

# Efficacy of local conjunctival immunotherapy in allergic conjunctivitis

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## Summary

**Background:** Allergic conjunctivitis was a chronic inflammatory disease, usually associated with rhinitis. Several modalities of treatment were available, but few studies mentioned of immunotherapy which might had benefits in chronic and severe cases.

**Objective:** To evaluate efficacy and safety of local conjunctival immunotherapy (LCIT) using a mixed Dermatophagoides extracts for treatment of allergic conjunctivitis (AC)

**Methods:** A prospective, double-blind and randomized controlled trial (RCT) was performed on eighteen patients with positive skin prick test (SPT) reactions to house dust mites. They were randomized into 2 groups: 1) treated with LCIT and 2) treated with balanced salt solution (BSS) as a control for a 6-month period. Allergen extracts were prepared in eyedrops and given once daily in LCIT group. Efficacy was assessed by clinical scores and conjunctival provocation test (CPT).

**Results:** At 6 months, the CPT scores for the LCIT group reached statistical significance compared to the control group ( $p = 0.038$ ), but there were no statistically significant differences in signs ( $p = 0.591$ ), symptoms ( $p = 0.885$ ) and medication scores ( $p = 0.338$ ) between both groups. Patients in LCIT group were able to tolerate the allergen without developing any serious adverse events.

**Conclusion:** LCIT treatment significantly reduced CPT scores which indicated that the patients were able to tolerate the antigen better than their counterparts. However, LCIT alone at short period did not alleviate symptoms and signs of allergic conjunctivitis from multiple allergens. (*Asian Pac J Allergy Immunol 2010;28:237-41*)

**Key words:** Immunotherapy, allergic conjunctivitis, allergic rhinoconjunctivitis, LCIT, local immunotherapy

## Introduction

For the treatment of allergic conjunctivitis, most ophthalmologists prefer to use a combination of medications (topical eye drops and oral tablets). Since some patients suffer from chronic illnesses, prolonged medication use may cause some serious side effects, such as glaucoma, severe dry eye and cataract. Therefore, new alternative treatments that can reduce or stop the use of combination therapy would be highly beneficial to the patients in improving their quality of life (QOL).

An alternative treatment, allergen-specific immunotherapy (SIT), is used to desensitize the patients' allergic response by periodically applying certain allergens to various tissues for a certain length of time. Nowadays, subcutaneous immunotherapy is accepted worldwide for the treatment of allergic rhinitis patients and in preventing asthmatic attacks.<sup>1-4</sup> Its effects are long lasting after the patients have completed their immunotherapy. Another type of allergen-SIT, local conjunctival immunotherapy (LCIT), was recently introduced to treat allergic conjunctivitis.<sup>5-6</sup> This procedure also uses small amount of eye drops containing specific allergens instilled onto the conjunctiva. The dosages of the allergen are gradually increased until there is an immune reaction. It has been shown that patients with allergic conjunctivitis undergoing LCIT for one year saw a significant decrease in clinical

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signs and symptoms compared to the controls.<sup>7, 8</sup> There have been no reports of serious side effects from using this technique. Therefore, LCIT should be able to increase the patients' tolerance to antigens and control ocular allergy without relying on pharmacotherapy. This desensitization should persist after completing LCIT as seen in patients who have completed their SIT.

To our knowledge, there have been few studies published on LCIT as a treatment for allergic conjunctivitis patients (AC). These studies showed clinical improvement and improvement in laboratory findings. Therefore we decided to study and evaluate the efficacy and safety of this new technique in Thai patients by using conjunctival provocation test (CPT) and clinical scores as an assessment tool.<sup>9</sup> We desensitized our participants with a mixture of *Dermatophagoides* extracts which is one of the three most common in-house allergens detected in Thai children.<sup>10</sup>

## Methods

### Study design

This study was a prospective, double-blind and randomized controlled trial (RCT). The study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Written informed consent was obtained from each patients or their parents before starting treatment.

### Patient selection

Patients diagnosed with allergic conjunctivitis who had positive skin prick test (SPT) reaction to house dust mite [*Dermatophagoides pteronyssinus* (Dp) and/or *Dermatophagoides farinae* (Df)] were enrolled into the study. The study was conducted in adults or those older than 6 years. Additional exclusion criteria included: severe ocular allergies/diseases [vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and Giant Papillary Conjunctivitis (GPC)], history of previous immunotherapy, history of anaphylaxis or severe asthmatic attack, history of any drug, food or chemical substance allergy, or have chronic eye/systemic diseases.

### Skin prick test (SPT)

The patients were screened by using SPT. Standard aeroallergens in glycerinated normal saline were used. Glycerinated normal saline and 10 mg/ml histamine HCL were used as negative and positive control, respectively. Those who had a positive reaction to *Dermatophagoides*

*pteronyssinus* (Dp) and/or *Dermatophagoides farinae* (Df) were enrolled into the study.

### Conjunctival provocation test (CPT)

CPT was performed to determine the extent of conjunctival reaction to allergen after the patients were included in the study. A drop of mixture of mite antigens was applied to the right eye whereas a drop of balanced salt solution (BSS) was applied to the left eye as a control. After every 10 minutes, the concentrations of the allergen were increased as follows: 10, 100, 1000, until 10,000 AU/ml. The eyes were examined using slit-lamp microscope and were scored accordingly. Whenever a total score reached 7, the test was discontinued and a drop of topical anti-histamine was immediately applied to the right eye to degrade the reaction. CPT was performed twice, in the beginning and at 6 months period. Comparison of CPT scores was used to evaluate whether the patient had developed any tolerance to the house dust mite antigen.

### Treatment protocol

The patients were randomized, using a block of 4 randomization, into 2 arms: 1) treatment/LCIT group and 2) placebo/control group. The treatment group underwent LCIT for 6 months using house dust mite extracts, while the other received BSS as placebo. In the LCIT group, a drop of diluted antigen (a mixture of *Dermatophagoides* extracts, Greer labs, USA) was instilled both eyes once daily for 6 months. Initially, all the patients started with 10 AU/ml of allergen which later was increased to: 20, 50, 100, 250, 500 and 1,000 AU/ml. The treatment was personalized for each patient according to their toleration of the antigen. Treatment efficacy was assessed by clinical signs (hyperemia, mucous discharge, chemosis) and symptoms (itching, tearing) which were scored according to Alberson.<sup>11</sup> Patients with a total score of >7 out of 15 was considered positive for intolerance and hence would continue to receive the same dose. Step up treatment was postponed until the next visit. All patients were examined by a single-masked ophthalmologist (NK) every 2 weeks for 6 months.

### Safety assessment

Side effects were accessed and recorded according to the localization of the inflammation (local or systemic) and reaction of immune response (immediate or delayed).

**Table 1.** CPT results for the LCIT group

| Patient ID # | CPT before immunotherapy |                        | CPT after immunotherapy (after 6 months) |                        |
|--------------|--------------------------|------------------------|--|------------------------|
|              | Scores                   | Concentration (AU/ml.) | Scores                                   | Concentration (AU/ml.) |
| 5            | 8                        | 10**                   | 8  | 1000                   |
| 1            | 9                        | 1000**                 | 13                                       | 10000                  |
| 8            | 11                       | 1000**                 | 14                                       | 10000                  |
| 13           | 12                       | 1000                   | 12                                       | 1000                   |
| 15           | 11                       | 1000**                 | 11                                       | 10000                  |
| 17           | 9                        | 1000**                 | 9  | 10000                  |
| 2            | 5*                       | 10000                  | 6  | 10000                  |
| 10           | 7                        | 10000                  | 1  | 10000                  |
| 11           | 11                       | 10000                  | 12                                       | 10000                  |

\* Have negative CPT scores or no reaction to the antigens tested when used at the highest concentration

\*\* Indicates tolerance because an immune response occurred when the allergen was used at the highest concentration

### Statistical analysis

The Wilcoxon Signed-Rank test was used to access the different scores of CPT, clinical parameters and medication scores before and after treatment within the same group. The Mann-Whitney Rank-Sum test was used to compare the scores of CPT, clinical parameters and medication scores before and after treatment between the treatment and placebo groups. P-value <0.05 was considered to be statistically significant.

### Results

Eighteen patients were enrolled into the study. There were 10 males and 8 females with a mean age of  $\pm$  SD =  $20.5 \pm 13.41$  (range 7-48 years). One patient from the control group withdrew from the study after developing a corneal infection which eventually resolved after an aggressive topical antibiotics treatment. The treatment group was composed of 4 males and 5 females with a mean age of  $\pm$  SD =  $20.7 \pm 14.9$  whereas the control group had 6 males and 3 females with a mean age of  $\pm$  SD =  $20.3 \pm 12.6$ . There were no statistical differences among both groups for age, sex and clinical signs and symptoms at baseline.

At baseline, all patients were sensitive to house dust mite (Dp and Df). Fifteen out of 18 patients (83.3%) were sensitive to more than one antigen. These patients were also sensitive to cockroach (72.2%), cat (38.9%) and dog (11.1%) allergens.

Before initiating immunotherapy, three patients had negative CPT scores when we

**Table 2.** Scores for clinical signs and symptoms within each group before and after immunotherapy

| LCIT                      | At baseline     | After 6 months  | P-value** |
|---------------------------|-----------------|-----------------|-----------|
| Scores for clinical signs | $0.70 \pm 1.14$ | $1.36 \pm 1.36$ | 0.235     |
| Scores for symptoms       | $0.89 \pm 1.05$ | $0.67 \pm 0.87$ | 0.671     |
| <b>Placebo</b>            |                 |                 |           |
| Scores for clinical signs | $0.76 \pm 0.74$ | $0.98 \pm 0.90$ | 0.339     |
| Scores for symptoms       | $1.00 \pm 1.22$ | $0.50 \pm 0.50$ | 0.317     |

\*\*Wilcoxon Signed-Rank test

administered the highest concentration of allergens, 10,000 AU/ml, indicating that there was no reaction whatsoever to the antigens. Therefore, these three patients were excluded from the CPT analysis but because they had positive SPT reactions to house dust mite before CPT, their scores for clinical signs and symptoms were included in that part of the analysis. At the end of the treatment period, five out of nine patients from the LCIT group showed increased tolerance to the allergen (Table 1). The CPT scores of the intervention group was analyzed before ( $7.26 \pm 1.87$ ) and after immunotherapy ( $4.6 \pm 2.31$ ) using the same concentration of allergen. We detected a significant reduction of these scores ( $p = 0.038$ ) after immunotherapy.

The mean time to achieve the maximum tolerated dose in LCIT group was 97.6 days.

For the LCIT group, the mean scores for clinical signs and symptoms at baseline were  $0.7 \pm 1.14$ ,  $0.89 \pm 1.1$  and  $1.36 \pm 1.36$ ,  $0.67 \pm 0.87$  at 6 months, respectively (Table 2). The changes in scores for clinical signs ( $p = 0.235$ ) and symptoms ( $p = 0.671$ ) did not reach statistical significance after 6 months of treatment. We also found no statistically significant differences for clinical signs ( $p = 0.591$ ) and symptoms ( $p = 0.885$ ) between the treatment and control groups at 6 months (Table 3).

### Safety assessment

Overall, the treatment was well-tolerated. None of the patients in the intervention group developed any serious adverse events. Common complaints among some patients from the LCIT group were mild ocular irritation and a burning sensation felt immediately after instilling the

**Table 3.** Scores for clinical signs and symptoms for the treatment group versus the control group before and after immunotherapy

| At baseline               | LCIT        | Placebo     | P-value* |
|---------------------------|-------------|-------------|----------|
| Scores for clinical signs | 0.70 ± 1.14 | 0.76 ± 0.74 | 0.366    |
| Scores for symptoms       | 0.89 ± 1.05 | 1.00 ± 1.22 | 0.849    |
| <b>After 6 months</b>     |             |             |          |
| Scores for clinical signs | 1.36 ± 1.36 | 0.98 ± 0.90 | 0.591    |
| Scores for symptoms       | 0.67 ± 0.87 | 0.50 ± 0.50 | 0.885    |

\* Mann-Whitney Rank-Sum test

allergens into their eyes. These adverse events disappeared within 30 minutes. However, cold compressions were used to relieve the irritations and burning sensations in some cases.

Notably, only one patient from the placebo group dropped out of the study after developing a corneal infection which was resolved after receiving topical antibiotics.

### Discussion

For some time now, SIT has been used to increase patients' tolerance to specific antigens for the treatment of allergy. The trick here is to administer the appropriate concentrations of allergen extracts to desensitize the patient to certain antigens. Since allergen-SIT regulates the responses of T and B cells and effector cells involved in allergic inflammation such as eosinophils, basophils, and mast cells,<sup>12,13</sup> it can suppress and significantly decrease inflammation as shown in an animal study.<sup>6</sup> Furthermore, it has been shown that in allergic inflammation, infiltration by eosinophils is directly associated with the severity of the disease so if we can block this process by using immunotherapy, this may be an ideal treatment for patients suffering from allergy.

Even though CPT is not routinely used in clinical practice due to its complexity and lengthy process, however in this study, we decided to utilize this tool based on other studies.<sup>8,9</sup> In addition, it has been shown that CPT can provide useful information in regards to allergic responses and efficacy of the drugs.

Since the literature on the effects of ocular immunotherapy using eye drops is limited, this study attempted to investigate the efficacy of LCIT. It has been reported that seasonal allergic conjunctivitis showed a significant improvement in the patients' clinical scores and cytology after undergoing LCIT for 12 months.<sup>7</sup> In another study, a significant reduction of CPT scores could be seen as little as 6 months of therapy.<sup>8</sup> Based on the latter results and budget constraints, we decided to use 6 months of therapy instead of 1 year. In contrast to the above mentioned studies, the results of our 6-month study did not show any improvement in the scores for clinical signs and symptoms in the LCIT group when compared to the controls or within the group itself. It is possible that the treatment period may have been too short to detect any changes in clinical signs and symptoms. However, this seems unlikely since the CPT scores did reach statistical significance after 6 months of immunotherapy indicating that the patients had developed some tolerance to the antigens.

Another limitation of the trial is the study population. Most of our patients were sensitive to multiple allergens; 83.3% of our patients had reactions to house dust mite, cockroach, cat and dog. This finding is also supported by another Thai study.<sup>10</sup> In that study, the three most common allergens detected in each group were house-dust mite, house dust, cockroaches and grass (Bermuda, Johnson and Timothy grass). This limitation is an important factor because it is very difficult to recruit patients allergic to a single antigen. As a result of this, we did not exclude these patients from our study. It is possible that this could have affected the results of our study because we only used house dust mite as our allergen. The reason for this is due to the fact that house dust mite is the most common allergen found among Thais.

Furthermore, we did not include other antigens (house dust, cats and dogs) based on safety issues. There are no efficacy or safety reports using cockroach, cat and dog antigens in the eye drops.

Nevertheless, future studies are warranted including other antigens such as cockroaches, cats and dogs to ensure that there are no other confounding factors affecting the study. Moreover, we recommend that there should be a long follow-up period after the immunotherapy to

verify that there are no long term adverse effects attributable to this new technique.

**Conclusions**

In conclusion, this randomized controlled clinical trial (RCT) showed that LCIT was safe, well-tolerated and could increase tolerance to house dust mite antigens which was measured by CPT. Further investigation regarding cost effectiveness may establish the use of LCIT as a novel therapeutic option for the treatment of allergic conjunctivitis.

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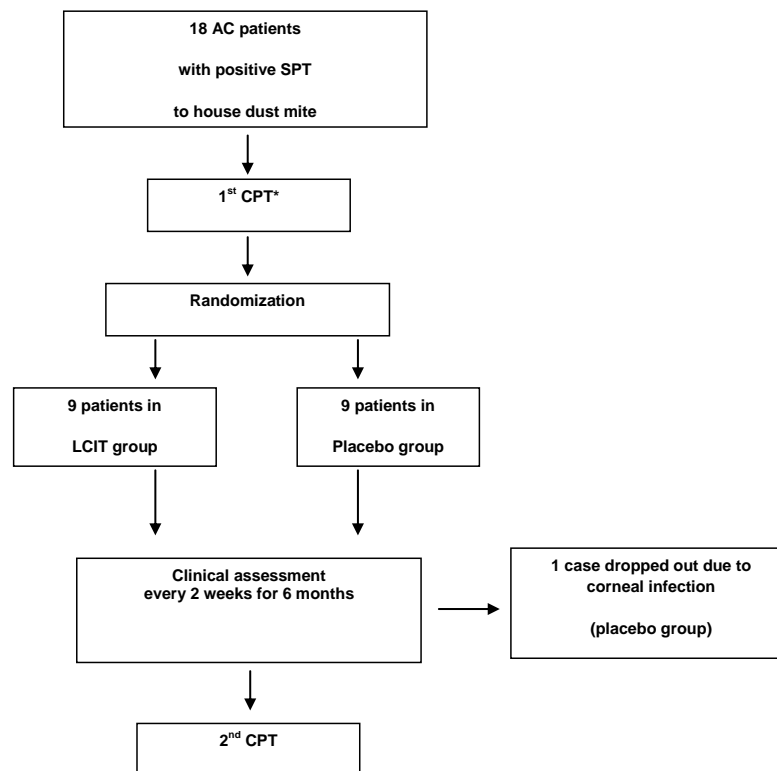
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**Study Design**



\* 15/18 had positive CPT