

Clinical trials in allergic conjunctivitis: a systematic review

F. Mantelli¹, A. Lambiase¹, S. Bonini² & S. Bonini¹

¹Department of Ophthalmology, Campus Bio-Medico University of Rome, Rome; ²Department of Internal Medicine, Second University of Naples, Naples, Italy

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Correspondence

Professor Stefano Bonini, Department of Ophthalmology, Campus Bio-Medico University of Rome, Via Alvaro del Portillo 21, 00128 Rome, Italy.
Tel.: (+39) 06-225419185
Fax: (+39) 06-22541456
E-mail: s.bonini@unicampus.it

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Abstract

Background: Ocular allergy represents one of the most common conditions encountered by allergists and ophthalmologists. However, there is wide variability of study designs in clinical trials of allergic conjunctivitis, which results in conflicting evidence on their optimal management. We conducted a systematic review of clinical trials to critically evaluate their quality and to highlight biases to be avoided in future clinical research in ocular allergy.

Methods: Clinical trials in allergic conjunctivitis performed since 1965 were retrieved, and data on patients, interventions, comparison of interventions, and outcomes were extracted. Four authors independently assessed articles for inclusion in the systematic review and assessed trials' quality using the Jadad scale.

Results: Three hundred and sixty-two trials were included in the study. Only a minority of trials fulfilled all the criteria of proper clinical trial design. In most of the studies, there was a very limited use of objective (quantifiable) parameters for both patients' selection and evaluation of drug efficacy and safety. Several outcomes of primary importance, such as disease relapses and recurrence rate, were omitted in clinical trials of allergic conjunctivitis.

Conclusions: Evidence coming out of clinical trials in ocular allergy is limited, and this affects the strength of recommendations to health care providers and policy makers for optimal management. Standardized diagnostic criteria for patient selection and quantifiable primary outcomes are recommended to improve the design of future clinical trials in allergic conjunctivitis.

Allergic diseases have dramatically increased in the last decades (1). Among them, ocular allergy represents one of the most common clinical conditions encountered in clinical practice. Moreover, in the last years, an increase in its worldwide prevalence has been observed because of an increased use of contact lenses, an increased exposure to environmental factors such as smoke and pollution, and an increase in associated atopic disorders (2–4). In a recent survey in Italy from tertiary referral centers, ocular allergy accounts for 25% of all the ocular surface diseases (5).

In fact, the term of ocular allergy includes distinct clinical conditions, such as Seasonal or Perennial Allergic Conjunctivitis (SAC and PAC), Vernal Keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC) (6, 7). Another form of allergic conjunctivitis, named Giant Papillary Conjunctivitis (GPC), is usually observed in contact lens wearers (8). The presence of conjunctival papillae or follicles, the type of conjunctival secretion, the involvement of the cornea, and the prevalence of specific symptoms, such as itching, redness,

burning, photophobia, tearing, or dryness, may help in the differential diagnosis between these different forms of ocular allergy (9).

While SAC and PAC generally represent a mild-to-moderate disease, in AKC and VKC, inflammation frequently involves the cornea, resulting in more severe symptoms and possibly permanent visual damage (10–12).

In spite of the clinical, immunologic, prognostic, and therapeutic differences of these clinical entities, they may all share a common allergen sensitization, similar symptoms, but a variable response to topical antiallergic, anti-inflammatory, or immunosuppressive agents (13). The efficacy of topical antiallergic compounds has been extensively studied in the last 45 years as their number increased after the launch of the first antiallergic eye drops, Cromolyn, in the 1980s (14–16).

In the present systematic review, we evaluated the clinical trials in allergic conjunctivitis published from 1965 to 2008, as well as the most recent clinical trials (registered on <http://www.clinicaltrials.gov>) that have started in the last 5 years

and are either currently recruiting patients or have recently been completed. These studies were evaluated following the evidence-based 'PICO question', retrieving data on: Patients, Interventions, Comparison of interventions, and Outcomes (primary and secondary) (17–19).

This review aims at a critical evaluation of the major flaws of clinical trials performed up to now, to recommend a more adequate study design for future studies in allergic conjunctivitis.

Materials and methods

The articles were identified through a computerized search of clinical trials, in the Cochrane Controlled Trial Register-CENTRAL/CCTR (which contains the Cochrane Eyes and Vision Group trials register), the Cochrane Library, MEDLINE, and EMBASE. Keywords/Search terms for disease were 'Allergic conjunctivitis', 'allerg* AND conjunctiv*' explode 'allergic AND conjunctivitis'/all subheadings, 'allergic rhinoconjunctivitis', 'allergic rhinoconjunctivitis', 'allerg* AND rhinoconjunctiv*' explode 'allergic AND rhinoconjunctivitis'/all subheadings, 'allerg* AND rhinoconjunctiv*' explode 'allergic AND rhinoconjunctivitis'/all subheadings. Articles in all languages with English abstract were obtained, and articles written in English, French, German, Italian, Portuguese, and Spanish were considered for selection. References in all relevant articles as well as the reviewers' personal collections of articles on allergic conjunctivitis were also searched. In this systematic review, we included trials in which any topical treatment (antihistamines, mast cell stabilizers, multiple action antiallergic drugs, vasoconstrictors, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, cyclosporine, and other immunomodulatory compounds) and/or immunotherapy have been compared to no treatment, placebo or to another antiallergic drug.

All types of study design were considered for inclusion in this systematic review, including masked and unmasked studies, single- or multi-center, as well as randomized, quasi-randomized, and nonrandomized studies. An evaluation of trials' quality based on their design was conducted using the Jadad scale (20).

This scoring system is based on a three-point questionnaire in which each question has to be scored with 'YES' (1 point) or 'NO' (0 points). The questions to be addressed are the following:

- 1 Was the study described as randomized?
- 2 Was the study described as double blind?
- 3 Was there a description of withdrawals and dropouts?

Based on the method of randomization and blinding used in the trials, additional two points may be given, resulting in a final score ranging from zero (poor quality) to five (excellent quality). It is generally accepted that studies with Jadad scores of 3 or greater reflect 'good' reporting quality, whereas ratings of <3 reflect qualitatively poorer studies, impacted by a lower internal validity.

Four observers – divided into two groups of two – independently performed the literature search. The search resulted in a total of 677 titles. After matching the decisions of the two groups of observers, 79 papers were immediately

excluded because they were not clinical trials. Of the remaining 598 titles, 255 were also excluded because not related to allergic conjunctivitis. Therefore, 343 full abstracts were retrieved. In addition, the most recent clinical trials registered on <http://www.clinicaltrials.org> in the last 5 years (up to April 2009) either recruiting patients, ongoing, or completed were searched with the same criteria, and additional 85 trials were found, for a total of 428 studies.

Reviewers assessed in pairs the abstracts resulting from electronic searches. The article's eligibility was initially determined by evaluating the titles, abstracts, and MeSH (medical subject headings). The full copy of all those that definitely or potentially met the inclusion criteria was obtained for further assessment of eligibility. Reviewers were not masked to trial results or publication details during the assessment. Articles were excluded if they were not clinical trials on allergic conjunctivitis, or if they were not retrieved after performing all available search strategies, including request to authors and editors. After matching the decisions of the two groups, 66 articles were accordingly excluded because they were not related to ocular allergies. Therefore, 362 trials were finally included in the systematic review for matching the inclusion criteria. The full text of these papers was retrieved, and data were extracted using a standard form to determine the characteristics of the patients enrolled, the interventions evaluated, a comparison among all interventions, the primary and secondary outcomes of the clinical trials.

Results

Study design

Out of the 362 studies included in this systematic review, 23% were multicenter and 77% single-center trials (Fig. 1A); 84% were masked, randomized trials, and 16% were open-label trials (Fig. 1B). Based on the study design, the trials under examination scored a mean 2.8 ± 1.2 points according to the Jadad scale. Specifically, 4% of the trials scored 0 points, 11% scored 1 point, 26% scored 2 points, 28% scored 3 points, 25% scored 4 points, 6% fulfilled all the established criteria of proper clinical trial design and scored 5 points (Fig. 1C).

Evaluations of therapeutic interventions in clinical trials of allergic conjunctivitis were most frequently performed through environmental studies (environmental allergen exposure). In 16% of the trials, the effectiveness of interventions was evaluated by conjunctival allergen challenge (CAC).

Population

The number of clinical trials performed in ocular allergic diseases indicates that most of the studies were performed on SAC and PAC. This tendency probably reflects the fact that these forms of ocular allergy are the most common in clinical practice (21). Together, they represent 81% ($n = 293$) of all the clinical trials performed. However, it must be noted that 90 of these trials on SAC and PAC enrolled patients affected with Rhinoconjunctivitis instead of patients with ocular symptoms alone.

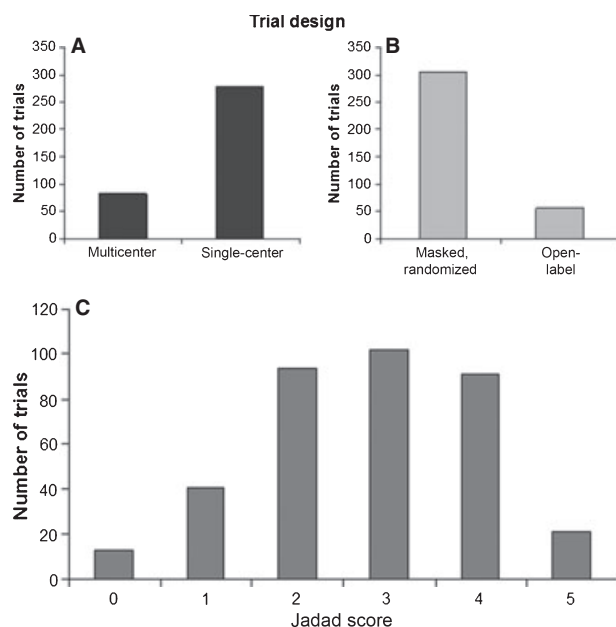


Figure 1 Graphic representation of clinical trials' design shows that only a minority of clinical trials performed from 1965 to 2009 were multicenter (A), and 16% of them were not masked, randomized studies (B). As shown in panel C, only a minority of trials fulfilled all the established criteria of proper clinical trial design according to the Jadad scale.

On the other hand, trials on VKC and AKC account only for 13% ($n = 47$) and 4% ($n = 14$), respectively, and trials on GPC for 2% ($n = 7$) (Fig. 2). A limited number of trials ($<1\%$) also enrolled healthy, nonallergic subject, to assess ocular comfort after topical application of antiallergic eye drops.

The overall number of patients enrolled in the clinical trials included in this systematic review was 44 206, with a mean 122 patients per study. The trials with the lower number of participants were those on AKC and VKC, with a mean 16 and 40 patients included per trial, respectively. The

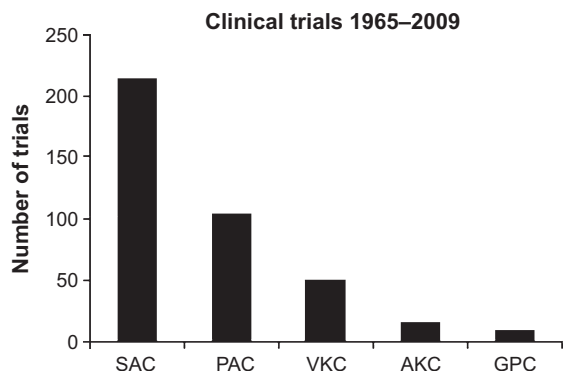


Figure 2 Graphic representation of ocular allergic diseases evaluated in clinical trials published since 1965.

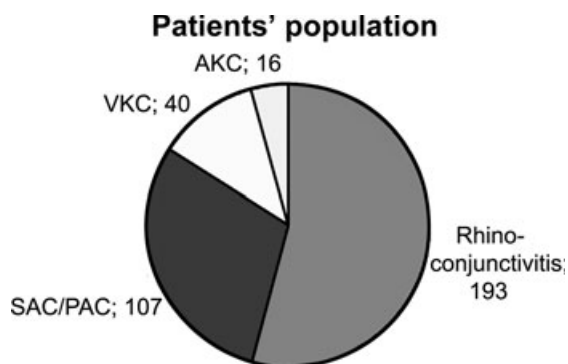


Figure 3 Graphic representation of the mean number of patients enrolled per trial. As shown, the trials on ocular allergic disease with the largest population were those on rhinoconjunctivitis, while those with the smaller population were on atopic keratoconjunctivitis.

trials with the highest number of participants were those on Rhinoconjunctivitis and SAC/PAC, with a mean 193 and 107 patients included per trial, respectively (Fig. 3).

Intervention

Most of the studies investigated the efficacy of antihistamines and antiallergic compounds – such as mast cell stabilizers and ‘multiple action’ drugs – (65%), followed by immunomodulatory agents such as corticosteroids, Cyclosporine-A and tacrolimus (13%), sublingual immunotherapy and vaccines (13%), – NSAIDs – (5%), and other therapies (4%) including Mytomicin-C, natural products, vasoconstrictors, and saline solution eye washes (Fig. 4). A large proportion of the studies evaluating immunomodulatory agents (38%) were performed on the more severe forms of allergic conjunctivitis – VKC and AKC – despite these forms of ocular allergy represent only a minority of the trials included in this study.

When evaluating the trend of clinical trials performed over the years (Fig. 5), after the launch of the first antiallergic eye drops (Cromolyn) in the 1980s, the number of clinical trials performed on allergic conjunctivitis rapidly increased up to 2003, when a decline began. The declining number of studies

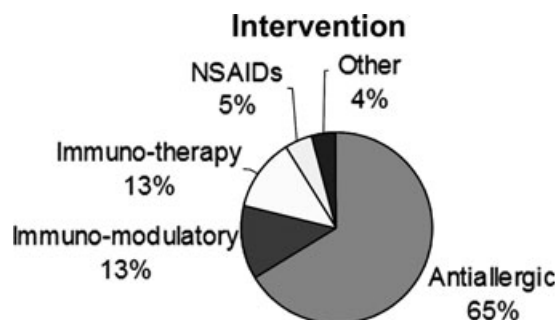


Figure 4 Graphic representation of therapies evaluated in clinical trials published since 1965.

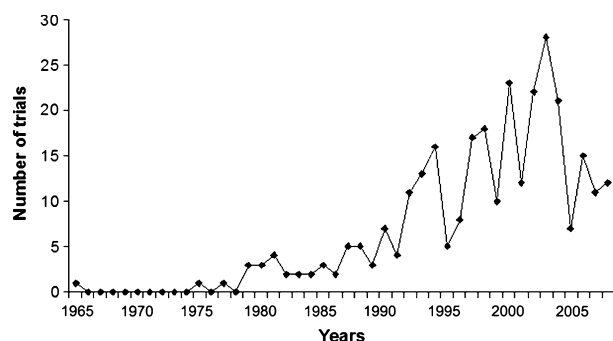


Figure 5 Graphic representation of the number of clinical trials published every year since 1965.

in recent years might be related to the limited number of new drugs introduced in the market and/or to a considerable number of ongoing clinical trials that have not yet been published.

Comparison of interventions

The vast majority of trials included in this study evaluated the efficacy of antihistamine drugs, mast cell stabilizers, and multiple action antiallergic molecules in a 'head-to-head' setting. In these studies, one antiallergic drug is compared to: (i) another antiallergic drug, or to the same drug in a different formulation or concentration (29%); (ii) other drugs (7%) including NSAIDs, immunotherapy and immunomodulatory agents, and antimetabolites (such as Mytomicin-C). Studies *vs* placebo – vehicle alone – only accounted for 27% of the total and mostly refer to immunomodulatory agents and immunotherapy. A relatively large number of trials (7%) evaluated an antiallergic drug, without using a placebo control or another comparator.

The limited number of trials performed on NSAIDs shows a higher variability of intervention, with trials performed 'head-to-head', *vs* placebo, *vs* antiallergic compounds, and *vs* immunomodulatory agents, in similar proportions.

Outcome measures

The majority of studies included in this systematic review focused on the efficacy of the drug under investigation, while few studies considered safety issues as primary outcome measures (Fig. 6).

In most of the studies, the main clinical parameters considered as primary outcomes were represented by composite scores, such as total symptoms and signs. In the remaining studies, specific parameters such as ocular itching and redness were used. Symptom scores were often based on the subjective assessment of the patients on the efficacy of the drug under investigation. Only very few clinical trials have considered validated patient-related outcome measures, such as the quality of life (QoL), or other validated tests became available in more recent years (22). It is also noteworthy that relapses/recurrences of the disease received minor consideration, while they represent a constant finding in the most severe forms of ocular allergy and a relevant outcome measure for evaluating disease control (23).

Discussion

In this study, we systematically and critically reviewed clinical trials in allergic conjunctivitis published in the last 45 years. Several major limitations were documented in the studies reviewed. The evidence coming out of our systematic review allows to make several considerations on the study design, patients' population, types and comparison of interventions, and outcome measures. It also allows to suggest

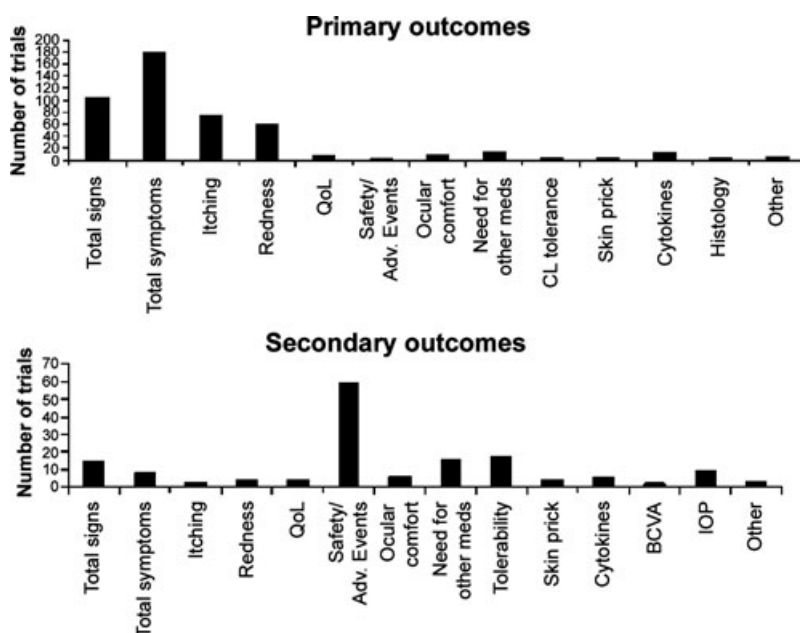


Figure 6 Graphic representation of primary and secondary outcomes evaluated in clinical trials investigating therapeutic interventions for ocular allergic disease, published since 1965. (QoL, quality of life; CL, contact lenses; BCVA, best corrected visual acuity; IOP, intraocular pressure).

some recommendations for future clinical research in allergic conjunctivitis.

Regarding trials' design, we have shown that only a minority of studies was conducted with a randomized, masked design, using placebo as comparator (as required by the lack of an accepted gold-standard treatment). In fact, only a limited number of trials fulfilled all criteria of proper clinical trial design according to the Jadad scale. Masked, placebo-controlled studies are not always feasible for ethical reasons in severe diseases with corneal involvement, which can result in long-term complications (including sight loss) if not properly treated (24). However, even when a masked design is used and the best available therapy is adopted as comparator, randomization is still essential to avoid a selection bias.

Most of the studies reviewed were single-center, parallel group studies. The optimal study design may depend on the type, severity, and prevalence of the different forms of allergic conjunctivitis. While single-center studies may reduce variability in patient selection and endpoints' evaluation, multicenter studies might be preferable for rare forms of allergic conjunctivitis – such as AKC and VKC – to increase the number of patients recruited and to reinforce the power of the study.

Therefore, while future clinical trials in allergic conjunctivitis may still require different clinical settings and study designs, they should always follow the widely accepted criteria of good clinical practice and reporting, as recommended by the Consolidated Standards of Reporting Trials – CONSORT – guidelines (25).

Regarding patients' population, we have shown that the majority of trials dealt with SAC and PAC. Only few trials enrolling small study populations were conducted on VKC and AKC, despite these forms are the most severe phenotypes of ocular allergy, still waiting for an adequate treatment. Moreover, studies performed on SAC and PAC often included patients with rhinoconjunctivitis (25% of trials) and used total symptom scores (composed of both ocular and nasal symptoms) as primary outcomes. In these circumstances, it is very difficult to distinguish between the effect on rhinitis and that on conjunctivitis.

Therefore, we feel to recommend that future clinical trials should give more importance to the severe forms of allergic conjunctivitis and possibly be based on standard diagnostic criteria and classification (such as those adopted by Allergic Rhinitis and its Impact on Asthma -ARIA- classification for allergic rhinitis) (26) to reduce heterogeneity in patients' populations.

Regarding clinical outcomes, we have shown that most of the trials used composite scores (such as total signs and symptoms) to evaluate the efficacy of the drugs tested. The use of composite scores is still largely debated with several arguments for and against (27). In our opinion, composite outcomes may be inadequate when combining minor endpoints (such as redness) to hard endpoints (such visual acuity). When unique endpoints are used as primary outcome measures, these should be specific and relevant for the type of ocular allergy considered. For instance, while itching can be a relevant endpoint for SAC and PAC ('there is no ocular

allergy without itching' (28)), the degree of corneal involvement represents a more reliable endpoint for AKC and VKC.

Although surrogate endpoints may be very useful for a better understanding of the disease mechanisms and for defining different phenotypes of ocular allergy, hard clinical endpoints should usually be preferred as primary outcomes. With reference to the above, while the majority of trials in allergic conjunctivitis is represented by environmental studies – in which patients suffer allergy symptoms triggered by environmental allergens – a large proportion (approximately 16%) of trials on SAC and PAC has also been performed using CAC (29). This test is used to test antiallergic compounds with a fast and reproducible response. However, while it has been accepted by FDA in USA, to date, it remains only supportive of environmental studies in Europe. Moreover, CAC remains limited to investigating active phases of mild-to-moderate forms of SAC and PAC, while it cannot be considered reliable in more severe forms such as VKC and AKC with corneal involvement.

Patient-related outcomes (e.g. QoL questionnaires) may be more appropriate for evaluating drugs' efficacy and should be more widely used in future clinical trials. In addition, other important parameters such as relapses and recurrence rate should also be included in future clinical trials as primary outcomes. In fact, in severe forms of ocular allergy, the number of relapses per year and recurrence rate represent parameters of primary importance making the difference between a life with and without long-term complications (sight loss, need of surgery, etc.) (30, 31). Safety criteria (e.g., side-effects, adverse events) were usually included among the secondary outcomes. Therefore, a few studies were empowered to provide reliable evidence about the safety of drugs under investigation. A drug's safety is at least as important as its efficacy and should not be relegated only to a secondary outcome. In fact, only a combined evaluation of safety and efficacy of a therapeutic intervention may allow a balanced risk/benefit ratio for evidence-based recommendations, as suggested by the more advanced methodologies for evaluation of clinical trials, such as the GRADE system (32–34). In this system, explicit judgments about which outcomes are critical, which ones are important but not critical, and which ones are unimportant and can be ignored, are formulated. We suggest that methodologists and clinicians jointly produce guidelines for future studies including standardized diagnostic criteria for selection of patients and grading of disease severity, as well as quantifiable efficacy and safety outcome measures.

In conclusion, our systematic review shows that only a minority of studies on allergic conjunctivitis performed in the last 45 years fulfilled all criteria of proper clinical trial design. The variability in study design and outcome measures makes it difficult for professionals and policy makers to come to any strong recommendation on the effectiveness of therapeutic interventions. There would be considerable interest in correcting the reported limitations of clinical trials, to better identify interventions that may improve the management of a disease with an increasing prevalence and burden on individuals and health care organizations (35).

Authors' contribution

All authors contributed to the study design, data extraction and evaluation, manuscript preparation and revision.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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