



Comparability of subcutaneous and sublingual immunotherapy outcomes in allergic rhinitis clinical trials

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Purpose of review

To conduct a qualitative comparison between the primary and secondary outcomes used in clinical trials of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) for allergic rhinitis.

Recent findings

Studies of SCIT and SLIT for allergic rhinitis published up to January 2012 were included in this systematic review. Different ways of defining primary and secondary outcome parameters in studies investigating specific immunotherapy are described. Whereas older studies often use the total symptom score and the total medication score individually for the primary efficacy analysis, more recent studies follow current international recommendations of applying the total combined score as primary outcome measure. Even wider is the range of secondary outcomes in clinical trials with few being validated or standardized.

Summary

As already recognized as a major concern in recent literature, standardized and validated primary endpoints are of paramount importance in order to improve the comparability of study results. The lack of consistency in the selection of primary outcome parameters represents a major problem when comparing the same therapeutic intervention. A main point of concern is the absence of validation data for those primary and secondary outcomes selected. In conclusion, the qualitative analysis of well powered studies confirms an urgent call from academics, regulatory agencies and the pharmaceutical industry for validated primary outcome parameters and standardized definitions.

Keywords

allergic rhinitis, outcome parameters, specific allergen immunotherapy, subcutaneous, sublingual

INTRODUCTION

Many clinical trials assessing the efficacy of both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) for respiratory allergies have been published in the last 100 years since the first publication of a successful trial of immunotherapy by Noon [1]. However, only few well designed and well powered studies have used the same type of primary and secondary outcomes, thus making comparability difficult to assess.

Prior to exploring the outcome measures used, it is important to explore the concept of a well designed study further. The study design and outcomes measured are vital in assessing efficacy of a proposed treatment [2,3]. The double-blind, placebo-controlled, randomized clinical trial (RCT) design remains the gold standard to determine efficacy of specific immunotherapy in allergic patients due to the variability in individual clinical

responses, unpredictability and variability of allergenic exposure and the subjective nature of symptom assessments [4,5]. According to the Allergic Rhinitis and its Impact on Asthma-Global Allergy and Asthma European Network (ARIA-GA²LEN) statement on immunotherapy, for pollen allergy specific immunotherapy, it is also important that

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KEY POINTS

- This article provides an overview on advantages and problems of different primary and secondary outcomes used in clinical trials using specific allergen immunotherapy.
- A literature search is given up to January 2012 using *PubMed* for double-blind, placebo-controlled, randomized controlled trial of subcutaneous and sublingual immunotherapy for respiratory allergies.
- To date, there is a lack of consistency in the selection of both primary (and secondary) outcome parameters in clinical trials on specific immunotherapy.
- Our qualitative analysis of well powered studies confirms former calls for validated primary outcome parameters and standardized definitions.

symptom scores are recorded according to the level of pollen exposure [6¹¹]. A large enough number of participants is required in each treatment arm in order to have power to detect clinically relevant effects and statistically significant differences in the outcomes [7]. If insufficient numbers of patients are included, the risk of a statistical type II error increases [4]. A power calculation should be performed prior to initiating a study. This requires four elements: a primary outcome for which the population variability is known for the population to be studied; a minimal desired difference between treatment of interest and either placebo or comparable treatment; an acceptable level of α error; and an estimate of the drop out rate [8]. Power not less than 90% and α 1 type error not greater than 0.05 have been recommended by the World Allergy Organization [4].

The different primary and secondary outcomes used in clinical trials using specific allergen immunotherapy, their advantages and problems will be discussed in this review. For the purposes of this review, a literature search up to January 2012 using *PubMed* for double-blind, placebo-controlled, RCT of SCIT and SLIT for respiratory allergies was performed. We identified trials with sufficient numbers of participants in order to evaluate and compare the outcome measures used.

OUTCOME PARAMETERS

In clinical research, different ways of defining primary and secondary outcome parameters investigating the effect of specific allergen immunotherapy have been described [4,9,10]. European as well as American guidelines and allergy groups

recommend the following outcomes as efficacy variables; each has its pros and cons.

PRIMARY OUTCOMES

The primary outcomes assessed in allergic rhinitis studies include the following.

Total symptom score

According to recommendations published by European Medicines Agency (EMA) [11], the preferred primary outcome measured in clinical trials on specific immunotherapy is the total combined symptom score (TCS) and medication score. Given the interdependent relationship between symptom severity and relief medication intake, not only the measuring and reporting of both parameters individually but more importantly combining them in a single score is necessary [4,6¹¹,8]. Moreover, Clark and Schall [12] consider the TCS as optimal because it shows the largest effect size, and therefore the highest power to show significant treatment efficacy. Unfortunately, no standardized and validated TCS exists to date [11,13¹²].

Total symptom score

Another still frequently applied primary outcome measure is the total symptom score (TSS). Although this patient-rated score may be reported separately, it lacks information on the complex interaction between symptoms and medication taken for relief, and thus cannot demonstrate efficacy thoroughly [4,12,13¹²]. Although the rhinoconjunctivitis TSS (RTSS) is commonly used in clinical trials, no standardized method is yet universally accepted [14].

Total medication score

Similarly to the TSS, the total medication score (TMS) is often used separately as a primary outcome parameter. As it is mandatory from an ethical point of view to hand out registered rescue medication in specific allergen immunotherapy clinical trials, its intake has to be reported either as primary or secondary outcome [11,12]. Despite the fact that many recent large studies employed a fairly standardized rescue medication score [6¹¹], only very recently has one symptom–medication score been validated [15].

SECONDARY OUTCOMES

The secondary outcomes that have been used in allergic rhinitis clinical trials include the following.

Individual symptoms

A valuable secondary outcome is the reporting of individual symptoms (nasal and ocular), as changes here allow assessment of the effect of the immunotherapy on each target organ affected by the allergy [4,16].

Quality of life

The assessment of health-related quality of life is a beneficial secondary outcome parameter to reflect the patients' apparent effect of the immunotherapy [13[■],17,18]. Unlike symptom or medication scores, rhinoconjunctivitis-specific quality of life questionnaires have been validated for adults and children [19].

Visual analogue scale

The visual analogue scale (VAS) is regarded as a valuable and sensitive tool to monitor the severity of symptoms and to detect changes from baseline to posttreatment conditions [4,20,21]. A significant disadvantage addresses the lack of extreme values of the VAS, as patients tend to rate their symptom severity avoiding the extremes [10,13[■]].

Well days

The evaluation of symptom-free or well days, described as 'days without intake of rescue medication and a symptom score below a predefined and clinically justified threshold' is recommended by EMA as a secondary endpoint [11]. A similar approach might be to assess worst days, namely 'days with severe symptoms' instead, to support the primary efficacy outcome parameter [6[■],22].

Pollen counts

In pollen allergy trials, pollen counts applying equivalent biometric techniques and reflecting the patients' distribution have to be evaluated [4,10]. Studies found out that pollen counts are only weakly correlated with symptoms [23] and an exact definition of the relevant pollen exposure including threshold values is still lacking [13[■]]. Moreover, recent studies have demonstrated that the expression of major allergens may highly vary between pollen in different areas and at different time-points [24].

Surrogate markers

Functional measures (objective measures such as conjunctival, bronchial or nasal provocation tests, acoustic rhinometry, spirometry and peak

expiratory flow rate) and *in vitro* parameters such as allergen-specific immunoglobulin E (IgE) and specific immunoglobulin G (IgG) levels are universally accepted as useful support of the primary clinical outcome [4,11,13[■]]. However, these surrogate markers or laboratory parameters can only provide additional information and not replace the primary endpoint for efficacy [11].

Safety

The thorough reporting of safety is of major importance in clinical trials [4]. As recommendations propose, all adverse events have to be classified according to their severity and to their relationship to the treatment [11]. Moreover, adverse events should be documented as local or systemic side effects applying the most recently approved international classifications [4,8,25–27,28[■]]. Despite these recommendations, there is still a great heterogeneity in classification and reporting of adverse events in SLIT and SCIT trials, making comparability difficult [4,8].

QUALITATIVE ANALYSIS OF WELL POWERED STUDIES

A qualitative analysis of well powered sublingual and subcutaneous immunotherapy studies was performed.

Sublingual immunotherapy studies

Our literature search identified six well powered trials assessing sublingual immunotherapy. These were published between 2006 and 2011. Although this review does not focus on statistical significance and efficacy of the product itself but rather on outcome measures and study design, a major search criterion was the sufficient number of participants (>100 per study arm). As all of the included studies are fairly recently published, we expected them to have been conducted in accordance with the latest guidelines and recommendations in order to present high-quality and reliable data. Whereas three studies [29[■],30,31] limited the participation to children and adolescents, three studies [32,33,34[■]] included only adults (>17 years). Both studies published in 2011 [29[■],34[■]] were conducted in North America (USA and Canada), whereas the earlier studies were all performed in Europe.

As displayed in Table 1, there is no uniform understanding of what outcome parameters should be assessed to show efficacy of SLIT. In general, three different primary outcomes were used, namely TSS, TMS and the total combined score (TCS), which is the sum of TSS and TMS.

Table 1. Summary of outcomes in well powered sublingual immunotherapy studies

Outcomes	Durham <i>et al.</i> [26] Adults ITT = 855	Didier <i>et al.</i> [32] Adults ITT = 569	Wahn <i>et al.</i> [31] Children ITT = 266	Bufe <i>et al.</i> [30] Children ITT = 253	Blaiss <i>et al.</i> [29 [¶]] Children ITT = 344	Nelson <i>et al.</i> [34 [¶]] Adults ITT = 438
Primary						
TCS	–	–	–	–	Daily SS ^{b,c,n} and daily MS ^{d,n}	Daily SS ^{b,c,n} and daily MS ^{d,n}
TSS	Average daily SS ^{a,c,n}	TSS ^{b,c,n}	TSS ^{b,c,n}	TSS ^{a,c,n}	–	–
TMS	Average daily MS ^{e,n}	–	–	Entire pollen season MS ^{d,n}	–	–
Secondary						
TCS	–	TSS ⁿ /6 and RMS ⁿ /2	–	–	–	–
TSS	–	–	–	–	–	–
TMS	–	TMS ^{f,n}	TMS ^{g,h,n}	–	–	–
TSS for peak season	TSS ^{a,c,n}	TSS ^{b,c,n}	–	–	TSS ^{b,c}	TSS ^{b,n}
TMS for peak season	TMS ^{e,n}	–	–	–	TMS ^{d,n}	TMS ^{d,n}
Individual symptoms	–	Nasal and ocular ⁱ	Nasal and ocular ⁱ	Nasal and ocular ⁱ	–	–
Overall effectiveness	–	yes ^{i,n}	–	–	–	–
VAS	–	–	–	–	–	–
Symptom and medication-free days	Yes ^{k,n}	–	–	Yes ^{k,n}	–	–
Well days	–	Yes ^{l,n}	–	Yes ^{m,n}	–	–
Quality of life	Yes ^o	Yes ^o	–	–	Yes ^o	Yes ^o
Safety	Yes	Yes	Yes	Yes	Yes	Yes
Specific IgG	Yes	Yes	Yes	Yes	Yes	Yes
Specific IgE	Yes	Yes	Yes	Yes	Yes	Yes
Pollen counts	Yes	Yes	Yes	Yes	Yes	Yes

ITT, intention-to-treat; MS, medication score; RMS, Rescue Medication score; SS, symptom score; TCS, total combined score; TMS, total medication score; TSS, total symptom score; VAS, visual analogue scale.

^a6 rhinoconjunctivitis symptoms (sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes) and four asthma symptoms (cough, wheeze, chest tightness/dyspnoea, exercise-induced).

^b6 rhinoconjunctivitis symptoms (sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes).

^cScale: 4-point scale, 0–3 (no, mild, moderate, severe).

^dScore per dose: loratadine tablets = 6, levocabastine eye drops = 1, budesonide nasal spray = 4, prednisolone tablets = 1.6, salbutamol spray = 2, fluticasone inhaler = 4.

^ePlacebo or loratadine as first treatment, budesonide nasal spray and prednisone tablet in a stepwise fashion.

^fScale: 0 = no, 0.5 ≥ 1 ocular antihistamines, 1 ≥ 1 oral antihistamines, 2 ≥ 1 nasal corticosteroid and 3 ≥ 1 systemic corticosteroid.

^gStepwise use of oral antihistamines, ocular antihistamines, intranasal corticosteroids and oral corticosteroids.

^hScale (0–3): 1 = antihistamines, 2 = intranasal corticosteroids, 3 = oral corticosteroids.

ⁱIndividual symptoms: sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes.

^j0 = worsening, 1 = no change, 2 = slight improvement, 3 = good improvement.

^kDays with no intake of rescue medication and with a rhinoconjunctivitis symptom score 2 or less.

^lNo symptoms for any of the six individual rhinoconjunctivitis symptoms.

^mExcellent rhinoconjunctivitis control 50% or more well days over the entire grass pollen season.

ⁿNo validation.

^oValidation.

Likewise, a great variety of secondary outcome parameters to confirm and support the study results were described: TCS, TMS, TSS for peak season, TMS for peak season, individual symptoms, overall effectiveness or global improvement, symptom-medication-free days, well days, quality of life, safety, specific IgG and IgE and pollen counts.

Despite the differences in defining the primary outcome, the assessment of symptoms is of major importance for the primary endpoint. All studies reported six identical rhinoconjunctival symptoms that need to be considered: sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes. Only the wording of each symptom differed slightly with some using the medical term, whereas others a more informal expression to describe the same symptom (e.g. rhinorrhoea=runny nose). However, as guidelines suggest allergic rhinoconjunctivitis should be defined by identical symptoms among the studies.

Furthermore, a uniform understanding exists regarding the scaling system for rating each of the relevant symptoms. A standardized 4-point scale ranging from 0 for no symptoms [4,11], 1 for mild symptoms, 2 for moderate symptoms to 3 for severe symptoms was applied in all studies.

On the contrary, far less standardized was the measurement of the TMS. Two studies [30,33] used apart from the TSS, also the TMS as a primary outcome parameter, whereas the North American studies [29,34] took both scores and combined them in one single outcome parameter, the TCS. Of those four studies, three applied the same rescue medication with the same scoring system, whereas one study used a different scale. A third and fourth way of calculating the medication score was described when taking the TMS as a secondary endpoint. In summary, six studies used four different types of rescue medication and four different scale systems with none of these medication scores being validated yet.

Similarly disconcerting is the fact that no uniform phrasing exists with many parameters. The symptom score used as primary outcome parameter may be called 'RTSS', 'average daily symptom score' or just 'daily symptom score', all describing the same symptoms. Likewise, with 'well days' or 'symptom-free days' or 'symptom-medication-free days' used in literature, there are identical terms for different definitions or different terms for describing identical parameters.

Disappointingly, the well acknowledged and highly recognized assessment of 'quality of life' was not performed in all studies and the VAS was not applied in any of the included trials.

Although only looking at a short time span of 5 years (2006–2011) primary outcome parameters

are developing towards a more complex construct. Whereas studies published in 2006/2009 only used the TSS as their primary endpoint, studies in 2009/2010 assessed both the TSS and TMS individually as primary parameters and the most recent studies in 2011 applied the recommended TCS as the primary efficacy outcome measure which shows promise for the future.

Subcutaneous immunotherapy studies

Despite the large number of published SCIT studies, the majority of them are carried out in small numbers of participants. Four well powered double-blind, placebo-controlled, RCTs were identified from our search [35–38] (Table 2). These were all carried out in adults. All except one study which was a multicentre study conducted in both North American and European centres [38] were conducted in European countries.

Similarly to the SLIT studies, different outcome measures were used. Three of the identified studies used a combined symptom and medication score as the primary endpoint for clinical efficacy [35,37,38]. The other study [36] used separate symptom scores and medication use scores during the grass pollen season. Participants in all studies recorded individual symptom scores varying from 7 to 9 nasal, eye and lung symptoms. All used a 4-point scale, that is, 0=no symptoms to 3=severe symptoms scoring but there was variability between the number of symptoms assessed.

Furthermore, there was significant variability in the rescue medication scoring systems used. For example, a 5 mg prednisolone tablet scored 2 points in one study, 4 points in another and even 12 points in another.

Two studies used a VAS as a secondary outcome; however, only one of these explained the point system used. Notably, they both included the same rhinoconjunctivitis quality of life questionnaire [19]. However, despite using the same measure there was variability in the time-points at which this was assessed, with one study [35] recording this before the first injection and every 2 weeks during the grass pollen season, whereas in the other study [36] it was completed before and at the peak of the pollen season. Only one study [38] used well and bad days measures.

Additional secondary outcomes, in the form of conjunctival provocation tests were performed in one of the studies [35]. Specific IgE and IgG were measured in three studies [35,37,38].

CONCLUSION

In summary, this review of primary and secondary outcomes evaluated in well powered

Table 2. Summary of outcomes in well powered subcutaneous immunotherapy studies

Outcomes	Corrigan <i>et al.</i> [35] Adults ITT = 154	Frew <i>et al.</i> [36] Adults ITT = 410	Pfaar <i>et al.</i> [37] Adults ITT = 184	DuBuske <i>et al.</i> [38] Adults ITT = 1028
Primary				
TCS	Daily SS ^{a,q} and daily MS ^{i,q}	–	TCS ^{b,c,d,q}	Daily TCS ^{e,f,g,q}
TSS	–	Mean SS ^{h,q}	–	–
TMS	–	Mean MS ^{i,q}	–	–
Secondary				
TCS	–	–	Yes ^k	Yes ^{l,q}
TSS	–	–	–	–
TMS	–	–	–	–
TSS for peak season	–	Yes	–	–
TMS for peak season	–	Yes	–	–
Individual symptoms	CPT	Nasal, ocular, respiratory		
Overall effectiveness	–	–	–	–
VAS	Yes ^m	Yes ⁿ	–	–
Symptom and medication-free days	–	–	–	–
Well days	–	–	–	Yes ^{o,q}
Bad days	–	–	–	Yes ^{p,q}
Quality of life	Yes ^r	Yes ^r	–	–
Safety	Yes	Yes	Yes	Yes
Specific IgG	Yes	–	Yes	Yes
Specific IgE	Yes	–	Yes	Yes

CPT, conjunctival provocation test; ITT, intention-to-treat; MS, medication score; SS, symptom score; TCS, total combined score; TMS, total medication score; TSS, total symptom score; VAS, visual analogue scale.

^aNine symptoms: nasal (sneezing, running, blocked), conjunctival (itching, tear flow, redness), bronchial (cough, wheezing, asthma with dyspnoea) were assessed. 4-point scale (0 = no symptoms to 3 = severe symptoms). Maximum score 27.

^bCombined symptom and medication score was defined as the time-weighted area under curve of the sum of the daily rescue medication score and the daily symptom score for all days of the pollen season.

^cSneezing, nasal itch, rhinorrhoea, nasal congestion, ocular itch, increased lacrimation and eye redness were included in the symptom score. Individual symptoms scored on 4-point scale (0 = no symptoms to 3 = severe symptoms).

^dDaily rescue medication score: 0 = no medication; 1 = topical or systemic antihistamines (desloratadine one 5 mg tablet, azelastine eye or nose drops, two drops), or salbutamol (two puffs) for asthma; 2 = nasal or inhaled corticosteroids; 3 = systemic corticosteroids for uncontrolled rhinitis or asthma.

^eDaily combined symptom + medication score. Determined by calculating a 3-day rolling average (previous, current and following days) measured during 4 peak weeks of the grass pollen season.

^fEight symptoms: itchy, burning, watery, and swollen eyes; nasal congestion; runny nose; nasal itching; and sneezing. 4-point scale (0 = no symptoms to 3 = severe symptoms). Maximum score 24.

^gThe medication score for each 24-h period was calculated by adding 5 points for every cetirizine tablet and 12 points for every prednisolone tablet to the TSS.

^hNose, eyes, lung symptoms were recorded. TSS was calculated over the entire pollen season. 4-point scale: (no, mild, moderate, severe).

ⁱScore per dose: topical antihistamines/cromoglycate/decongestants = 1, oral antihistamines = 6, nasal steroids = 3, short acting bronchodilators = 1, prednisolone = 4 per 5 mg.

^jMedication use recorded daily over pollen season (sodium cromoglycate, one per drop; steroid nasal spray, two per puff; oral antihistamine two per capsule; prednisolone (5 mg), two per tablet; and salbutamol (100 mg), one per puff.

^kEvaluated at different birch pollen cut-off points: 250, 300, 400 and 500 grains/m³ per 24 h.

^lDaily combined symptom score + medication score during the entire grass pollen season.

^m10-point visual rating scale (1 = very weak to 10 = very strong) at the screening visit and at the end of each grass pollen season.

ⁿWeekly during pollen season.

^oWell days calculated based on TSS at least 2–4.

^pBad days defined as days when the combined symptom medication score was at least 8–10.

^qNo validation.

^rValidation.

SLIT and SCIT studies reveals and stresses the major problem of a lack of consistency in the selection of primary outcome parameters. A main point of concern is the absence of validation data for those primary outcomes selected. As it

has been already recognized in recent literature as a major concern, standardized and validated primary endpoints are of paramount importance in order to improve the comparability of study results.

Although guidelines and allergy groups have already published recommendations on how to define efficacy and safety variables, validation of primarily the symptom and medication scores is still lacking. Primary parameters should provide the most clinically relevant and convincing evidence directly related to the primary objective of the trial. Interestingly, although the TSS is calculated in the same manner throughout the studies, we found major differences in the rescue medication itself and the scoring systems used. Furthermore, no uniform opinion about how to combine both individual scores into the TCSs exists. Different ways have been described but none of them has been validated yet.

An important consideration when considering the selection of the proper primary outcomes in any clinical trial is the interdependence between allergic symptoms and the use of antiallergic medication. We need to evaluate the effect of therapeutic interventions as closely as possible to real-life circumstances. For that reason, both symptom scores and medication scores should not be evaluated separately but be calculated as a combined score [4]. This concept has been endorsed by the EMA guidance that a weighted sum of the symptom and medication score shall be used in clinical trials [11,39].

At present, there is no standardized and generally accepted method for the combination of both scores available but one possible approach is the 'adjusted symptom score' which is primarily based on the RTSS that is calculated forward ('last-observation-carried-forward') [12].

A great variety of secondary outcomes were assessed by the studies included in this review. The VAS was not applied in any of the SLIT studies and 'quality of life' assessment was not performed in all of the SLIT studies but in the SCIT trials. Interestingly, a trend towards more pretentious and sophisticated primary outcome parameters can be seen.

Very recently, a combined symptom–medication-score has also been validated by taking into account the global allergy severity, allergy-related consultations and the (also validated) rhinitis quality of life for the analysis of the 'allergy control score' [15].

Considering the new technological developments in clinical research, there is also a need to reevaluate the use of surrogate outcomes in clinical trials. These should be standardized and validated properly for their potential to replace the need for seasonal trials [40].

Evaluation with unified criteria and outcomes carried out by independent investigators is now

mandatory. Regulatory agencies and academic international boards should work together in this aim.

In conclusion, this qualitative analysis of well powered studies confirms former calls for validated primary outcome parameters and standardized definitions. It is important that this need is addressed urgently in order for further progress in the immunotherapy field to occur.

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Conflicts of interest

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- 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. 000–000).

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