

Practical approach to diagnosis and treatment of ocular allergy: a 1-year systematic review

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Purpose of review

A 1-year systematic review in the field of ocular allergy was carried out to select new information which may be useful for a practical approach to allergic conjunctivitis.

Recent findings

Out of the 56 articles listed by PubMed, 27 papers were included in the review following a consensus achieved among the authors who had independently reviewed all abstracts. Selected articles were classified according to their main focus: antihistamines, omalizumab, new treatments for vernal keratoconjunctivitis and inflammatory ocular disorders, and sublingual immunotherapy.

Summary

The data reviewed are discussed with the aim of underlining unmet needs and making recommendations for future studies on diagnosis and treatment of ocular allergy which may better guide clinical practice in this important area of allergy and clinical immunology.

Keywords

allergic conjunctivitis, antihistamines, ocular allergy, sublingual immunotherapy, vernal keratoconjunctivitis

Introduction

Pharmacology of ocular allergy has recently been reviewed by Schultz in this journal [1[•]]. We made a systematic review of all the articles published after this paper to select new information which may help in forming a practical approach to diagnosis and treatment of allergic conjunctivitis.

Method

A literature search was carried out of all articles published in the last 12 months which are listed on the National Library of Medicine (PubMed) as of 30 April 2007. Key words used were ocular allergy, diagnosis; ocular allergy, treatment; allergic conjunctivitis (with the following limits: articles in English; human studies). On the basis of listed abstracts, the authors independently selected articles relevant to the objective of the review. After discussing and agreeing on criteria for the selection of papers suitable for the review, these papers were grouped according to their major focus. They were then reviewed and discussed in order to draw conclusions on the information obtained, the unmet needs and recommendations for future work.

The list of ongoing clinical trials reported on the web site <http://www.clinicaltrials.gov> at the same time point was also considered.

Results

Fifty-six papers were found, including clinical trials, editorials, reviews, metaanalyses, and practice guidelines.

After exclusion of overlapping articles and articles not dealing with a practical approach to diagnosis and treatment of ocular allergy (allergic conjunctivitis), 27 articles were selected: 11 reviews and 16 clinical trials, all dealing with treatment.

Reviews

Only a few reviews were based on a systematic search of the literature [2[•]]. Some of them dealt with the different forms of allergic conjunctivitis (such as vasomotor perennial chronic conjunctivitis [3^{••}]; atopic conjunctivitis [4]; contact lens conjunctivitis [5]; vernal conjunctivitis [6]; and conjunctivitis in children [7[•]]). Other reviews dealt with general [1[•],8] or specific [9,10] treatments. One review [11[•]] addressed the interesting issue of ocular toxicity of systemic asthma and allergy treatment.

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Abbreviations

IgE immunoglobulin E
RCT randomized controlled trial
VKC vernal keratoconjunctivitis

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Clinical trials

Out of the 16 clinical trials published during the review period, 12 were randomized controlled trials (RCTs). Only a few papers had been published in journals ranked for impact factor at the top of the specialty list [12]. Most of the papers were published in journals with a low impact factor or not indexed by ISI (more frequently allergy journals, rarely in ophthalmology journals).

According to the type of treatment under study, papers were grouped according to four major topics: antihistamines, omalizumab, new treatments for vernal keratoconjunctivitis (VKC) and ocular inflammation, and sublingual immunotherapy. Ongoing clinical trials were also reviewed.

Antihistamines

The effects of levocetirizine on ocular allergy were studied in a RCT of 50 patients [12]. The study, however, was primarily aimed at evaluating the effects of the drug on symptoms, quality of life and inflammatory parameters in patients with allergic rhinitis and asthma. Ocular symptoms were only included as a secondary outcome of the study.

The three other papers [13–15] deal with olopatadine versus epinastine, levocabastine and ketotifen. The effects of the treatment are evaluated through a surrogate marker of allergic conjunctivitis – largely used in ocular allergy studies – that is, the conjunctival response to allergen challenge.

Omalizumab

The study reports on the efficacy and safety of an anti-IgE humanized monoclonal antibody in Japanese cedar pollen-induced seasonal allergic rhinitis [16^{*}]. Daily ocular symptom medication score and related variables were considered as secondary efficacy variables. Primary and all secondary efficacy outcomes were significantly better in the omalizumab group than in the placebo group ($P < 0.01$). Adverse reactions were similar (apart from local reactions at the injection site) and no omalizumab antibodies were detected.

New treatments for vernal keratoconjunctivitis and ocular inflammation

Topical 2% cyclosporine A in preservative-free artificial tears (14 weeks) and short-term low-dose (0.01% for 2 weeks) mitomycin C were proven effective in severe forms of VKC [17,18], while tacrolimus ointment was used with success for treatment of refractory anterior segment inflammatory disorders [19].

Sublingual immunotherapy

Eight studies deal with this new form of hyposensitization in allergic individuals [20–24,25^{*},26,27^{**}]. As previously noted, these studies also often refer to rhinoconjunctivitis and the effect of treatment on symptoms of ocular allergy has to be dissected from the effects on nasal symptoms or is considered as a secondary outcome (Table 1).

Although no metaanalysis was performed, all studies document the clinical efficacy and safety of sublingual immunotherapy on allergic eye symptoms in both adults and children [24] with pollen allergy, independently from the different administration schedule used: preseasonal [23], ultra-rush [22], high dose [21], low dose [26], once daily [20,24].

Ongoing clinical studies

Ten ongoing clinical trials are listed on <http://www.clinicaltrials.gov> – eight in the recruiting phase, two not yet recruiting. One study focuses on facial thermography as a diagnostic tool in allergic conjunctivitis. Among treatment studies, two studies deal with contact lens conjunctivitis and three with VKC (Nova 22007, Cyclosporin A, Lactobacillus Rhamnosus GG). Olopatadine, Bepotastine besilate and Sublivac are also under study for treatment of allergic conjunctivitis.

Discussion

In spite of the high prevalence and clinical relevance of ocular allergy, there were not many ad-hoc rigorous clinical trials in the period under review when compared with the number of reviews or with the many large RCTs performed in other allergic diseases. Moreover, ocular symptoms were often considered as ancillary symptoms

Table 1 Studies of sublingual immunotherapy in ocular allergy

Authors	Type of trial	No. of patients	Diagnosis	Endpoints
Worm [21]	RCT, DM, PC	88 children	RC, grass	SMS IgG1, IgG4 antibodies
Valovirta <i>et al.</i> [25 [*]]	RCT, PC three arms		RC, trees	SMS
Bordignon and Burastero [26]	Open	64	RC grass or birch	Drug consumption skin reactivity
Dahl <i>et al.</i> [27 ^{**}]	RCT-DM, PC	634	RC grass	SMS
Vervloet <i>et al.</i> [22]	DM, PC	76	RC cypress	SMS
Rodriguez <i>et al.</i> [20]	RCT, DM, PC	135	RC	Adverse events
Rak <i>et al.</i> [24]	RCT, DM	855	RC	Quality of life
Palma-Carlos <i>et al.</i> [23]	RCT, DM, PC	33	RC	SMS

DM, double masked; Ig, immunoglobulin; PC, placebo controlled; RC, rhinoconjunctivitis; RCT, randomized controlled trial; SMS, symptoms/symptom score.

to a nasal disease. Allergic conjunctivitis is a heterogeneous disease including different pathophysiological and clinical phenotypes [2[•],3^{••},4–6,7[•]]. Clinical trials not focussed on ocular allergy do not provide enough information on the type and severity of ocular involvement.

Moreover, the number of patients in the studies reviewed – apart from those focusing on sublingual immunotherapy – was low, ranging from 100 [16[•]] to four [19]. While this may be acceptable for the two studies investigating a rare disease such as VKC – which recruited 20 and 28 patients, respectively [17,18] – it is certainly less acceptable in a highly prevalent disease such as intermittent or persistent allergic conjunctivitis.

Fifty percent of the clinical trials on ocular allergy dealt with sublingual immunotherapy (Table 1), confirming the increasing interest in this form of treatment in allergic patients [28[•]]. The reported efficacy of sublingual immunotherapy on eye symptoms – as on airways symptoms – together with its safety, make this easy form of hypo-sensitization particularly useful in allergic individuals with multiorgan involvement, also from a pharmacoeconomics point of view. Different treatment schedules, however, were used in the studies reviewed. Only comparative studies may provide information on the best schedule to be followed in clinical practice.

Anti-IgE treatment represents a new fascinating approach to the treatment of allergic diseases, and asthma in particular [29]. The study by Okubo and coworkers [16[•]] shows that omalizumab is also effective and safe in the treatment of allergic conjunctivitis (and rhinitis) in Japanese cedar seasonal allergic rhinoconjunctivitis. The costs and the recent warnings of the potential risks of this form of treatment, however, do not support including pollen allergic rhinoconjunctivitis among the primary indications of anti-IgE. These factors should not, however, preclude its use in uncontrolled moderate-persistent/severe asthma – with or without nasal and ocular symptoms. By contrast, the favourable results reported by Okubo and coworkers on ocular allergy should stimulate clinical trials of omalizumab in other forms of severe allergic conjunctivitis – such as atopic and vernal keratoconjunctivitis – in which the lack of effective and safe treatments often results in serious eye complications and even vision loss.

Unmet needs and recommendations

On analysing the findings from reviewed studies, various unmet needs were highlighted that should guide further translational research in ocular allergy:

Study population

The articles selected for this review [2[•],3^{••},4–6], clearly underline the pathophysiological and clinical features of

the different forms of ocular allergy. No practice parameters or practical flow charts are available, however, for dissecting the heterogeneity of a ‘red eye’. Surprisingly, no single study was performed in the period under review on diagnostic methods, which may be useful in classifying patients with ocular allergy. Ocular symptoms, however, were often evaluated in a subjective way in patients classified on the basis of their sensitization or rhinitis or asthma. No one would study the effect of a drug on asthma by selecting patients with rhinitis and considering bronchial symptoms as secondary outcomes! Accordingly, clinical trials of ocular allergy should be specifically targeted to patients with allergic eye diseases, adequately classified for the type and severity of the ocular involvement according to standard diagnostic procedures.

Study design

Only RCTs on a large number of well selected patients may provide evidence robust enough to be included in specific guidelines for practical management of ocular allergy. A metaanalysis of studies on a small number of patients and with different endpoints cannot provide the same convincing information that may arise from large polycentric studies with standardized outcome measures. Polycentric studies appear to be mandatory, particularly in phenotypes of ocular allergy – such as VKC – which are rare, variable with time, and lack standardized diagnostic endpoints and outcome measures.

Evidence produced

Management of diseases, in general, and ocular allergy, in particular, must be based on concrete evidence. Only registration of trials can avoid duplication of studies, allow polycentric collaboration with an increased number of patients recruited and raising the power of the trial, and enable the research to be published in a top journal. Moreover, registration of trials is the only way to guarantee that negative results are considered as well as positive ones. The low number of ongoing trials listed on <http://www.clinicaltrials.gov> is not a good premise that the evidence likely to be produced in the next few years will be more reliable than that found in the studies reviewed here.

Centralized archives of registered trials, including those promoted by the pharmaceutical industry, and independent collaborative research – with special emphasis on head-to-head trials – would certainly guarantee a grading of the evidence produced and better evaluation of its quality.

Conclusion

Ocular allergy is a challenging issue for allergists and ophthalmologists in clinical practice. The studies reviewed, although limited in number, give valuable

information on new options for treatment but, mainly, provide indications for future translational research in allergic eye disease.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 456–457).

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