

Photodocumentation of Allergic Severity under Conjunctival Provocation

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Abstract. The aim of this work was to evaluate conjunctival redness as an objective allergy symptom during the conjunctival provocation test (CPT). The CPT is an instillation of ophthalmic solution containing an allergen into the ocular mucosa. Allergic severity using the CPT was evaluated in the multicenter, randomized, controlled, double-blind, dose-finding study of 159 patients with birch pollen allergy where the mucosal sensitivity of the eye was assessed based on subjective and objective symptoms such as itching and redness, respectively. High-resolution digital photos were taken, arranged in image matrices, and analyzed by an external central observer to assess conjunctival redness. The photodocumentation method described here was successfully applied in a dose-finding study using the CPT. The evaluations of allergic severity carried out by an external observer agreed with the investigators' assessments.

Keywords. photodocumentation; conjunctival provocation; composite score; allergic rhinoconjunctivitis

Introduction

The conjunctival provocation test (CPT) is an established diagnostic procedure used to test sensitivity to airborne allergens that cause allergic rhinoconjunctivitis. It has been thoroughly evaluated with regard to its precision [1] and compared with nasal provocation tests [2]. Nowadays, the CPT is utilized to evaluate allergic rhinoconjunctivitis [3] and is accepted by regulatory authorities as an outcome parameter. Here, we present the photodocumentation method developed for clinical studies with the CPT diagnosis as exemplified in a randomized, controlled, double-blind, dose-finding study of 159 patients with birch pollen allergy.

All study documents, including the study protocol, were reviewed and approved by the competent independent Ethics Committee and subsequent regional Ethics Committees on July 24, 2012, number: 2012185, and by an agency of the German Federal Ministry of Health (Paul Ehrlich Institute) on August 21, 2012, number: 1612/01. The EudraCT number is 2012-001822-89. The therapy and testing period of 12 weeks took place outside of the pollen season. The CPT was carried out using the instillation of one diluent without an allergen and 3 ophthalmic solutions with allergen concentrations of 100, 1000 and 10 000 SQ/ml of "ALK-lyophilized SQ" at 3 visits: at the beginning of therapy (t₀); during therapy, 4 weeks after t₀ (t₁ = t₀ + 4 weeks); and at the end of therapy, 12 weeks after t₀ (t₂ = t₀ + 12 weeks).

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1. Testing procedure

Before provocation, one (control) eye was treated with a diluent containing no allergen to reveal possible nonallergic sensitivity. In the case of a positive control eye reaction to the diluent without allergen, the patient was excluded from the study. The CPT was allowed only if the control eye showed no reaction. Investigators were instructed to wait 10 minutes to make sure the control reaction was negative. If so, the CPT started with instillations of allergen solutions into the provocation eye:

1. 100 SQ/ml dose was applied. If the severity score was $s_1 \geq T$ (threshold value), the test was positive and complete at the number of provocations $n = 1$. Otherwise:
2. 1000 SQ/ml dose was applied. If $s_2 \geq T$, the test was positive at $n = 2$. If $s_2 < T$:
3. 10 000 SQ/ml dose was applied. If $s_3 \geq T$, positive CPT was reached at $n = 2$.

Only provocations starting with instillation of the lowest dose and continuing with stepwise increasing allergen concentration solutions were permitted. Thus, each next allergic reaction resulted in equal or higher severity: $s_1 \leq s_2 \leq s_3$. To summarize the estimated allergic severity, a composite score C has been proposed [4] and successfully applied in several clinical studies with CPT:

$$C_j = \frac{\sqrt{\sum_{i=1}^n s_i^2}}{n^2}. \quad 1)$$

Here, s_i is a severity score at the i -th provocation and n^2 is the square number of provocations for the j -th patient. The decreasing C_j value indicates an improvement of the allergic severity. Each combination of the s_i results in a unique C_j .

2. Method: photodocumentation

During the CPT an investigator carried out the corresponding photodocumentation. Each center was furnished with the technical set for the CPT photodocumentation, which consisted of a foldable (35×15×15 cm) and lightweight (less than 4 kg) stand, LED macro ring, and camera. According to the instructions, the photodocumentation had to be produced according to the following requirements:

1. The camera configuration parameters for macrophotography are set and activated.
2. Before photographing the patient's eye, the investigator must take a photo of the adhesive label. The label has to clearly show the study name, visit number, patient ID, and the concentration of the provocation solution. A definite assignment of the patient's photo is only possible based on the corresponding adhesive label.
3. Focus on the conjunctival region is to be ensured.
4. The patient is to be asked to pull down his/her lower eyelid and fix his/her sight on a certain point to get a clear view of the conjunctiva. The patient's sight has to be fixed on the same point during all eye expositions throughout the study.
5. The investigator is to switch the macro LED light on, take a photo, and then switch the macro LED light off.

The set of original photos, produced as JPEG images of about 3.6 MB each, having a resolution of 3648×2736 dpi, was copied from the camera's SD card to the local server. The copied images were treated and arranged in an image matrix as shown in Figure 1.

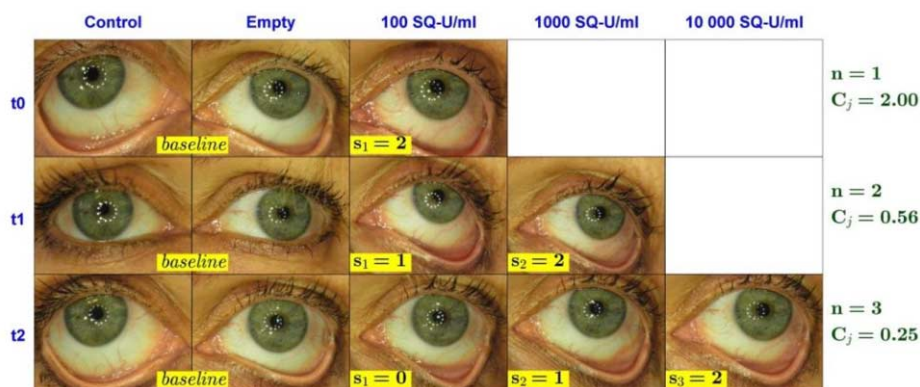


Figure 1. Image matrix with corresponding severity scores s_i , assessed by CPT. A row of images represents the photodocumentation at one visit: t0, t1 and t2 – before, during and after therapy, respectively. The number of provocations n and composite score C_j are shown in the right margin for each visit.

Figure 1 illustrates photodocumentation of j -th patient. The first two columns contain images taken at baseline (before provocation). After the study an external observer evaluated the collected images according to the following scale: 0 – no inflammation, 1, 2 and 3 – mild, moderate and severe redness of the conjunctiva, respectively. The assessed severity scores s_i are shown in the lower left-hand corners of the photos. The rows show when the CPT was carried out: t0, t1, and t2 represent the visits before, during and after therapy, respectively. The corresponding composite score C_j , calculated using Eq. (1), and the number of challenges n for each visit are presented in the right margin of each row. As described previously, a positive allergic reaction in the CPT can be reached after one, two, or three provocations. Figure 1 depicts all these possibilities: before therapy (t0) the CPT was stopped after the first challenge with instillation of 100 SQ/ml. During therapy (t1), the first provocation resulted in $s_1 = 1$, and the severity threshold was reached at the second challenge, $s_2 = 2$. After completion of therapy (t2), the mucosa resistance to allergen clearly improved in comparison to the previous visits. After the end of therapy, the j -th patient no longer reacted to 100 SQ/ml, $s_1 = 0$ and the reaction to 1000 SQ/ml was under the threshold: where $s_2 = 1$. The last challenge using 10 000 SQ/ml resulted in $s_3 = 2$.

This method, however, has two limitations: 1) the absence of the corresponding adhesive label results in a missing value, because the eye photo cannot be properly assigned to the corresponding CPT step, and 2) each time the eye must be exposed identically, *i.e.*, line of sight, lighting, and high quality focusing should be similar in all photos.

3. Results

Photodocumentation in form of image matrices was included in the analysis of the randomized, double-blind, controlled, dose-finding study of 159 patients with birch pollen allergy. The therapy and testing period of 12 weeks took place outside of the pollen season. The study medication at four dosages – M1 = 300, M2 = 600, M3 = 1000, and M4 = 2000 UA/day – was randomly distributed to the corresponding dosage groups of 41, 39, 39 and 40 patients, respectively. Each patient was treated

exclusively with one dosage. Before the end of treatment, 9 patients dropped out and 150 completed the study: 37, 36, 38 and 39 patients treated with M1, M2, M3 and M4, respectively. The corresponding image matrix was produced for each patient. The use of this photodocumentation enabled an external observer to independently evaluate conjunctival redness at any time after the end of the study. In Figure 2 an average allergic reaction versus time is shown for the groups of patients treated during the current study with medication at one of the four different dosages M1 – M4.

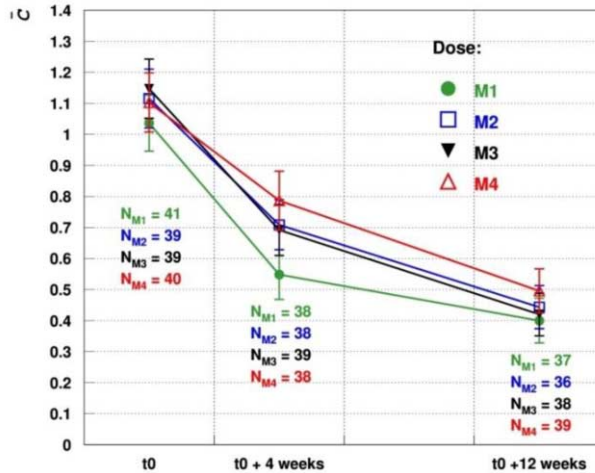


Figure 2. Mean composite score ($\bar{C}$), calculated using Eq. (1) and averaged over the corresponding treatment group is shown for three patient visits: t_0 , $t_1 = t_0 + 4$ weeks and $t_2 = t_0 + 12$ weeks – before, during and after therapy, respectively. Error bars represent standard errors of the mean.

4. Conclusions

The method described here constitutes a compact, demonstrative concept and permits control of the exact time at which the testing steps were carried out. These features are important with respect to healthcare management. Photodocumentation and the evaluation of allergic inflammation severity under conjunctival provocation were successfully applied in this study. The evaluations of allergic severity carried out by an external observer agreed with the investigators' assessments.

References

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