

Subcutaneous Allergen-specific Immunotherapy Versus Topical Treatment in Vernal Keratoconjunctivitis

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Purpose: The study evaluated the treatment of cases with vernal keratoconjunctivitis by subcutaneous allergen-specific immunotherapy (SCIT) versus topical treatment according to clinical improvement and total serum immunoglobulin (Ig) E.

Design: Prospective randomized study.

Methods: The study included 64 patients with bilateral vernal keratoconjunctivitis. Cases were divided into 2 groups: group 1, 32 patients who were subjected to topical treatment; and group 2, 32 patients who were subjected to intradermal skin reactions to different allergens. Prepared subcutaneous injections of different allergens were administered. Follow-up was performed to detect criteria of improvement according to clinical data and total serum IgE.

Results: The study revealed that the treatment by SCIT was more effective in improving the clinical symptoms and reducing the serum IgE than topical treatment because there was a greater reduction in symptoms in group 1 of immunotherapy (72%) than in group 2 of medical treatment (59%) ($P < 0.05$). Also, there was a significant reduction in total serum IgE ($P < 0.05$) in group 1 (62%) compared to group 2 (42%). However, the intradermal test for each group of patients showed that 62% of the patients were sensitive to pollens, 19% to house dust, and 19% to more than one allergen.

Conclusions: Treatment of vernal keratoconjunctivitis by SCIT was more effective than topical treatment in improving the clinical symptoms and reducing the total serum IgE.

Key Words: subcutaneous allergen-specific immunotherapy (SCIT), topical, vernal keratoconjunctivitis

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The treatment of vernal keratoconjunctivitis is a formidable challenge facing many ophthalmologists. It is a common clinical entity that causes considerable ocular morbidity. The results of common medical treatment for vernal

keratoconjunctivitis do not meet our expectations in most cases. The benefits of long-term use of corticosteroids decrease over time, and the application of corticosteroids is always risky because of its associated complications, such as raised intraocular pressure and cataract formation.¹

Immunotherapy is a process that gradually desensitizes the body to allergens by injecting tiny amounts of the allergen under the skin over the course of disease for certain durations. During immunotherapy, the body begins to develop a normal immune response to the allergen without the patient experiencing any violent symptoms, such as severe itching, burning sensations, redness, or watery eyes. Thereafter, every time the body is exposed to the allergens an immune response will be triggered.² Although immunotherapy may take several months or even years to produce acceptable results, it has a great ability to diminish the need for topical or systemic medications that may cause serious ocular complications.^{3,4}

The use of allergen-specific immunotherapy in treatment of allergic diseases was first described by Noon.⁵ However, many successful studies have promoted the development of allergen-specific immunotherapy. Subcutaneous allergen-specific immunotherapy (SCIT) was developed by Bousquet et al,⁶ involving injection of increasing quantities of allergen extract.⁷

Werfel⁸ encouraged the use of SCIT because he considered it one of the safest methods for desensitization. However, Burastero et al⁹ and Malling et al¹⁰ preferred the use of sublingual immunotherapy in the treatment of allergic diseases. Serum immunoglobulin (Ig) E is considered a good indicator for the progression of vernal keratoconjunctivitis because it represents the immune system's reaction to allergens, which is expressed in the serum and tear film.^{11,12}

PATIENTS AND METHODS

The prospective randomized study was carried out in the Ophthalmology and in the Microbiology and Immunology Departments of Zagazig University in Egypt from December 2007 to December 2009 and included 64 patients with bilateral vernal keratoconjunctivitis with positive intradermal test of allergens.

Cases were subjected to:

1. Ophthalmic history:

- Age, sex, occupation, and its relation to allergens such as dust, heat, and pollens.
- History of the disease, onset, course, duration, and medications.

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- History of the suggesting symptoms such as eye redness, itching, lacrimation, photophobia, ocular discomfort, and ropy eye discharge.
- Excluded from the study were cases with histories of other allergic diseases such as urticaria and bronchial asthma.

2. Full ophthalmological examination:

- With special consideration to conjunctival examination, for the presence of conjunctival injection, limbal vernal masses, palpebral cobble stone papillae, corneal epithelial plaques, ulcer, superficial punctate keratopathy, epithelial defects and shield ulcer.
- Intraocular tension using applanation tonometer.

The protocol for the research project was approved by a suitably constituted ethics committee of the institution where the work was undertaken, and it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Tokyo, 2004). The subjects gave informed consent, and the patients' anonymity was preserved.

- The intradermal skin test was conducted for all cases by injection of 0.1 mL of allergens intradermally on the inner side of the forearm at 10 separated areas 4 cm apart. Patients were told to discontinue systemic and topical medications 4 days before injection. Ten prepared allergens were used: pollen, smoke, fungi, house dust, hair, wool, cotton, agriculture dust, flower, and hay. The areas of reaction were measured according to the diameter of the erythematous skin; the reaction had to be more than 1 cm in diameter surrounding the puncture site, 30 minutes after injection.
- Subjects with negative intradermal tests were excluded from the study.

Patients were divided into 2 groups according to similar histories and intradermal test results:

1. Group 1 contained 32 patients who were treated topically:
 - Topical fluoromethonolone drops 5 times a day for 10 days during the period of exacerbation, followed by gradual tapering for another 10 days.
 - Topical antihistaminic drops, mast cell stabilizer (sodium chromoglycate) 3 times a day for the warm season.
2. Group 2 contained 32 patients who were subjected to immunotherapy.

SCIT was prepared in the Microbiology and Immunology Department of SCIT from the unfractionated extract of allergens in the aqueous form; allergen extracts were standardized as bioequivalent allergy units according to the Joint Task Force On Practice Parameters 2007¹³ to form standardized quality units.

The allergen extraction was made of Coca solution (pH 8.2) (4 g phenol crystals, 5 g sodium chloride and 2.5 g sodium bicarbonate in 1 liter of distilled water). The crude allergens were soaked with the Coca solution in a ratio of 1 g dry weight of sample per 10 ml of Coca solution for 24 hours at room temperature in a magnetic mixer. The extracts were concentrated to one-tenth of the original volume by dialysis in air and filtered through Millipore filter units (Millipore UK, Ltd). The protein concentrations were measured by BCA protein assay kit. The potency of homemade allergic extracts

was determined by in vitro comparison to a reference standard allergen. The extracted allergens were kept in labeled vials that contained 0.4% phenol as a preservative.

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

- Starting daily dose by 100 units (0.05 mL) of standardized quality units for 1 month.
- Increase the dose by 100 units to be taken of the vaccine for 24 months.
- Monthly systemic general medical examination, via the outpatient general medicine clinic, monthly during the study to evaluate any systemic clinical changes for the patients under therapy.
- An emergency medical care team was standing by for management of any acute side effects of immunotherapy, such as hemorrhagic skin reactions or anaphylactic reactions.

Both groups were subjected to:

1. Ophthalmological examination during study weekly for the first 2 months and monthly for further durations to determine the degree of improvement on the following criteria:
 - Symptomatic relief from ocular discomfort, itching, lacrimation, photophobia, and ropy eye discharge.
 - The disappearance of conjunctival injection, papillae, and limbal masses, healing of the preexisting shield ulcer, and resolving punctate keratitis.
2. Total serum IgE was measured using immunoblotting at a 1:100 dilution; bound IgE was detected with iodine-labeled antihuman IgE (pharmacia) at the start of the study (before treatment) and after 24 months of treatment.

Statistical analysis of results of both groups was performed using unpaired *t*-test; *P* < 0.05 indicated significance.

RESULTS

Sixty-four patients aged 8 to 21 years with a mean age of 13.5 years in group 1 and 13.6 years in group 2 were included in the study. Each group contained 23 males and 9 females. Ophthalmological examination revealed 22 cases of the palpebral type, 6 cases of the limbal type, and 4 cases of the mixed type of vernal conjunctivitis. For each group, intradermal skin tests with different allergens showed that 20 cases (62%) were sensitive to pollens, 6 cases (19%) were sensitive to house dust, and 6 cases (19%) had mixed allergen hypersensitivity.

Of the eyes receiving topical treatment, 19 (59%) had marked clinical improvement, 16 of which showed significant reduction in total serum IgE. Ten cases (31%) had intermittent clinical improvement during the period of steroid use, with 2 cases showing a reduction in total serum IgE. Three cases (10%) of group 1 showed no clinical improvement, 2 of which showed elevated serum total IgE.

Of the eyes receiving SCIT treatment, 23 (72%) had marked clinical improvement, 21 of which showed a significant reduction in total serum IgE. Nine cases (28%) had neither clinical improvement nor a reduction in serum IgE, except for 2 cases that showed a reduction in serum IgE despite persistent

TABLE 1. The Results of Detected Serum Total IgE in Both Groups

Patients	Group 1		Group 2	
	Before Treatment	After Treatment	Before Treatment	After Treatment
1	0.0167	0.0120	1.220	0.007
2	0.0238	0.200	0.876	0.005
3	1.067	0.764	0.879	0.276
4	0.956	0.743	1.002	0.278
5	0.076	0.071	1.657	0.378
6	1.768	0.276	1.999	1.992
7	1.987	1.123	0.980	0.289
8	0.778	0.777	0.876	0.209
9	1.670	0.876	1.002	0.001
10	1.765	1.763	1.236	0.003
11	0.976	0.810	0.871	0.278
12	2.007	0.867	0.025	0.025
13	0.876	0.300	0.671	0.265
14	0.760	0.122	0.023	0.002
15	0.065	0.012	1.209	0.120
16	0.544	0.045	1.098	0.006
17	0.875	0.870	1.118	0.654
18	1.870	1.870	2.003	0.287
19	1.007	0.760	1.980	0.922
20	1.980	1.129	0.870	0.188
21	0.099	1.098	0.761	0.211
22	0.670	0.670	0.087	0.087
23	0.555	1.120	0.990	0.991
24	1.007	0.178	1.980	0.098
25	1.000	0.003	1.650	0.298
26	1.098	1.097	1.098	0.654
27	0.878	0.878	0.909	0.909
28	0.998	0.999	0.888	0.112
29	0.996	0.995	0.189	0.098
30	1.096	1.096	0.098	0.001
31	1.467	0.008	0.092	0.092
32	1.900	1.100	1.008	0.233

symptoms. Among the 9 improved cases, 6 cases had mixed allergen hypersensitivity.

Group 2 (SCIT treatment) showed clinical improvement in 72% of cases compared to 59% in group 1 (topical treatment) ($P < 0.05$). All subjects that were sensitive to pollens had a reduction in serum total IgE.

In addition, there was reduced serum IgE in 18 cases (56%) in group 1 with topical treatment, compared to 23 cases (72%) in group 2 with SCIT treatment ($P < 0.05$). The present study reported no side effects in patients who were treated with SCIT (Tables 1 and 2).

DISCUSSION

Vernal keratoconjunctivitis is considered to be one of the most common immunological problems facing ophthalmologists, especially in seasons of warm weather in Egypt. Topical treatment has not always been a satisfactory

TABLE 2. Distribution Data of Both Groups

Data	Group 1		Group 2	
	Number	%	Number	%
Men	23	72	23	72
Women	9	28	9	28
Palpebral type of vernal conjunctivitis	22	69	22	69
Limbal type of vernal conjunctivitis	6	19	6	19
Mixed type of vernal conjunctivitis	4	12	4	12
Sensitivity for pollen	20	62	20	62
Sensitivity for dust	6	19	6	19
Mixed sensitivity	6	19	6	19
Cases with marked improvement	19	59*	23	72*
Intermittent improvement	10	31	—	—
No improvement	3	10	9	28
Reduction in serum IgE	18	56*	23	72*

* t test of significance.

treatment in most cases; SCIT treatment against the causative allergens may become the preferred treatment in such cases. As recommended by Frew et al,⁴ the present study was carried out using intradermal skin test, which was widely used for similar immunological diseases such as bronchial asthma, urticaria, and others.

In the present study most patients were sensitive to pollens (62%) and house dust (19%), which is in agreement with Prakash and Murthy¹⁴, who reported a similar ratio in their study and who consider pollens to be one of the most common allergens that trigger vernal keratoconjunctivitis. However, Mimura et al¹⁵ reported that “most cases were sensitive to house dust.”

The present study revealed that there was marked clinical improvement in 72% of subjects treated with SCIT for a period of 24 months, compared to 59% of topically treated subjects in group 1. Prakash and Murthy¹⁴ showed an improvement in 62% of cases treated by hyposensitization for 12–24 months, but Bulawa et al¹⁶ reported that “there was an improvement in 97% of the cases treated for a period of 3 years of hyposensitization.” The difference in the results could be attributed to either the duration of treatment or the types of allergens; it has been shown that longer durations have the highest percentage of improvement. By using serum total IgE as an indicator for the efficiency of the treatment and for monitoring the allergic conditions, Satwani et al¹² obtained laboratory evidence asserting that treatment with SCIT was far superior to topical treatment in managing cases of vernal keratoconjunctivitis. However, for a longer duration of immunotherapy, a higher success rate is required.

There were no systemic or local side effects for subcutaneous immunotherapy in any patients during this study. Wahn et al¹⁷ stated that “sublingual immunotherapy was safer than any subcutaneous injection immunotherapy,” particularly in children. Because only 2 of our subjects were children, it is very difficult to reach a valid conclusion regarding the safety of subcutaneous injection immunotherapy in children.

CONCLUSIONS

The treatment of vernal keratoconjunctivitis by SCIT was more effective than any topical treatment in improving the clinical symptoms and reducing the total serum IgE. Further research is required to determine the role of combined therapy using both methods in the treatment of such cases.

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