Clinical outcomes and adverse effect monitoring in allergic rhinitis

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The subjective recording in diary cards of symptoms of itch, sneeze, nose running, and blockage, with the use of a rating scale to indicate the level of severity, is usual for clinical trials in allergic rhinitis. The primary outcome measure is usually a composite score that enables a single total symptoms score endpoint. It is appreciated, however, that rhinitis has a greater effect on the individual than is reflected purely by the recording of anterior nasal symptoms. Nasal obstruction is troublesome and may lead to sleep disturbance in addition to impaired daytime concentration and daytime sleepiness. These impairments affect school and work performance. Individuals with rhinitis find it socially embarrassing to be seen sneezing, sniffing, or blowing their nose. To capture these and other aspects of the disease-specific health-related quality of life, questionnaires such as the Rhinoconjunctivitis Quality of Life Questionnaire have been developed and validated for clinical trial use. The adoption of health-related quality of life questionnaires into clinical trials broadens the information obtained regarding the effect of the therapeutic intervention and helps focus on issues relevant to the individual patient. It must be appreciated that it is not only the disease that may adversely affect health-related quality of life; administered therapy, although intended to be beneficial, may also cause health impairment. Adverse-event monitoring is thus essential in clinical trials.

The first-generation H_1-histamines, because of their effect on central H_1-receptors, are classically associated with central nervous system (CNS) effects such as sedation. Although this is not always perceived by the patient, it is clearly evident with objective performance testing, and positron emission tomography scanning has directly demonstrated the central H_1-receptor occupancy. The second-generation H_1-antihistamines have reduced central H_1-receptor occupancy and considerably reduced or absent CNS sedative effects. Therefore, the CNS effects are entirely avoidable, and the first-generation H_1-antihistamines should no longer be used in the management of allergic rhinitis. The considerably rarer but potentially very serious cardiac arrhythmogenic effects of H_1-antihistamines are appreciated to be molecule-specific rather than class-specific. The *in vitro* screening of new compounds to eliminate the further development of those with cardiotoxicity ideally will lead to this adverse effect being historic. The incorporation of electrocardiogram recording in clinical trials provides direct information relating to prolongation of QT interval corrected for heart rate.

Although administered at low doses, intranasal steroids still have the potential for systemic absorption and adverse consequences. However, it is appreciated that meaningful differences exist in the bioavailability of different steroid molecules, and although a small but statistically significant effect on growth in children has been identified with the long-term use of intranasal beclomethasone when administered twice daily for 1 year, this is not evident with all intranasal steroids. In addition, twice-daily intranasal steroid administration may have more effect—from the endocrinologic perspective—than once-daily administration in the morning, which coincides better with the natural diurnal variation in cortisol. Thus, once-daily intranasal steroid administration is preferable, and when used in studies in children, measurement of height change during the study period is an important outcome variable together with other indices of systemic steroid

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bioavailability (eg, tests of hypothalamic-pituitary-adrenal axis function). These considerations have even greater relevance if children are concurrently also receiving inhaled steroids for asthma, because the total steroid load will be greater. (J Allergy Clin Immunol 2005;115:S390-413.)

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Abbreviations used

AML: Ascending methods of limits procedure
BMD: Bone mineral density
CNS: Central nervous system
FDA: US Food and Drug Administration
HPA: Hypothalamic-pituitary-adrenal
HRQL: Health-related quality of life
ICS: Inhaled corticosteroid
INS: Intranasal steroid
MRI: Magnetic resonance imaging
PEA: Phenyl ethyl alcohol
PET: Positron emission tomography
QOL: Quality of life
QTc: QT interval corrected for heart rate
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
RQLQ(S): Standardised Rhinoconjunctivitis Quality of Life Questionnaire
SAR: Seasonal allergic rhinitis
SF-36: Medical Outcomes Survey Short Form 36
SS: Single staircase procedure
STT: Smell Threshold Test
UPSIT: University of Pennsylvania Smell Identification Test

NASAL SYMPTOM RECORDING

Clinical trials in allergic rhinitis standardly involve patients recording their nasal symptoms in daily diary cards, with separate recording of the severity of their symptoms of nasal itch, sneeze, nasal discharge, and nasal obstruction. Classically, simple rating scales from 0 to 3 are used, with defined criteria to assign the appropriate rating, such as 0 = no symptoms, 1 = mild symptoms (symptoms that are present but not particularly bothersome), 2 = moderate symptoms (symptoms that are bothersome but do not interfere with daily activities), and 3 = severe symptoms (symptoms that are bothersome and interfere with daily activities or disturb sleep).

Alternative methods of symptom reporting have also been used, such as 10-cm visual analogue scales with defined limits—for example, ''no symptoms'' and ''worst-ever symptoms.'' Such an approach allows the use of a continuous variable scale rather than an interrupted scale but is disadvantaged by a tendency in recording to avoid the extremes of the scale, thereby narrowing the spectrum of response. Furthermore, the recordings require accurate measurement and are thus more labor-intensive to analyze. Additional outcomes, such as global evaluation of effectiveness at the end of the trial by the patient and investigator, have been used, but when this latter outcome is based on the subjective reporting by patients of their sense of well-being, the investigator assessment can only mimic that of the patient and is of little value.

A Draft Guidance document provided by the US Department of Health and Human Services Food and Drug Administration, Allergic Rhinitis: Clinical Development Programs for Drug Products (www.fda.gov/cder/guidance/2718dft.htm) recommends the use of rating scale self-assessment by patients as the primary outcome, with an overall summed symptom score of individual symptoms of nasal itch, sneeze, rhinorrhea, and congestion to provide a composite single symptom score. Both an instantaneous symptom score (ie, an evaluation of symptom severity immediately before the next dose of medication) and a reflective symptom score (ie, an evaluation of symptom severity over a predefined period such as 12 hours or 24 hours) are suggested. These measures provide information about whether the administered medication still provides symptom relief at the end of its dosing regimen compared with placebo, and also provide information on the overall magnitude of effect of the therapeutic intervention throughout the treatment period.[1] Individual symptom parameters can also be evaluated separately as secondary endpoints. The bases for the recommendation that subjective symptom reporting is the most appropriate endpoint are that such an approach is the best validated method and that alternatives are less substantiated.

This method of evaluation provides insight into the specific nasal symptoms surveyed but does not provide any insight into the overall effect of the disease on the individual and thus provides limited information. For example, although adults with rhinitis and rhinoconjunctivitis are certainly bothered by the symptoms themselves, particularly having a stuffy/blocked nose, a runny nose, and sneezing, they are also bothered by not being able to sleep well at night and the consequences of feeling tired during the day. A recent study compared the daytime sleepiness score, based on the Epworth Sleepiness Scale, and outcomes from formal polysomnography sleep studies in adult subjects with seasonal allergic rhinitis (SAR) and a matched group of healthy control subjects.[2] The study found that daytime sleepiness was a feature of allergic rhinitis and that this related both to severity of disease and to impairment in quality of life (QOL). Although there were statistically significant effects of SAR on selected sleep parameters, when the effects were monitored objectively, the authors felt that these were minor and not clinically relevant, and concluded that the daytime sleepiness was a feature of the allergic disease per se and not related to disturbed nocturnal sleep. However, such a conclusion is questioned by the results of an open study in children showing that the introduction of intranasal budesonide as a therapy for persistent allergic