Original Article

Conjunctival Provocation Tests: A Predictive Factor for Patients' Seasonal Allergic Rhinoconjunctivitis Symptoms

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What is already known about this topic? Conjunctival allergen challenge (CPT: conjunctival provocation test) is a well-established diagnostic test used to demonstrate the topicality of an allergic sensitization.

What does this article add to our knowledge? The CPT can be used to predict symptoms that occur during the pollen season after a first course of preseasonal immunotherapy.

How does this study impact current management guidelines? Patients who react positively to the CPT after a first course of immunotherapy will benefit from the regular intake of symptomatic medication; others may use medication only as needed.

BACKGROUND: No parameters currently exist that can reliably predict the impact of preseasonal immunotherapy on the symptoms occurring during the season.
OBJECTIVE: The purpose of our studies was to prove a correlation between preseasonal conjunctival allergen challenge and coseasonal primary clinical endpoints using the total combined score, ie, a combination of symptoms and medication score, as the primary outcome parameter.
METHODS: Twelve weeks before both the birch and the grass pollen seasons, 2 separate prospective, double-blind, randomized, controlled studies were conducted followed by posttrial observations for each study during the active season. In the studies, patients who reacted to conjunctival allergen challenge were treated with sublingual immunotherapy tablets that contain either birch and/or alder or grass pollen allergoids.
RESULTS: In all, 158 patients were included in the grass and 160 in the tree pollen study; of these, 100 and 109 patients, respectively, took part in the posttrial observations. When comparing patients with and without a positive reaction in the final conjunctival allergen challenge, the results revealed a significant difference in the total combined score (grass: $P < .001$; birch: $P = .039$). The same applied to the rescue medication score ($P = .005$; $P = .025$). A significant difference regarding the rhinoconjunctivitis symptom score was shown in the grass pollen study ($P = .002$), and the difference of well days was significant in the tree pollen study ($P = .049$).
CONCLUSION: When comparing patients based on their reaction to allergen challenge after immunotherapy, each study leads to similarly significant results. Therefore, conjunctival allergen challenge can be used effectively as a parameter to predict allergic rhinoconjunctivitis symptoms during the season in patients treated with preseasonal sublingual immunotherapy tablets. Whether this can be transferred to untreated patients needs to be determined. **© 2015 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2015;■:■-■)**

Key words: *Conjunctival allergen challenge; Rhinoconjunctivitis; Outcome parameter; Sublingual immunotherapy*

Various outcome parameters have been proposed to assess the efficacy of specific allergen immunotherapy (AIT) in the treatment of allergic rhinoconjunctivitis (AR).[1] These endpoints are symptom scores, medication scores, and the combination of both, ie, the total combined scores (TCS) that can only be recorded during the pollen season. Additional parameters for assessing efficacy outside of the pollen season,[2,3] such as the patients' reactions in environmental exposure chambers[4] or to provocation tests, include the conjunctival provocation test (CPT), the nasal provocation test (NPT), bronchial provocation,

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The two prospective, double-blind, randomized, controlled studies were funded by Lofarma SpA, Milan, Italy. The funders had no role in study design, data collection, analysis and decision to publish or preparation of the manuscript.
Conflicts of interest: R. Mösges has received research support from Lofarma SpA, Ursapharm, Stallergenes, Optima, Convidia, Kooperation Phytotherapie, Klosterfrau, Hal, Hulka, Bitop Biotech Tools, Bencard, and AllPrevent; is on the board for ALK-Abelló, Stallergenes, Bencard, Meda, Biotech Tools, Menarini, Allergopharma, Leti, and ThermeMeran; has received consultancy fees from Alcon, Allergy Therapeutics, Bayer, Lofarma GmbH, Johnson & Johnson, Schwabe, and Asklepios; has provided expert testimony for Stada and Servier; has received lecture fees from Bencard, Meda, Bayer, GlaxoSmithKline, MSD, Novartis, Stallergenes, UCB Pharma (Union Chimique Belge), FAES Farma, BerlinChemie, and NeilMed; receives royalties from MIT Press and Urban & Vogel; and has received travel support from EAACI (European Academy of Allergy and Clinical Immunology), and HNOBerufsverband. A. Eichel and K. Shah-Hosseini have received research support from Lofarma SpA. The rest of the authors declare that they have no relevant conflicts.
Received for publication January 28, 2014; revised October 15, 2014; accepted for publication October 29, 2014.
Available online ■■
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2213-2198
© 2015 American Academy of Allergy, Asthma & Immunology
http://dx.doi.org/10.1016/j.jaip.2014.10.015

Abbreviations used
AIT- Allergen immunotherapy
AR- Allergic rhinoconjunctivitis
CPT- Conjunctival provocation test
dSS- Daily symptom score
DWD- Deutscher Wetterdienst
EMA- European Medicines Agency
IPD- Individual patient data
NPT- Nasal provocation test
NSS- Nasal symptom score
OSS- Ocular symptom score
PTO- Posttrial observation
RCS- Rhinoconjunctivitis symptom score
RMS- Rhinoconjunctivitis medication score
SLIT- Sublingual immunotherapy
TCS- Total combined score

and titrated skin tests.[2,3] Although the CPT is used in many studies for the evaluation of the efficacy of AIT,[5-7] it is also commonly used in the diagnosis of AR.[8] The CPT has been validated,[9] it is reproducible, and its results are independent of the choice of the eye used for the testing procedure.[10] Causing only a minimum of systemic allergic reactions, it is regarded as safe[10,11] and shows concordant results with skin prick tests in terms of systemic sensitizations, with the advantage of detecting more conjunctival sensitizations than skin tests.[12] Radcliffe et al confirmed the reproducibility of the skin prick test and the CPT. They did not, however, find a relationship between the CPT and seasonal symptom scores.[13] CPT results are highly comparable with those of the NPT[14] and bronchial provocation.[15] Furthermore, the CPT is performed easily.[9]

However, a rigid correlation between the results of the preseasonal CPT and coseasonal primary clinical endpoints such as the TCS has not been shown to date. For the treatment of AR in clinical daily practice, it would be of great advantage to have a parameter that can reliably predict the severity of symptoms expected to occur in the next pollen season.[6] We therefore performed a secondary analysis of 2 prospective, double-blind, randomized, controlled studies followed by posttrial observations (PTOs) for each study during the pollen season.

METHODS

Study population

These studies were conducted in 10 clinical centers in Germany with the consent of the Medical Ethics Committee, Ärztekammer Nordrhein, EudraCT No.: 2011-002174-23 ("grass pollen study") and 2012-001822-89 ("birch pollen study"), and the Paul-Ehrlich-Institute.[16,17] For the PTO, a positive vote was obtained by the Ethics Committee of Cologne University's Faculty of Medicine.

In the first study, grass pollen-allergic patients were treated with sublingual immunotherapy (SLIT) using grass pollen allergoid tablets. The second study focused on patients allergic to birch pollen who were treated with SLIT using birch and/or alder allergoid tablets. Both tablets are available on the German and the Italian markets. Female and male patients between 18 and 75 years of age were included who had a clinically relevant sensitization to the respective allergen and a history of AR of at least 2 years, with or without seasonal controlled asthma. A positive skin prick test and a positive response to the CPT were required in either case. This response was perceived as positive if the reaction of the eye was at least stage II (defined as itching, reddening, foreign body sensation, tearing, and vasodilation of the conjunctiva bulbi). Patients with a history of perennial AR, partly controlled or uncontrolled asthma, previous immunotherapy during the preceding 5 years, other significant medical conditions, and pregnancy, and patients under treatment with psychoactive drugs were excluded.

TABLE I. Stages of the reactions to the conjunctival provocation test (CPT)

Stage	Findings
0	No subjective or visible reaction
I	Itching, reddening, foreign body sensation
II	Stage I + tearing, vasodilatation of conjunctiva, bulbi
III	Stage II + vasodilatation and erythema of conjunctiva tarsi, blepharospasm
IV	Stage III + chemosis, lid swelling

Assignment and intervention

In the birch pollen study, 160 patients started the preseasonal SLIT treatment with LAIS birch pollen allergoid tablets (manufactured by Lofarma SpA, Milan, Italy)[18-20] in 4 different dosages: 300 UA/tablet (equals 1.05 μg Bet v 1), 600 UA/tablet, 1000 UA/tablet, and 2000 UA/tablet. The treatment phase lasted 84 days and was conducted preseasonally in the fall of 2012. The tablets were dissolved under the tongue for at least 3 minutes and then swallowed.

In the grass pollen study, 158 patients started the preseasonal SLIT with grass pollen allergoid tablets from the same manufacturer over a period of 3 months in the fall of 2011. The treatment plan was the same as that of the birch pollen study. All patients were supplied with an oral antihistamine as rescue medication (10 mg of loratadine) for control of local or systemic side effects, if required.

Randomization and blinding

Treatments were assigned to the subjects by means of a centralized, computer-generated randomization list divided in blocks of 8. The respective identification number was allocated to the patient in ascending order. Once a patient was randomized, no replacement of the patient was allowed. Both the investigators and patients were blinded as to treatment dosage. A copy of the randomization list was placed in a secure safe with restricted access. The individual, patient-related randomization codes were deposited in sealed opaque envelopes in the investigator site file, only to be opened in case of emergencies.

Measurement and assessment

During the SLIT treatment period the patients underwent 3 CPT procedures: at inclusion, after 4 weeks, and after 12 weeks (end of the study). In the clinical trial centers, otorhinolaryngologists specialized in the diagnosis and treatment of allergies performed the CPTs using 3 different test solutions (100 SQ-E/mL, 1000 SQ-E/mL, and 10,000 SQ-E/mL) in accordance with Riechelmann's method.[11] After all contraindications were ruled out, a control solution was administered into the conjunctival sac of one eye. If the patient reacted to the control solution, he or she was excluded from the trial. Otherwise, the lowest test solution (100 SQ-E/mL) was administered into the other eye. If after 10 minutes the response to the test solution was negative, the next higher solution (1000 SQ-E/mL) was administered. If it was again negative after 10 minutes, the highest solution (10,000 Sq-E/mL) was applied. If the highest allergen concentration still did not provoke a positive reaction,

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