

Allergic Conjunctivitis and Nasal Allergy

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Abstract Allergic conjunctivitis (AC) can be divided into the primary form (caused by an allergic reaction occurring primarily in the conjunctivae) and the secondary form (induced by allergic reaction originating primarily in the nasal mucosa, where the released mediators can reach conjunctiva through the lacrimal system, the blood, the lymphatic network, or the neurogenic network). Patients with primary AC develop an immediate, late, or delayed conjunctival response (CR) during conjunctival provocation tests. Patients with secondary AC develop an immediate, late, or delayed type of secondary CR, induced by the nasal allergic reaction, due to the nasal allergen challenge. Various hypersensitivity mechanisms may be involved in the particular CR types. The secondarily induced AC and CRs can only be confirmed by nasal provocations tests, performed by rhinomanometry combined with recording of conjunctival signs. The existence of the primary and secondarily induced AC has an impact on treatment of this disorder.

Keywords Allergic conjunctivitis · Nasal allergy · Nasal challenge with allergen

Introduction

Allergic conjunctivitis (AC) belongs to a group of very common disorders affecting a wide adult and pediatric population. Its incidence varies from 15% to 25%, depend-

ing on the population analyzed [1•, 2–6]. Seasonal allergic conjunctivitis (SAC) occurs most frequently, followed by atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), and perennial allergic conjunctivitis (PAC), whereas giant papillary conjunctivitis (GPC) appears sporadically. The SAC and PAC occur in relatively milder forms, whereas AKC and VKC, in which the cornea is also affected, appear usually in a bilateral and more severe form [1•, 2–6].

AC can be classified according to various criteria:

1. Acute, recurrent, or chronic form
2. Pollen- (SAC, VKC) or perennial allergen-related (AKC, PAC) forms
3. Forms limited to conjunctiva (SAC, PAC) or forms in which the cornea is also affected (AKC, VKC)
4. Regarding the presumably involved mechanism(s) in the primary form, in which the initial antigen–antibody interaction is located in the conjunctiva, or a secondary (induced) form, in which the initial antigen–antibody (sensitized lymphocytes) interaction, taking place in another organ (eg, nasal mucosal membrane), then induces secondarily the conjunctival response (CR)
5. With respect to the CR type (immediate, late, or delayed type), caused by different hypersensitivity mechanisms [1•, 2, 3, 5–10].

Symptomatology

The SAC and PAC exhibit clinical features related to the conjunctiva and lacrimal ways without producing cornea-related signs. The conjunctival signs include hyperemia (injection), chemosis, hyperlacrimation, sometimes palpebral edema, and sporadically limbus phenomenon. The

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subjective symptoms include itching, burning, blurred and “vague” vision, and photophobia. Under massive or long-term allergen exposure, papillary hypertrophy may also be observed [1•, 2–6].

The objective features of AKC and VKC are dominated by corneal signs, such as diminished corneal sheen, transparency and reflection, Horner-Trantas dots, cobblestoning, punctuate epithelial erosions, epithelial defects, and sometimes scars and papillary hypertrophy, in addition to the previously mentioned conjunctival signs. The accompanying subjective symptoms include itching, burning, disturbed (blurred) vision, foreign body sensation, photophobia, and ocular pain [1•, 2–6].

The SAC and PAC are represented by functional, reversible processes, whereas VKC, AKC, and (to an extent) GPC are characterized by functional-morphologic processes associated with mostly reversible damage of corneal epithelium, sometimes with temporary damage of the conjunctival epithelium, limbus, papillae, lacrimal way contractures, and complications (eg, scar formation or uveitis) [1•, 3, 6].

The objective signs and subjective symptoms of AC as well as their appearance during the conjunctival (CPT) and the nasal provocation tests (NPT) with allergens can be evaluated by a scoring (grading) system. Various scoring systems have been proposed in the literature [11–15]. However, the scoring system suggested by Abelson et al. [11, 12] is widely used. Nevertheless, the proposed scoring systems differ by the parameters registered and numbers of the grading points. Moreover, these scoring systems do not include all conjunctival and corneal signs and subjective symptoms typical of particular AC forms. Therefore, we have developed an improved modification of the scoring system (Pelikan’s scoring system), adding chemosis, palpebral edema, burning, blurred vision, and photophobia (Table 1) [9, 16•, 17•].

Pathogenesis of Allergic Conjunctivitis

The pathogenesis of SAC and PAC differs from that of VKC, AKC, and GPC in various aspects, already described in the literature [1•, 2–10, 16•, 17•, 18–22]. However, most of these studies deal with the role of immediate (IgE-mediated) hypersensitivity, including the mast cells, eosinophils, epithelial cells and T-helper type 2 (Th2) lymphocytes, and their products, in this disorder. The causal involvement of non-immediate types of hypersensitivity, such as late (type III) and delayed (type IV, cell-mediated) types in particular AC forms, remains insufficiently investigated [2, 7–10, 16•, 17•, 18–28].

Moreover, there is a dearth of information concerning the detailed role of other cell types, such as neutrophils, monocytes, thrombocytes, plasma cells, macrophages, fibroblasts, endothelial cells, goblet cells, glandular cell types, particular lymphocyte subsets (Th1, T-regulatory, cytotoxic T, and natural killer cells), and their products, in individual clinical AC forms. Knowledge is also sparse regarding the possible role of various factors in the pathogenesis of AC, such as individual H-, muscarinic, CD, and other receptors, both on the cellular membrane of various circulating cells and on the ocular tissue cell types, compounds mediating individual steps of particular immunologic mechanisms (eg, AA pathway metabolites), cellular traffic and signalling systems, ocular connective tissue, blood, and lymphatic capillary networks [1•, 2–10, 16•, 17•, 18–41].

Nevertheless, significant progress has been made in research of the pathophysiologic and immunologic mechanism(s) underlying the AC during the past years. Various factors and their concentration changes as well as new aspects of the role of various cell types have been detected in the conjunctival, corneal, and lacrimal tissue and the tears of patients with particular AC forms and in response to the allergen challenge. These data

Table 1 Survey of Abelson’s and Pelikan’s “modified” conjunctivitis grading scales and symptom scores

	Abelson I [11] ^a	Abelson II [12, 13] ^a	Pelikan ^b
I. Objective signs			
Hyperemia (injection, redness)	0–4	0–3	0–4
Chemosis	–	0–3	0–4
Hyperlacrimation (tearing)	–	0–3	0–4
Palpebral edema	–	–	0–4
II. Subjective symptoms			
Itching (burning)	0–4	0–4	0–4
Photophobia	–	–	0–4
Blurred vision	–	–	0–4

^a Abelson’s grading scale: 0—none; 1—mild (intermittent); 2—moderate; 3—severe; 4—extremely severe or “incapacitating” itching; significant threshold: ≥ 2

^b Pelikan’s evaluation scale: 0—absent; 1—mild (present to a slight degree or intermittent); 2—moderate; 3—pronounced (moderately severe); 4—severe; significant difference: ≥ 4 points ($P < 0.05$) with respect to the prechallenge value, recorded for at least 3 consecutive time points

differ with respect to the individual AC forms and their location [1•, 2–10, 16••, 17••, 18–41].

One of the important outcomes of many of these studies is the evidence for causal involvement of delayed (cell-mediated) hypersensitivity in some AC patients and for the key role of Th1 lymphocytes and their products. In such mechanisms, the Th1 cells may execute the causal effector and not only a regulatory role. This evidence would be consistent with our findings of delayed type of conjunctival and nasal response to allergen challenge, probably due to the cell-mediated (Th1-mediated) hypersensitivity [16••, 17••, 27, 28].

Mechanism(s) of Allergy Involvement in Allergic Conjunctivitis

The role of allergy in the pathogenesis of AC has already been widely discussed in the literature. Allergy can be involved in AC by various mechanisms:

1. The allergic reaction (the antigen–antibody or antigen-sensitized Th1 cell interaction, with subsequent steps), due to the direct exposure of conjunctiva to an external allergen, takes place primarily in the conjunctiva. In this case, the conjunctiva is the primary site of the allergic reaction, resulting in the development of the primary (or classical) AC form [1•, 3, 6, 9]
2. The allergic reaction occurs primarily in the nasal mucosa due to an intranasal exposure to an external allergen, resulting in nasal mucosal edema, which causes a nasal obstruction, hypersecretion, and sneezing. This nasal allergic reaction, leading to release of various mediators/factors and activation/inhibition of various cell types, may then induce a secondary AC form (Figs. 1, 2 and 3) via the mechanisms described subsequently [9, 16••, 17••, 27, 28]
3. The initial allergic reaction in the nasal mucosa does not cause any nasal response, but the released mediators/factors and relevant cells may reach the conjunctivae through one of the mechanisms described subsequently, inducing the secondary CR there [9, 16••, 17••, 27, 28]
4. The allergic reaction originates primarily in other, conjunctiva-unrelated organ(s), such as the nasopharynx with adjacent lymphatic structures, or intestinal mucosa in the case of food allergy, and the released mediators/factors and activated cells reach the conjunctivae through the hematogenic or lymphatic way, inducing the secondary CR there [16••, 17••, 27, 28, 40].

The allergic component involved in all AC forms may be a result of different hypersensitivity types, such as

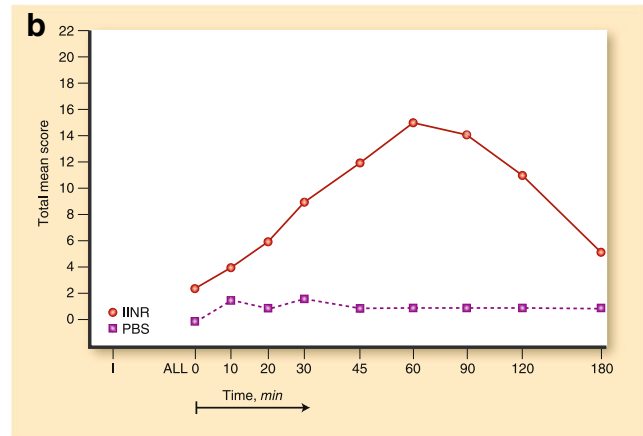


Fig. 1 The conjunctival responses accompanying the isolated immediate nasal responses (IINR, $n=27$). *B* refers to the mean total score of conjunctival signs and symptoms during IINR and PBS. ALL—allergen challenge; I—initial (baseline) value; PBS—phosphate buffered saline. (From Pelikan [16••]; with permission)

immediate (type I, IgE-mediated), late (type III), or delayed (type IV, cell-mediated), taking place primarily in the conjunctivae or in another organ with subsequent progression into the conjunctivae [1•, 2, 3, 5–10, 16••, 17••, 20, 23, 27, 28, 30, 31, 40]. The involvement of various hypersensitivity types in AC may result in three types of CR—immediate, late, and delayed—in the primary as well as secondary AC forms (Figs. 1, 2 and 3) [1•, 2, 5, 7–10, 16••, 17••, 20, 23, 27, 28, 31]. The particular types of CR are analogous to the three types of nasal response [16••, 17••, 28]. Additionally, the nonspecific hyperreactivity resulting from direct stimulation of mucosal, glandular, or neurogenic receptors by nonspecific agents might participate in the conjunctivitis complaints, although usually to an unimportant degree [5, 28, 32].

The Role of the Nose and Nasal Allergy in Allergic Conjunctivitis

The relationship between the conjunctivae and lacrimal ways and the nasal cavity and nasal mucosa is realized on both the anatomic and functional levels. These aspects include not only the connection of the conjunctiva with the nasal cavity by means of the lacrimal duct through its opening into the nasal cavity, thus facilitating the tear drainage, but also the connection of both organs through blood vessels, lymphatic tissue, and the neurogenic network, all expressing some links and sharing common properties. Thereby, the two organs can influence each other [1•, 2, 9, 16••, 17••, 27, 28, 30, 33, 38, 40–50].

Hypersensitivity reactions occurring primarily in the nasal mucosa as a consequence of intranasal exposure to external inhalant or food allergens may affect the conjunctiva

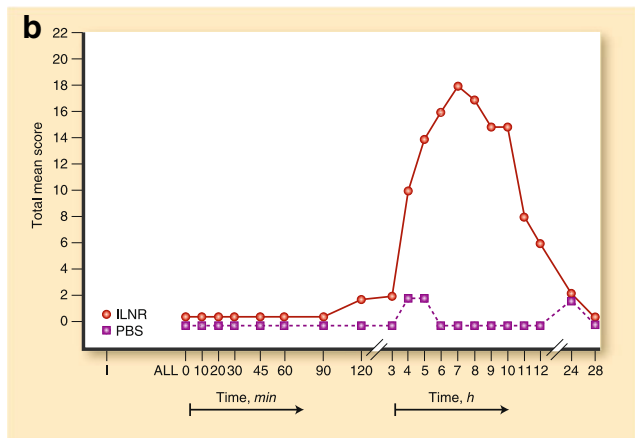


Fig. 2 The conjunctival responses accompanying the isolated late nasal responses (ILNR, $n=41$). *B* refers to the mean total score of conjunctival signs and symptoms during ILNR and PBS. ALL—allergen challenge; I—initial (baseline) value; PBS—phosphate buffered saline. (From Pelikan [16••]; with permission)

and lacrimal ways, and subsequently also the cornea, in various ways and upon involving different mechanisms:

1. The mediators, cytokines, immunoglobulins, adhesion molecules, and other factors released during allergic reactions in the nasal mucosa may reach the conjunctiva and subsequently also the cornea directly via the retrograde penetration through the lacrimal duct and system
2. The released factors can also be transported to the conjunctiva by the bloodstream through the related local blood vessel system, including arteria maxillaris-pars pterygopalatina, vena facialis, and plexus pterygoideus
3. Many cell types activated by the nasal allergic reaction, such as mucosal mast cells, basophils, eosinophils, neutrophils, thrombocytes, plasma cells, B lymphocytes, particular subsets of T lymphocytes (Th1, Th2, T-regulatory cells, and natural killer cells), dendritic cells, monocytes, and macrophages, can migrate through the bloodstream and/or the lymphatic stream into the ocular tissue
4. The local neurogenic network (sensory nerves, sympathetic and parasympathetic fibers), stimulated by the nasal allergic reaction, can release neuropeptides (neurotransmitters), which reach conjunctiva through the appropriate neurogenic links (nervus trigeminus, nervus nasociliaris, and ganglion pterygopalatinum)
5. The factors released by the nasal allergic reaction may stimulate the local nasal mucosal lymphatic system (“nose-associated lymphatic tissue”), belonging to the general “mucosa-associated lymphatic system.” This expresses manifold mutual communication with the lymphatic network both of the lacrimal system, such as “tear duct-associated lymphatic tissue” and “lacrimal

drainage-associated lymphoid tissue,” and of the conjunctiva (“conjunctiva-associated lymphatic tissue” and “eye-associated lymphatic tissue”) [28, 38, 42–48]. In this way, the transmission of various signals and the traffic of various cell types, such as B lymphocytes (plasma cells) producing immunoglobulins of various classes, T lymphocytes (Th1 and Th2, cytotoxic, T-regulatory, and natural killer cells), and other cell types, can be effectuated [1•, 3, 5–7, 9, 10, 16••, 17••, 18–26, 28, 30, 34–38, 42–50]. The cell traffic is realized not only by means of attraction mechanisms, governed by chemotactic factors, cytokines, lymphokines, and adhesion molecules, but also through the so-called “homing” mechanism of the B and T lymphocytes, controlled by several homing factors. The disturbed homing mechanism leads to the migration of the particular cell types to different localities. The particular subsets of lymphocytes, which were initially activated in one tissue before migrating into the bloodstream and/or lymphatic network to finish their maturation process, do not return to this original tissue, but due to the disturbed homing factors, they migrate into other tissues on different localities (so-called “wrong homing”) [16••, 17••, 38, 49, 50].

Diagnostic Confirmation of the Allergy and Nasal Allergy in Allergic Conjunctivitis

The diagnostic confirmation of allergy in a patient’s ocular complaints can be performed using various techniques, with skin tests and radioallergosorbent test/ImmunoCAP (the

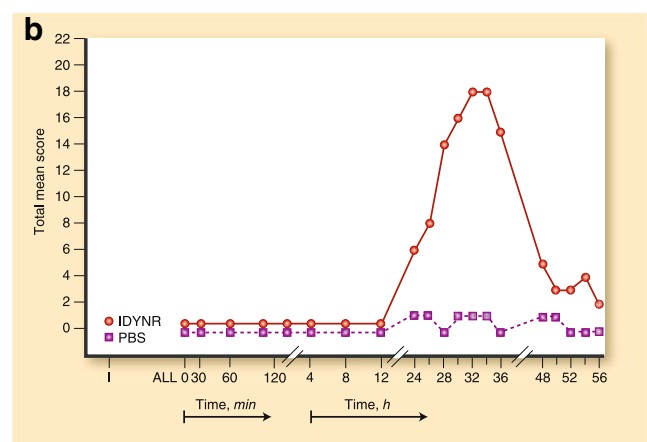


Fig. 3 The conjunctival responses accompanying the isolated delayed nasal responses (IDYNR, $n=8$). *B* refers to the mean total score of conjunctival signs and symptoms during IDYNR and PBS. ALL—allergen challenge; I—initial (baseline) value; PBS—phosphate buffered saline. (From Pelikan [16••]; with permission)

allergen-specific IgE in serum; Phadia, Uppsala, Sweden) being the most frequently used. However, these tests provide only general evidence for the existence of hypersensitivity mechanism(s) elsewhere in the body, without specification of their localization in the particular organ. They cannot reveal which of the hypersensitivity mechanisms results in the particular response type in a particular organ. Moreover, these tests cannot detect the possible engagement of the organ-related local antibodies. These tests generate only static data at a certain time interval without any information on the dynamic aspects. Finally, they did not correlate satisfactorily with the clinical features of AC [1•, 4, 5, 9, 16••, 17••, 27, 28, 30, 39].

The provocation tests with allergens are the only method capable of: 1) confirming an allergic component in the particular or related organ, 2) demonstrating the causal role of the particular allergen in the patient's complaints, 3) measuring quantitatively the individual organ response types in their dynamic course, 4) distinguishing between the participation of the allergic component and the nonspecific hyperreactivity in the patient's complaints, 5) detecting the causal role of an allergic component originating in one organ in the secondarily induced response in another organ, and 6) investigating the effects of particular drugs on the individual organ response type [12, 16••, 17••, 18, 23, 28, 31, 40, 51]. As a well-established technique, CPTs are not usually included in routine diagnostic procedure [1•, 4, 5, 7, 8, 11, 12, 18, 23, 31, 39, 51]. These tests, performed directly on the conjunctiva, are capable of showing different types of the primary CR, such as an immediate and late response, resulting from direct exposure of the conjunctiva, and subsequently also the cornea, to a certain allergen [1•, 4, 5, 7, 8, 11, 12, 18, 23, 31, 39, 51]. The immunologic mechanisms underlying the particular CR types may be different. Evidence has been found for the existence of a primary form of delayed (cell-mediated) type of CR mediated by Th1 cells [1•, 2, 5, 10, 12, 19, 20, 24]. However, CPTs cannot detect CRs induced secondarily by an allergic reaction initiated in another organ, such as the nasal mucosa. Such secondary CR forms can only be demonstrated by NPT, performed by rhinomanometry, in combination with simultaneous registration of ocular and subjective symptoms (Figs. 1, 2 and 3) [9, 16••, 17••, 27, 28].

Additionally, several techniques investigate various physiologic, pathologic, and immunologic functions and features in the eye. These tests, usually conducted for research purposes, may sometimes also be useful for diagnostic conclusion and/or therapeutic decision. The functional tests include measurement of tear production, function of lacrimal glands and system, and blood flow in the conjunctival capillaries. The morphologic, pathologic, and immunologic tests consist of those performed on the

conjunctival biopsy specimens (eg, histo-, radio-, and immunochemical examination of various structures, cells, intracellular structures, and factors); those performed on tears (eg, determination of mediators, cytokines, adhesion molecules, chemotactic factors, CD molecules, constituents, and products of various cell types in different stages [activation/inhibition]); morphologic aspects of particular cell types; and their intravasal, extravasal, and tissue-related traffic, such as migration, penetration, and mutual interaction. These tests can be performed as a single determination or repeatedly in conjunction with allergen provocation tests to follow the dynamic aspects of particular changes [3–8, 10, 19–26, 30, 34–37].

Allergic Conjunctivitis and Food Allergy

Food allergy also may be involved in the pathogenesis of AC in some patients. In practice, the possible role of food allergy is incidentally suspected in patients with allergic rhinitis, but not in AC patients. The diagnostic procedures for food allergy, usually limited to the skin tests and/or serum determination of specific IgE antibodies, are insufficient in consideration of the possible involvement of food through different hypersensitivity mechanisms, some of which being even non-IgE-mediated. Moreover, skin tests as well as specific IgE determination are single static tests generating neither organ-specific data nor dynamic aspects of a certain organ-related response type to a particular food. Such results can only be generated by the food ingestion challenge. There is a dearth of information on this topic. According to our as-yet-unpublished data, CR induced by the primary nasal response to food ingestion challenge has been recorded. Nevertheless, primary CR without the initial nasal response to food ingestion challenge has also been observed sporadically. We have recorded all three types of primary and secondary CR (immediate, late, or delayed) analogous to the three types of nasal response to food ingestion challenge. According to our preliminary data, the CR to food were prevented significantly by oral cromolyn (Nalcrom; Sanofi-Aventis, Paris, France) analogously to its effect on the nasal response caused by foods [28, 40, 52].

Therapeutic Management of Allergic Conjunctivitis

Effective treatment may be a logical consequence of the adequate diagnostic procedure [25, 49, 50]. General management of AC consists of allergen avoidance as much as possible, protection of the eyes with glasses/goggles, concomitant disorder treatment, and rinsing of the conjunctivae and/or nose with sterile saline [1•, 53••].

Therapeutic measures include pharmacologic treatment and immunotherapy. Specific pharmacotherapy and choice of particular drugs depend on various factors:

1. The primary AC form should be treated with local ocular drugs, whereas the secondary AC form should be treated with a combination of intraconjunctivally and intranasally administered drugs
2. Differences between AC affecting only the conjunctivae (SAC, PAC, GPC) and that also targeting the cornea (AKC, VKC)
3. The additional participation of the nonspecific hyper-reactivity component in the patient's complaints
4. The type of allergens involved: seasonal versus perennial, occupational allergens, incidental versus continuous exposure, mono- versus polyallergenic exposure
5. The involvement of the particular CR type—an immediate, late, or delayed type—or a combination of CR/nasal response
6. The aspects concerning the considered drugs: indications/contraindications, administration form, effectiveness, side effects, tolerability, and suitability for intervention versus preventive treatment [1•, 52, 53••].

Many excellent surveys concerning the drugs used for treatment of ocular allergy have already been published [1•, 2, 3, 5, 6, 30, 52, 53••, 54, 55]. However, reports concerning the clinical effects of particular drugs in AC patients vary. The variations of the effectiveness of particular drugs may be caused by selection of patients who are not always comparable and/or by inadequate diagnostic procedures, especially the lack of allergen challenges.

The results of our early studies using CPTs as well as NPTs demonstrated excellent protective effects of ocular cromolyn on the primary immediate and late CR types, whereas it had no effect on delayed CR. The comparable effects of intranasal cromolyn have been observed in the secondarily induced CR types. Intranasal cromolyn prevented in a highly significant manner induced immediate and late CRs, but not induced delayed CR. In some patients who developed a primary or secondarily induced late CR, the conjunctival administration of cromolyn did not prove to be fully effective. In these patients, a combination of ocular and intranasal cromolyn yielded the full therapeutic effects [9, 27, 28, 52].

In contrast, topical ocular glucocorticosteroids demonstrated significant protective effects on the primary delayed CR, whereas they were ineffective on the primary immediate and late CRs. Intranasally administered glucocorticosteroids significantly prevented both the secondarily induced late and delayed types of CRs, but not the induced immediate CR [28, 52].

Nedocromil sodium, administered topically in the conjunctiva, demonstrated highly significant protective effects against the primary immediate and late CRs and partial protective effects against the primary delayed CR. Administered intranasally, this drug was significantly effective in preventing the secondarily induced immediate and late CRs and partially also the delayed type of CR [28, 52].

In our long-term clinical experience, cromolyn and/or nedocromil sodium administered simultaneously intraconjunctivally and intranasally and supplemented with one of the H1-receptor antagonists have been distinctly effective in 75% to 80% of AC cases, especially those induced by allergic rhinitis [27, 28, 52]. The insufficient effects of both drugs as reported in some papers were probably a result of inappropriate selection of patients, deficient diagnostic procedures, lack of ocular and/or nasal allergen challenge, inadequate indication for treatment, and/or insufficient daily dosage (<4 times/d) [28, 52].

Ocular glucocorticosteroids may be used only in cases of severe AC, for a short period of time (<2 weeks), and under monitoring of intraocular tension with respect to the possibility of serious side effects, especially an increase in intraocular pressure, cataracts, and infections [53••, 54, 56].

Interestingly, H1-, H2-, and H3-receptors have not yet been demonstrated on the membranes of human mast cells. Evidence has been provided for the existence of H2-receptors on human circulating basophils. Receptors for glucocorticosteroids have not yet been confirmed on the membranes of human mast cells, whereas they have been demonstrated on human basophils, eosinophils, and T lymphocytes. In contrast, receptors for disodium cromoglycate and partially for nedocromil sodium have been found on the membranes of human mast cells, basophils, eosinophils, and neutrophils. These facts are consistent with our results and will give rise to an important unanswered question concerning the mode of action of both H1-receptor antagonists and glucocorticosteroids [28, 52].

Immunotherapy must be considered a treatment relevant only for selected AC patients with well-defined indications. This treatment is suitable only for SAC or PAC patients sensitized to a low number of allergens, in whom the IgE-mediated hypersensitivity is confirmed almost exclusively and who demonstrate only an immediate type of primary or secondary CR to allergen challenge. The polyallergenic sensitization and nonimmediate types of CR and/or NR represent a relative contraindication for this treatment [52, 53••, 55]. During the past few years, vaccines with recombinant allergens have been under investigation, and preliminary results are very promising.

Currently, a sublingual immunotherapy is being studied intensively. However, in most of these studies, not fully appropriate methods (eg, the inaccurate selection of patients and controls, inadequate diagnostic procedures, lack of

provocation tests with allergens, and inappropriate monitoring of therapeutic effects) resulted in presentation of unconvincing data.

Conclusions

Two forms of AC may be distinguished, a primary AC form resulting from an allergic reaction occurring in the conjunctiva and a secondary AC form induced by an allergic reaction originating primarily in the nasal mucosa. Patients with primary AC form may develop an immediate, late, or delayed CR during the CPT. Patients with secondarily induced AC form may develop analogous types of CR during nasal challenges with allergen. Different hypersensitivity mechanisms may participate in the particular CR types. Nasal challenges with allergen performed by rhinomanometry in combination with recording of ocular and subjective symptoms may be a useful diagnostic procedure for detection of the secondarily induced AC. They may also have an important therapeutic impact.

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- Of major importance

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