



Nasal challenges in allergen immunotherapy trials

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Purpose of review

The nasal allergen challenge (NAC) model can be a valuable diagnostic tool for allergic rhinitis. Alongside its clinical use, NACs can be used as primary and secondary endpoints in studies evaluating allergen immunotherapy (AIT) products for allergic rhinitis treatment. This review will discuss the technical aspects of the NAC model and provide a summary of recent studies using NACs to assess existing and new AIT treatments.

Recent findings

Over the last 2 years, both titrated and single-dose nasal challenge protocols have been used to evaluate immunotherapies targeting grass, birch, house dust mite, and cat allergens. Early efficacy and dose-finding trials showed improvements in allergic symptoms and nasal tolerance to allergens after AIT treatment with standardized extracts or modified forms of whole allergen. NACs were also used in two proof-of-concept studies to illustrate the efficacy of intralymphatic immunotherapy with two concomitant allergens and subcutaneous immunotherapy with Fel d 1-specific IgG-blocking antibodies.

Summary

Along with existing therapies, nasal challenges are useful in evaluating AIT treatments in the very early stages of clinical development. However, because of the variety in challenge techniques and symptom assessments available, special attention must be placed in the protocol design in order to compare the study results with existing NAC publications.

Keywords

allergen immunotherapy, allergic rhinitis, mucosal challenge, nasal allergen challenge

INTRODUCTION

Allergic rhinitis is an IgE-mediated inflammatory disorder with symptoms of sneezing, nasal congestion, rhinorrhea, and associated ocular symptoms following exposure to sensitized aeroallergens [1,2]. Even with standard-of-care pharmacologic therapy (e.g. second-generation antihistamines and intranasal corticosteroids), 61% of allergic rhinitis patients still report their symptoms as not well controlled [1]. Allergen immunotherapy (AIT) aims to modify the underlying disease, providing both symptomatic and long-lasting clinical benefits [3].

Prior to market approval, the clinical efficacy of AIT products was evaluated in large phase II and III trials performed in the field or in controlled allergen challenge facilities (CACFs) [4–9]. The controlled nasal allergen challenge (NAC) model is also able to provide allergen exposure under regulated conditions [10]. To date, NACs have been used to assess the efficacy of market-approved antihistamines and intranasal corticosteroids, and AIT products [11–17]. Compared with traditional field trials and CACFs, NACs require fewer participants and are more cost-effective to perform [10,18]. They can also serve as primary endpoints for preliminary

dose-finding and proof-of-concept trials as recommended by the European Medicines Agency guidelines for AIT product development [19].

The objective of this review is to provide a general overview of the NAC model and a summary of recent clinical trials using NACs to evaluate the clinical efficacy of AIT products. Extract-based AIT products used in intralymphatic immunotherapy (ILT) and local allergic rhinitis (LAR) treatment reviewed here are not labeled for these uses under discussion. All modified hypoallergenic derivatives and synthetic products discussed in this review are still investigational.

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KEY POINTS

- Nasal allergen challenges can be used as primary, secondary, and exploratory endpoints for preliminary proof-of-concept, dose-finding trials, and phase II efficacy trials of new allergen immunotherapy treatments.
- Immunotherapy treatment regimens with standardized extracts, modified allergens, and synthetic products can show reductions in allergic symptoms and improved nasal tolerance after nasal allergen challenge.
- Titrated or single-dose nasal allergen challenge protocols may be performed separately or together with a combination of subjective and objective symptom assessments.
- Nasal allergen challenges require fewer participants, are more cost-effective than large field trials, and can provide immunotherapy efficacy data prior to initiating phase II and III trials.
- International standardization of different nasal allergen challenge protocols is needed to better compare findings between different allergen immunotherapy treatments trials using nasal allergen challenges.

OVERVIEW AND PURPOSE OF CONTROLLED NASAL ALLERGEN CHALLENGES

The NAC is an internationally recognized diagnostic tool for allergic rhinitis [20,21,22[■],23]. Apart from their role in clinical practice, NACs can be used to study allergic rhinitis pathophysiology and efficacy of allergic rhinitis medications. During nasal challenges, allergen extract is delivered directly into the nasal cavity, producing an immediate allergic response. Compared with the prolonged exposure periods associated with field trials and CACFs, allergen exposure is acute during NACs. In research settings, NACs are performed using titrated challenge protocols, single-dose protocols, or a combination of both [24].

TITRATED NASAL ALLERGEN CHALLENGE

Often limited to research settings, titrated NACs typically occur over a single study visit [21,22[■],25]. Following acclimatization to the study facility and measurement of baseline symptoms, a control challenge is performed with extract diluent to exclude participants with nasal hyperresponsiveness [26]. Subjective and objective assessments of symptoms are done 10 min later [22[■]]. If control challenges are negative, NACs with increasing concentrations of allergen extract are performed with symptom assessments every 10–15 min between

challenges. The titrated NACs are stopped once a positive challenge response (i.e. a predetermined threshold of symptom severity) is observed or the highest concentration is delivered [23]. The resulting symptom evaluations and allergen concentrations used during challenge can then be compared to assess treatment efficacy.

SINGLE-DOSE NASAL ALLERGEN CHALLENGE

Similar to titrated NACs, single-dose protocols include a baseline and NACs with the control solution and allergen. However, participants are instead challenged once with a single dose of allergen extract at a concentration likely to induce allergic rhinitis symptoms in most participants. A two-visit variation of this protocol includes the performance of titrated NACs prior to the single-dose challenge. Here, titrated NACs are performed during the first visit to determine the appropriate dose of allergen extract required to elicit adequate symptoms (i.e. qualifying dose) for each participant [10,23]. Participants then return to the study facility 1–4 weeks later and a single-dose NAC is performed with their qualifying dose. Symptom assessments are done at regular time intervals and can extend up to 24 h post-challenge. The qualifying dose is often calculated as the concentration needed to produce adequate symptoms, or as the sum of all doses received during the titrated challenges (i.e. cumulative allergen dose) [10,23,27]. Contrasting titrated NACs, symptom evaluations alone are often used to assess treatment efficacy.

TYPES OF ALLERGEN EXTRACTS AND DELIVERY METHODS

Compared with the natural forms of allergen used in CACFs (e.g. pollen grains and house dust mite bodies/feces), the corresponding extracts are frequently used during the nasal challenges. However, international consensus is lacking regarding the type and processes used during extract preparation, and the assessment of extract potency (e.g. SQ-U/ml, SBU/ml, AU/ml, wt/vol%, and µg/ml of major allergen). Glycerinated and lyophilized extracts can be administered during NACs with a pump-aerosol spray device as the most common delivery method [10,21,22[■],28]. Alternative delivery methods include direct pipetting, dripping and paper disks [10,21].

SUBJECTIVE SYMPTOM ASSESSMENT

There are several assessment tools available for participants to quantify the severity of their symptoms

during challenge. The total nasal symptom score (TNSS) is a Food and Drug Administration (FDA)-recognized composite score constituted of at least three of the four individual nasal symptoms: rhinorrhea, nasal itch, sneezing, and nasal congestion [29]. Symptom severity can then be quantified using a 4-point Likert scale (0–3) ranging from no symptoms (0) to severe nasal symptoms (3, maximum score) [23]. The visual analogue scale (VAS) is an alternative method to the Likert scale and provides participants with a 10-cm long scale (0–100) to rate their symptom severity with 0 cm as not bothersome, 1–3 cm as mild, 4–7 cm as moderate, and 8–10 cm as extremely bothersome [2,30]. Two additional assessment tools include the Lebel and Linder symptom score scales. Both methods assess nasal (sneezing count, itchiness, rhinorrhea, obstruction) and ocular symptoms using a point scale for a maximum score of 11 and 13, respectively [31,32].

OBJECTIVE SYMPTOM ASSESSMENT

Peak nasal inspiratory flow (PNIF) is an objective measure of nasal patency [27,33]. Using a sealed mask that covers the mouth and nose, participants forcefully inhale through their nose while keeping their lips closed. When performed correctly, the resulting air flow measurements strongly correlate with subject assessments of TNSS [23]. In contrast, acoustic rhinometry (AcRh) is a standardized procedure that assesses nasal patency by detecting changes in the nasal cavity volume using sound waves [34]. Active anterior rhinomanometry (AAR) measures airway resistance using a pressure sensor placed in the nasal passage. AAR is internationally recognized as a method for objectively measuring unilateral nasal airway resistance [35].

POSITIVE CHALLENGE CRITERIA

Alongside the variety of assessment tools to quantify allergic rhinitis symptom severity, several valid measures defining a positive challenge response have been published. As recommended by the European Academic of Allergy and Clinical Immunology (EAACI) task force for the standardization of NAC protocols [22[¶]], clearly positive NAC responses can be defined as an increase of more than 5 points in TNSS, Lebel scores, or Linder scores. Symptom severity graded as 5.5 cm or more using VAS indicates the same. For objective assessments, a minimum decrease of 40% in air flow (PNIF and AAR) or nasal cavity cross-sectional area (AcRh) would also be classified as a clearly positive challenge response [22[¶]]. It is suggested to incorporate both subjective

and objective criteria when interpreting NAC reactions to reduce false-positive assessments [23].

USE OF NASAL ALLERGEN CHALLENGES IN ALLERGEN IMMUNOTHERAPY TRIALS WITH WHOLE ALLERGEN EXTRACTS

Over the last 2 years, AIT products targeting grass, birch, house dust mite (HDM), and cat allergens have been assessed using NACs. In a five-arm, placebo-controlled, dose-finding study of 269 birch-allergic participants, the efficacy of a sublingual preparation of liquid birch pollen drops was evaluated using a 5-month treatment regimen of five drops per day [36]. Using titrated NACs with birch pollen extract, a linear dose–response curve was observed after treatment, with the highest dose of birch pollen drops (40 000 AUN/ml) leading to the largest reduction in mean Lebel symptom scores compared with placebo (–3.63 vs. –1.98) [36]. More recently, a phase II trial evaluated the continued efficacy of 2 years of grass sublingual immunotherapy (SLIT) treatment in 106 grass-allergic participants randomized to grass SLIT (daily tablets), grass subcutaneous immunotherapy (SCIT, monthly injections), or placebo [37[¶]]. Bilateral NACs with Timothy grass pollen extract were performed at baseline, years 1 and 2 (on treatment) and year 3 (1 year off-treatment). Although a significant reduction in mean TNSS was observed in the SLIT vs. placebo group at year 2 (between-group difference of –1.42 favoring SLIT), this was not observed at year 3 (between-group difference of –0.18) [37[¶]].

For perennial allergens, titrated NACs were also used to assess the effect of HDM SCIT on nasal tolerance to HDM (Der p 1) in patients with HDM-induced LAR [38]. In a phase II study, 36 participants with HDM-induced LAR were randomized to a 24-month regimen of HDM SCIT (monthly injections) or placebo. Mirroring the improvements seen in the primary endpoints (total daily symptom and medication scores), SCIT-treated participants demonstrated a significant increase in nasal tolerance at 24 months compared with placebo; 67% of SCIT-treated participants tolerated Der p 1 concentrations 10-fold greater than at baseline [38]. In a more recent phase I study, 23 HDM-allergic participants were randomized to HDM SLIT tablets or placebo taken daily for 12 weeks [39[¶]]. Following post-treatment, NACs with HDM allergen extract, the HDM SLIT group demonstrated a significant reduction in early phase TNSS compared with placebo at week 12 (57 vs. 10%) [39[¶]].

Allergen injections directly into the inguinal lymph nodes (ILT) serve as an alternative delivery route to conventional SLIT and SCIT. Typical dosing

regimens include a total of three intralymphatic injections given approximately 3–4 weeks apart. To date, NACs have been used to demonstrate improved nasal tolerance following ILT treatment with standardized allergen extracts [40,41]. The efficacy of ILT with two allergens at the same time was also recently evaluated using NACs in a randomized, double-blind, placebo-controlled, proof-of-concept study [42[■]]. A total of 60 birch-allergic and grass-allergic participants were randomized to three intralymphatic injections of a combination of five grasses and birch extracts (one allergen in each side) or double placebo given 4 weeks apart. Following grass pollen NACs, a significant reduction in total symptom scores from baseline (primary outcome) was observed in the active group compared with placebo (–28 vs. –12%) 6–9 months after treatment completion [42[■]]. Together, these studies showcase the sensitivity of the NAC model in evaluating new immunotherapy products.

MODIFIED HYPOALLERGENIC DERIVATIVES AND SYNTHETIC PRODUCTS

Modified forms of whole allergens have been developed to reduce the frequency of adverse reactions associated with conventional extract-based AIT [43,44]. Allergoids are derivatives of allergen extracts chemically modified to alter or destroy native IgE-binding epitopes, reducing allergenicity and preserving immunogenicity [45]. In a placebo-controlled, dose-finding study, 290 HDM-allergic participants were randomized to one of four doses of an HDM SCIT allergoid given monthly for 12 months [46]. Using titrated NACs with HDM extract, only the middle two doses (20 000 and 50 000 AUeq/ml) demonstrated a significant reduction in mean Lebel symptom scores compared to placebo (–2.46 and –2.45 vs. –1.78), and an acceptable safety profile [46]. The efficacy of SCIT with a Timothy grass allergoid was also assessed using titrated NACs. In a phase II trial, 56 participants with grass pollen-induced LAR were randomized to receive monthly injections of Timothy grass SCIT allergoid for 2 years (Group A) or placebo for year 1 and the SCIT allergoid for year 2 (Group B) [47[■]]. Mirroring the symptom improvements observed during the grass pollen season in both groups, 83% of participants treated with more than 6 months of SCIT allergoid tolerated 50-fold greater concentrations of Timothy grass allergen compared with baseline [47[■]].

Peptide immunotherapy uses short synthetic peptides derived from T-cell epitopes from major allergens to induce tolerance [48]. In a recent open-label, phase I clinical trial conducted across two study sites, NACs were used to evaluate the efficacy of Cat-peptide antigen desensitization (Cat-PAD), an

equimolar mixture of seven peptides derived from Fel d 1, for the treatment of cat allergy [49[■]]. In a small cohort of 19 cat-allergic participants, four intradermal injections of 6 nmol Cat-PAD were given 4 weeks apart. NACs with standardized cat dander extract were performed at baseline and 1 month after the last injection. Following treatment, a significant reduction in peak mean TNSS at 15 min post-NAC was observed compared with pretreatment TNSS (5.42 vs. 7.32). In contrast, changes in PNIF before and after treatment were comparable [49[■]].

In another small phase IIa study, the efficacy of a novel selective toll-like receptor 7 (TLR7) agonist was evaluated using NACs [50[■]]. A total of 42 participants with seasonal allergic rhinitis triggered by ragweed, grass, or birch pollens were randomized to an in-season dosing regimen of eight weekly nasal sprays of the TLR7 agonist (20 or 80 ng dose) or placebo. NACs with ragweed, grass, or birch extracts were performed at baseline, 1 and 3 weeks, and 1 year (20 ng group only) after the final dose. At the 1-week and 3-week assessments, modest reductions in TNSS at 15 min post-NAC (exploratory endpoint) were observed in both 20 (–1.9 and –1.3, respectively) and 80 ng (–1.8 and –1.4, respectively) groups compared with placebo [50[■]]. A treatment effect was not observed at the 1-year follow-up challenges. Thus, this study illustrates how NACs can be used for exploratory clinical outcome evaluations of new immunomodulatory compounds.

Finally, passive immunization with two human, monoclonal, Fel d 1-specific blocking IgG4 antibodies (REGN1908-1909) was assessed as an alternative AIT treatment for cat allergy [51[■]]. In a multicentre, randomized, double-blind, placebo-controlled, proof-of-mechanism, phase Ib study, 73 cat-allergic participants were randomized to a single subcutaneous injection of REGN1908-1909 or placebo. Clinical efficacy was evaluated using NACs with cat hair extract at baseline, and days 8, 29, 57, and 85 post-injection. Compared with placebo, REGN1908-1909 led to a significant reduction in the absolute TNSS over the first hour of the NAC on day 8 (primary endpoint; –3.394 vs. –1.523). Significant reductions in TNSS were also observed on days 29 (–61 vs. –28%) and days 85 (–51 vs. –28%) with similar findings in the PNIF assessments [51[■]]. This proof-of-mechanism study demonstrated the potency of a single dose of allergen-specific IgG4 antibodies in suppressing cat allergen-induced allergic symptoms.

CONCLUSION

The NAC model can serve as a valuable and cost-effective tool to assess the efficacy of AIT products.

Compared with CACF trials, NAC studies can be performed with smaller groups of participants, indicating NACs as a tool to generate preliminary efficacy data prior to initiating larger confirmatory phase II and III trials.

Although national recommendations are available [23], only recently has the need for international protocol standardization been addressed in a 2018 position paper by the EAACI Task Force on the Standardization on Nasal Allergen Challenges formed in 2016 [22^o]. Following the decision to use NACs to assess the efficacy of immunotherapy treatments, careful attention must be paid to the overall NAC protocol design, types of allergen extracts, delivery method, and techniques of symptom evaluations. This will allow for a better comparison of results from different AIT studies using NACs.

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Conflicts of interest

A.K.E. has participated in advisory boards for ALK Abello, Circassia Ltd, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pediapharm, Pfizer, Sanofi and Shire, and has been a speaker for ALK Abello, Aralez, AstraZeneca, Boehringer Ingelheim, Meda, Mylan, Merck, Novartis, Pediapharm, Pfizer, and Takeda. Her institution has received research grants from Bayer LLC, Circassia Ltd, Green Cross Pharmaceuticals, GlaxoSmithKline, Sanofi, Sun Pharma, Merck, Novartis and Pfizer. A.K.E. has also been a consultant to Bayer LLC and ALK Abello. The remaining authors have no conflicts of interest.

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- of special interest
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