pollen, tobacco smoke, fungi, house dust, hair, wool, cotton, agricultural dust, and Hay flower—after stoppage of the systemic and topical medication for 4 days. The reaction was measured according to the diameter of skin erythema greater than 1 cm in diameter from the puncture site 30 minutes after the injection (Figure 1).



Figure 1. The intradermal skin test.

The intradermal skin test was repeated for each patient after 6 months of the study.

The SCIT samples were prepared from the unfractionated extract of allergens in an aqueous solution in our institution. The allergen extracts were standardized (bioequivalent allergy units) according to the Joint Task Force on Practice Parameters in 2007 (11) to form standardized quality units (SQU).

The crude allergens were dissolved in a Coca's solution (pH 8.2, 4 g phenol crystals, 5 g sodium chloride, and 2.5 g sodium bicarbonate in 1 liter of distilled water) with a ratio of 1 g dry weight of sample in 10 mL of Coca's solution for 24 hours at room temperature in a magnetic mixer. The extracts were concentrated to one-tenth of the original volume by evaporation in air and filtered through Millipore filter units (Millipore UK Ltd., Watford, UK). The protein concentration was measured by BCA Protein Assay Kit (Thermo Scientific, Rockford, IL, USA). The potency of homemade allergic extracts was determined by *in vitro* comparison with a reference standard allergen. The extracted allergens were kept in labeled vials containing 0.4% phenol as a preservative.

Repeated subcutaneous injections of the different allergens (vaccines) were administrated as follows:

- A 100-unit (0.05-mL) dose of the standardized quality unit (SQU) was given daily for 1 month.
- The daily vaccine dosage was increased by an additional 100 units monthly for different durations of 12, 18, or 24 months in addition to the topical vasoconstrictor and antihistamine eye drops 5 times daily. Patients were divided into groups of different durations: 20 patients for 24 months, 9 patients for 18 months, and 7 patients for 12 months.

Patients underwent ophthalmologic examination weekly for the first 2 months and then monthly for the duration of the study to determine the degree of improvement based on the following criteria:

- 1) Relief of symptoms such as eye discomfort, itching, lacrimation, photophobia, and ropy eye discharge.
- 2) Disappearance of the conjunctival injection, papillae, and limbal masses.
- 3) Negative sensitization results on intradermal testing.

Systemic general medical examination

The patients underwent a monthly systemic general medical examination in the outpatient general medicine clinic during the study to detect any systemic clinical changes. The acute side effects of immunotherapy such as hemorrhagic skin reaction and potential anaphylactic

reactions were monitored, with appropriate emergency medical care always available.

Results

Thirty-six patients were included in the study. Ages ranged from 10 to 35 years (Table 1). Most of the cases (22 cases) were of the palpebral type, with 6 limbal type cases and 8 of a mixed type of vernal keratoconjunctivitis (Table 2). Thirty of the 36 cases (83%) were diagnosed during the summer.

Intradermal skin tests by different allergens showed that most of the patients (23 cases; 65%) were sensitive to pollen, followed by house dust (20 cases; 55%) and tobacco smoke (14 cases; 40%) (Table 3). Twenty-four of the patients responded to more than 1 type of allergen hypersensitivity.

The total number of improved cases resulting from the immunotherapy (Table 4) was 15 cases based on the criteria for improvement, for a total of 42% for all cases. The success rate for improvement was 50% among patients treated with hyposensitization for 24 months, 33.3% among patients treated for 18 months, and 27% among patients treated for 12 months. Most of the patients showing improvement were sensitive to pollens (80%) (Table 5).

The repeated intradermal test for the clinically improved cases showed negative reaction based on the area of skin erythema. The repeated test for the unimproved cases showed the same positive results of sensitivity.

No reported cases changed their sensitivity in the repeated intradermal tests, and there were no reported cases with local or systemic side effects of the immunotherapy.

Table 1. Age and gender distribution of the patients.

Age groups in years	Number of patients		Gender distribution			
			Male		Female	
	No.	%	No.	%	No.	%
10-14	6	16	4	16	2	17
15-19	16	44	11	47	5	41
20-24	7	20	4	16	3	25
25-29	4	12	2	9	2	17
30-35	3	8	3	12	—	—
Total	36	100	24	100	12	100

Table 2. Distribution of patients by type of vernal keratoconjunctivitis.

	Palpebral	Limbal	Mixed
No. of patients	22	6	8
%	61	17	22

Table 3. Results of the intradermal skin tests.

	Pollen	Tobacco smoke	Fungi	House dust	Hair	Wool	Cotton	Agricultural dust	Hay flower
No.	23	14	6	20	4	3	—	—	3
%	65	40	16	55	11	8	—	—	8

Table 4. Results of hyposensitization by duration of immunotherapy.

	12 months	18 months	24 months
No. of patients	7	9	20
No. of patients who improved	2	3	10
% of patients who improved	27	33.3	50

Table 5. Results for improvement of patients by type of allergens.

	Pollen	House dust	Tobacco smoke	Fungi
No. of patients	12	6	3	2
%	80	40	20	14

Discussion

Vernal keratoconjunctivitis is one of the immunologic problems that ophthalmologists encounter, especially during the warm seasons. The use of corticosteroids, one treatment option, has many complications. According to Frew et al. (4), immunotherapy or hyposensitization of patients against the causative allergens may be a future approach in the treatment of such cases.

The present study, carried out using the intradermal skin test, reported that most of the patients were sensitive to pollens (65%), which is in agreement with Prakash and Murthy (12), who reported a similar rate in their study, as pollens are considered one of the allergens most likely to trigger vernal keratoconjunctivitis. Mimura et al. (13), however, reported that most of their patients were sensitive to house dust (52%); in the present study, 55% of patients were sensitive to house dust, indicating that many individuals are sensitive to more than a single allergen (24 patients presented with sensitivity to more than 1 allergen in the present study). This sensitivity to more than a single allergen may explain the small difference in the rates between the present study and other similar studies.

The present study showed that the rate of improvement was 50% among patients treated for 24 months and 33.3% among patients treated for 18 months. Prakash and Murthy (12) reported an improvement in 62% of patients treated by hyposensitization for 12 to 24 months, whereas Bulawa et al. (14) reported that there was an improvement in 97% of patients treated for 3

years. The difference in results may be attributed to the duration of treatment, as longer durations carry higher rates of improvement. The type of allergen also may play a role: This study reported that most of the patients who experienced improvement were sensitive to pollens (80%) and house dust (40%), as the prepared vaccine from these allergens showed the maximum effects.

No systemic or local side effects from the subcutaneous immunotherapy involving any of the patients, especially the 2 patients below the age of 18 years, were reported. Wahn et al. (15) have suggested that sublingual immunotherapy was safer than subcutaneous injection immunotherapy, especially in children; however, since the present study reported only 2 pediatric cases, conclusions about the safety of subcutaneous injection immunotherapy use in children should not be drawn until larger numbers of cases are reported.

Treatment of vernal keratoconjunctivitis by immunotherapy is still a challenge in the management of this condition and needs more study using more allergens and a longer duration of treatment to verify its validity.

Conclusion

The use of intradermal skin reactions to determine different stimulating allergens in resistant cases of vernal keratoconjunctivitis was conclusive for determining the triggering factors for the disease. Treatment by hyposensitization of these patients had an acceptable success rate, especially in patients treated for 24 months. Future studies are needed to determine other allergens and longer durations of hyposensitization, and more immunologic studies are essential for developing a strategy of management of such resistant cases of vernal keratoconjunctivitis.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Ortega ZB, Vargas RMA, Tsuchiya IFM, Navarro dBE, Monge SJJ. Allergic conjunctivitis in children. *Rev Alerg Mex* 2007; 54(2):41-53.

2. Foster CS. Randomized clinical trial of topically administered cromolyn sodium in vernal keratoconjunctivitis. *Am J Ophthalmol* 1980; 90:175.
3. Niederberger V. Allergen-specific immunotherapy. *Immunol Lett* 2009; 122(2):131-134.
4. Frew AJ, Powell RL, Christopher CL, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment of resistant allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 9(8):65-69.
5. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911; 1:1572-1573.
6. Bousquet J, Lockery R, Malling HJ. Allergen immunotherapy: therapeutic vaccine for allergic diseases. A WHO position paper. *J Allergy Clin Immunol* 1998; 102:558-562.
7. Ronalland JL, Gardner LM, O'Hehir RE. Allergen-related approaches to immunotherapy. *Pharmacol Ther* 2009; 121:273-284.
8. Werfel T. Epicutaneous allergen administration: a novel approach for allergen-specific immunotherapy? *J Allergy Clin Immunol* 2009; 124:1003-1004.
9. Burastero SE, Mistrello G, Paolucci C, Breda D, Roncarolo D, Zanotta S, et al. Clinical and immunological correlates of pre-co-seasonal sublingual immunotherapy with birch monomeric allergoid in patients with allergic rhinoconjunctivitis. *Int J Immunopathol Pharmacol* 2009; 22:343-352.
10. Malling HJ, Montagut A, Melac M, Patriarca G, Panzner P, Seberova E, et al. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis. *Clin Exp Allergy* 2009; 39:387-393.
11. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter second update. *J Allergy Clin Immunol* 2007; 120(3 suppl):S25-S85.
12. Prakash OM, Murthy KR. Immunotherapy in allergic conjunctivitis. *Indian J Ophthalmol* 1992; 40(1):9-10.
13. Mimura T, Yamagami S, Amano S, Funtasu H, Arimoto A, Usui T, et al. Allergens in Japanese patients with allergic conjunctivitis in autumn. *Eye* 2005; 19:995-1001.
14. Bulawa E, Borysewicz G, Markiewicz K, Derentowicz P. Efficacy of specific immunotherapy in children with seasonal allergic rhinitis and conjunctivitis, sensitized to grass pollen [Polish]. *Med Wieku Rozwoj* 2001; 5: 351-358.
15. Wahn U, Taber A, Kuna P, Halken S, Montagut A, Beomont O, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2009; 123(1):160-166.