

Health-Related Quality of Life and Rhinitis Control Measures in Allergic Rhinitis

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Published online: 9 January 2014

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Keywords Health-related quality of life · Patient-reported outcomes · Rhinitis control measures · Allergic rhinitis

Opinion statement

The personal burden of illness as perceived by allergic rhinitis patients extends beyond clinical symptoms with an impact on sleep, social life and daily activities including work and school performance. Health-related quality of life (HRQoL) is now recognised as one of the most important patient-reported outcomes in patients with allergic rhinitis and asthma. Several validated HRQoL instruments are currently available, aiming to quantify the degree to which the medical condition or its treatment impacts on the individual's life in a valid and reproducible way. Recently, there has been an increased interest in disease control, and it is now being considered as an alternative to disease severity in the management of allergic rhinitis patients. To that effect, different rhinitis control measures have been developed and validated. This review will explore the HRQoL instruments and rhinitis control measures currently available, and discuss their advantages and disadvantages and potential use in research and clinical practice.

Introduction

Allergic rhinitis, being the most common allergic disorder, is recognised as an emerging global health issue conservatively estimated to affect 500 million people of all ages, socio-economic conditions and ethnic groups [1]. It is defined as a symptomatic disorder of

the nose induced by an IgE-mediated inflammation of the membranes lining the nose after allergen exposure, and presents with sneezing, rhinorrhoea, nasal obstruction and nasal itching [2], accompanied in the majority of patients with ocular symptoms. Impor-

tant comorbidities, such as asthma, rhinosinusitis or otitis media, are also frequently present [3]. Fifteen to 38 % of patients with allergic rhinitis are estimated to suffer with asthma [1], and rhinitis on its own has been found to be an important predictor of adult-onset asthma [4].

Although studies on the prevalence of allergic rhinitis in different populations present with great heterogeneity due to different criteria and methodological approaches used, the reported prevalence ranges from 10 % to 30 % for adults and up to 40 % for children, with differences among and within countries [5, 6].

It is well recognised that although not life-threatening, allergic rhinitis can adversely affect the quality of life of affected patients, and cause a significant burden on both the individual and society [7]. The symptoms have the potential to lead to both physical and mental complications, with allergic rhinitis patients reporting problems sleeping, increased fatigue, impaired cognition, and psychological distress [8, 9]. In addition, the symptoms of allergic rhinitis have been shown to compromise the ability to perform at work or school [10, 11].

Recently, increased interest has appropriately been shown to the patient's viewpoint about their illness and treatment options. All these viewpoints, which in-

clude symptoms, illness perception, quality of life, satisfaction with or adherence to treatment, health status, well-being, work productivity, as well as control of disease reported directly by the patients, without interpretation by physicians or others, are grouped under the definition of Patient-Reported Outcomes (PROs) [12•]. PROs focus the attention only on the patient, because she/he is the only person authorised to provide information about the personal experience of the disease, treatment and care [13].

Among these PROs, health-related quality of life (HRQoL) has been the one most extensively studied. HRQoL is now recognized by the Global Allergy and Asthma European Network (GA2LEN) as one of the most important PROs in patients with rhinitis and asthma [13, 14•]. The European Medicines Agency (EMA) has also suggested that in non-life threatening chronic disease, results based on PROs could provide a useful indication for the choice of drug, when two or more drugs are shown to have similar efficacy [15].

In this review, we will discuss the different health-related quality of life instruments used in clinical trials of allergic rhinitis, as well as the ones applicable in clinical practice. We will also review new developments in this area, particularly the various rhinitis control measure tools that have been developed.

Health-related quality of life (HRQoL)

Quality of life has been defined by the World Health Organisation as “the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” [16]. Health related quality of life (HRQoL) is the component of overall quality of life that pertains to an individual's health. This includes the psychological, physical and social aspects of one's quality of life that are related to someone's health [17].

HRQoL instruments can be used to assess the impact of an illness on a patient as perceived by the patient. They are the only systemic scientific way to study differences in HRQoL between patients with a similar level of objective clinical impairment [18]. HRQoL instruments can also be used as outcome measures for studying the impact of diagnostic or management interventions from the patient's perspective. They have also been suggested as one of the most relevant secondary outcomes in allergen immunotherapy trials [19].

HRQoL can be measured using qualitative or quantitative methods. Qualitative methods are useful for identifying new areas of interest and forming hypotheses due to their relatively open structure. Quantitative research may be

described as the numerical representation of observations to describe and explain HRQoL. Quantitative methods require validated instruments and provide precise outcomes that are useful as research tools or clinical practice.

HRQoL instruments

There are two major types of HRQoL instruments: generic and disease-specific questionnaires.

1) Generic questionnaires

These are intended for general use and can be used to evaluate and compare different disease states, treatment interventions and populations. Typically, they include consideration of physical functioning, ability for self-care, physiological status, level of pain or distress, and amount of social integration. Generic instruments can also serve as health profiles [20]. However, the disadvantages are that they may not focus adequately on problems specific to a particular disease, and they simultaneously measure the impact of co-morbid conditions.

The best-validated and most commonly applied generic questionnaire is the Health Status Questionnaire Short Form-36 (SF-36). It is comprised of 36 questions in nine health domains, and renders mental component summary scores, as well as a psychometrically based physical component summary. This has been shown to be a valuable tool in discriminating between patients with perennial allergic rhinitis and healthy subjects [21]. It has been used as a secondary outcome in allergic rhinitis trials assessing efficacy of pharmacological treatments [22–24], as well as allergen immunotherapy [25, 26].

Other generic HRQL questionnaires that have been used in allergic disorders are the Medical Outcome Study Short Form-20 (SF-20) [27], the Satisfaction Profile (SAT-P) [25], the EuroQol Questionnaire (EQ-5D) and 15-Dimensional Health-related QOL (15D) [28].

The Satisfaction Profile (SAT-P) questionnaire asks individuals to evaluate their satisfaction about 32 life aspects with reference to the last month (on 32 visual analogue scales) independently of their objective health status. It provides 32 individual scores and five factor scores, all ranging from 0 (lowest level of satisfaction) to 100 (highest level of satisfaction). SAT-P has been used in seasonal allergic rhinitis and was found to correlate with the SF-36 data [29].

The EQ-5D instrument is an alternative health state descriptive system that consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each item has three levels: no problems, some problems, or extreme problems. Thus, this system represents 243 possible health states [28].

The 15D questionnaire can also be used both to obtain a profile across 15 dimensions and a single index score ranging from 0 (being dead) to 1 (full health) [28].

2) Disease-specific questionnaires

Disease-specific instruments are more responsive than generic instruments and they can be targeted to a specific population, disease or function. Specific instruments are more likely to detect clinically important impairments specific for a particular disease or HRQoL differences over time, and are better suited to evaluate the impact of interventions for specific diseases [30, 31].

In patients with allergic rhinitis and rhinoconjunctivitis, the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) developed by

Juniper et al. is the most widely used questionnaire in assessment of HRQoL. This instrument has been adapted in several forms: the standardised form of RQLQ, Nocturnal RQLQ for measurement of nocturnal rhinitis, age-specific: the Adolescent RQLQ for patients 12–17 years of age and the Paediatric RQLQ for patients 6–12 years and the miniRQLQ [32–35].

The standardised version of the RQLQ has 28 questions in seven domains (practical problems, activity limitations, sleep problems, emotional condition, nasal symptoms, eye symptoms, non-nose/eye symptoms), all of which are scored by the patients using a seven-point Likert scale ranging from 0 (not troubled/none of the time) to 6 (extremely troubled/all the time). For the domain “activities”, three items can be freely selected by the patient from a list of 29 activities. These activities should be the three considered by the patient to be most affected by the disease [32]. This instrument has been translated into different languages. It has been tested in adult patients with seasonal, perennial as well as intermittent and persistent allergic rhinitis, and is used extensively in both clinical studies and clinical practice [31]. In controlled clinical trials, a difference of 0.5 or greater in RQLQ domains between active and placebo-treated patients is regarded as clinically relevant [34].

The Mini Rhinoconjunctivitis Quality of Life Questionnaire (miniRQLQ) only has 14 of the 28 questions of the standardised version of the RQLQ. Although this is a useful tool for group studies such as clinical trials and cross-sectional surveys, the standardised version is considered to be more sensitive for use in clinical practice [36].

The Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire (NRQLQ) was designed to measure the functional problems that are most troublesome to patients with nocturnal allergic rhinoconjunctivitis. The instrument consists of 16 items over four domains (sleep problems, symptoms during sleep time, symptoms on waking and practical problems). The NRQLQ asks patients to recall their experiences during the previous week and score each item on a seven-point scale. A validation study has shown that the NRQLQ has strong evaluative and discriminative measurement properties and can be used in both clinical practice and clinical trials [35].

It is important to use age-specific questionnaires, as different aspects of HRQoL can be affected in different age groups. The Adolescent RQLQ has been specifically designed for adolescent rhinoconjunctivitis clinical trials for patients 12–17 years of age, while the Paediatric RQLQ is applicable to 6–12 year old patients.

The Adolescent RQLQ has 25 questions in six domains (nose symptoms, eye symptoms, practical problems, activity limitation, non-hayfever symptoms, and emotional function) [33]. The items identified by 12- to 17-year-old patients were not identical to those previously identified by adults. This suggests that impairment of quality of life may not be the same in the two groups, and that it is appropriate to have a separate questionnaire. Interestingly, adolescents in the validation study indicated that they experience important problems in doing their work (school), and also they are troubled by generally not feeling well; these were not considered important by adults.

The Paediatric RQLQ has 23 questions in five domains (nasal symptoms, ocular symptoms, other symptoms, practical problems, and activities) and children are asked to score their experiences during the previous 7 days [37]. Of note, children are not as bothered by emotional problems or limitations of activities, as is the case for adults and adolescents. Validation of this questionnaire has found that children provide reliable and accurate responses and the Paediatric RQLQ can be used in clinical trials, clinical practice, and surveys.

The RQLQ has been used in many well-powered clinical trials as a secondary outcome both for subcutaneous [38, 39] and sublingual immunotherapy [40–43] in adults and children [44]. These studies have shown that immunotherapy improves HRQoL in allergic rhinoconjunctivitis patients. Furthermore, this seems to parallel the clinical outcomes of a reduction in symptoms and/or medication intake.

The RQLQ can also be a useful tool in daily clinical practice. For example, the patient can fill in the questionnaire prior to their clinical appointment. Review of this by the clinician can identify how the patient is doing and identify specific aspects that need to be explored further in the consultation [30]. Furthermore, repeated measurements can allow improvements or exacerbations to be easily identified, as well as enable assessment of response to treatment. The main drawback of the RQLQ is that it comprises a one-week evaluation, and days with significant symptoms may be missed. Furthermore, it does not specifically assess allergic rhinitis control, nor predict future outcomes of treatment [12•].

Of note, the RQLQ only evaluates HRQoL in relation to allergic rhinoconjunctivitis symptoms but not to allergic asthma, although both diseases are linked and often coexist. The Rhinasthma questionnaire consists of 30 items and has been developed and validated for assessing the functional, physical, and emotional status of adult patients with allergic rhinitis and asthma [45]. It evaluates the HRQoL in the previous 2 weeks.

Following on from the Rhinasthma questionnaire, the RhinAsthma Patient Perspective (RAPP), a simple eight-question questionnaire with good measurement properties and sensitivity to health changes, has been found to provide a valid, reliable and standardised HRQoL measurement in patients with asthma and comorbid allergic rhinitis in clinical practice [46].

Other specific questionnaires include the ESPRINT-15, which is a validated specific instrument to assess HRQoL in allergic rhinitis that is particularly recommended for use in Spanish-speaking populations [47]. It contains 15 items grouped into four dimensions: symptoms (five items), activities of daily living (three items), sleep disturbances (three items), psychological impact (three items), and one general question. All items are scored on a seven-point Likert scale, ranging from 0 (minimum impact on HRQoL) to 6 (maximum impact on HRQoL). The 15 items provide an overall score on a five-point scale (0-excellent to 4-bad). This questionnaire has been used in a trial assessing the effect of an antihistamine on allergic rhinitis [48].

The Work Productivity and Activity Impairment-Allergy Specific Questionnaire has been developed and validated to measure the effect of allergic rhinitis on work productivity (adults), classroom productivity (students), and regular activities. It assesses function-related end points, providing a measure of the economic impact of allergic rhinitis and the potential of

therapeutic interventions [49]. The medical treatment of rhinitis has been found to improve work productivity in persistent and also seasonal allergic rhinitis using this tool [50, 51].

Rhinitis control measures

As has already been done with asthma, where patients have similar difficulties in correctly evaluating the control of their illness, there has recently been an increased interest in developing and validating self-assessment control measure scores for assessing allergic rhinitis clinical control.

The Rhinitis Control Assessment Test (RCAT) was developed to measure rhinitis symptom control from the patient's perspective. It aims to identify patients whose nasal symptoms, ocular symptoms, or both, might warrant a change in management, referral to an allergy specialist, or both. It has six items that include nasal congestion, sneezing, watery eyes, sleep problems caused by rhinitis, activity avoidance, and rhinitis symptom control assessed over the previous one-week period. Responses are measured on five-point Likert-type scales and the scores range from 6 to 30, with higher scores indicating better rhinitis control [52, 53]. Aside from being a useful tool for identifying patients experiencing problems with rhinitis symptom control, the RCAT might also be useful in assessing the effect of therapeutic interventions and in identifying deterioration in rhinitis symptom control, and thus can be a useful tool both in clinical practice and for clinical research. A score of 21 or less is considered to be useful in identifying patients who are experiencing control problems. The recommended minimal important difference (MID), which is the minimum change in RCAT score that might be clinically meaningful, was found to be greater than 2.4 points. This suggests that differences in mean RCAT scores of greater than 2.4 points between groups are likely to be clinically significant [54].

In addition, a study of 1,051 patients compared the MiniRQLQ and the RCAT to each other regarding content and predictive abilities. This found that baseline RCAT scores were strongly correlated with baseline MiniRQLQ scores in both allergic and non-allergic patients. Baseline MiniRQLQ and RCAT scores were significantly related to patient reports of missed school/work, medication use, and effectiveness over the next 3 months, and to dispensing during the following year of total, and some individual, rhinitis medications [55].

The Allergic Rhinitis Control Test (ARCT) was developed based on the Asthma Control Test (ACT). It includes five items scored from 1 to 5, assessing the rhinitis over the two previous weeks. The questionnaire was validated by testing it in 902 patients before treatment and two weeks after treatment. The score at inclusion correlated significantly ($p < 0.0001$) with the patient's overall clinical status and the impact of allergic rhinitis on social and sporting activities. A score of 20 was found to be the optimal cut-off for poor versus well-controlled rhinitis. It was concluded that this self-completion questionnaire could be used in daily practice at each consultation to determine, in a standardised manner, the level of control of the allergic rhinitis of an individual patient [56].

A tool developed to assess both asthma and rhinitis is the Control of Allergic Rhinitis and Asthma Test (CARAT). Initially, a version consisting of 17 questions was developed to be used in the concurrent management of these diseases, as recommended by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [57]. This was then shortened to the CARAT10, consisting of ten questions that refer to the control of these diseases in the previous 4 weeks. Seven questions address the frequency of symptoms, one sleep impairment, one activities limitation and one the need for more medication. The response options for all questions are four-point Likert scales. The range of possible scores for CARAT10 is 0-30, 0 being the complete absence of control. This tool has been found to have good test-retest reliability, responsiveness and longitudinal validity, making it useful to compare groups in clinical studies and also in clinical practice [58, 59].

There are no studies currently comparing these tools with each other. Also, they have not yet been tested in allergen immunotherapy randomised control trials. Furthermore, additional development and testing of these tools is required so that they can also be applicable in paediatric populations [60].

Patient satisfaction

Patient satisfaction has been shown to affect patients' health-related decisions and treatment-related behaviours, which in turn have a substantial effect on the success of treatment outcomes.

The 'Patient Benefit Index' (PBI) is a global score of patient relevant benefit. It is a calculated index that compares the patient rating before (Patient Needs Questionnaire, PNQ) and after treatment (Patient Benefit Questionnaire, PBQ). Both questionnaires consist of a 25-item list that the patient rates with respect to personal importance, from 'not at all' to 'very'. The PBI is computed by dividing each rating on a need item by the sum of all ratings in the PNQ, and multiplying this fraction with the respective benefit rating (PBQ). The PBI is the sum of these products and ranges from 0 'no benefit' to 4 'maximum benefit'. A PBI greater or equal to 1 is considered as a threshold of 'relevant benefit'. It has been validated in 104 patients with allergic rhinitis and has been found to be a feasible, reliable and valid instrument known as PBI-AR, for the standardised assessment of patient-relevant benefits in the treatment of allergic rhinitis [61].

Satisfaction with treatment is especially relevant in long-term treatments such as allergen immunotherapy. A Satisfaction Scale for Patients Receiving Allergen Immunotherapy (ESPIA) questionnaire has been developed. This was assessed in 429 patients undergoing allergen immunotherapy (AIT). The overall score for the ESPIA questionnaire was strongly associated with months receiving AIT, type of allergic rhinitis and intensity, presence of conjunctivitis, self-perceived health status, effect of allergic rhinitis on daily life, and expectations about the AIT treatment. This has been found to have good sensitivity to change for

improved health status, and was recommended for use in clinical practice [62].

Recently, a new Allergic Rhinitis Treatment Satisfaction and Preference (ARTSP) scale was evaluated in 185 allergic rhinitis subjects. The ARTSP was designed to differentiate between treatments based on patient-reported satisfaction in comparative clinical trial settings. This scale was found to be a reliable, valid, and responsive measure of patient evaluations of alternative therapies, providing detailed information about treatment characteristics that are likely to influence adherence levels and subsequent allergic rhinitis clinical control. A shorter version of the ARTSP is being developed that will better support decision making in the clinical practice setting [63].

Discussion

Assessment of PROs is gaining increasing importance both in research and in clinical practice. This approach enables better understanding of patient-related factors influencing management outcomes, as well as identifying patient subgroups that can benefit from specific treatments. It further allows tailoring of treatment to address PROs and improve rhinitis management [14•]. Currently, assessment of PROs is rarely the primary, but rather a secondary outcome in clinical trials. The development of clinical trials in which PROs are the primary or co-primary outcome is recommended because appropriate tools are available [13].

There are several reliable and validated HRQoL questionnaires that can be used in clinical trials and clinical practice. These include generic and disease-specific questionnaires. Disease specific instruments, such as the RQLQ, have gained acceptance as methods to obtain a measure of disease perception in individuals with allergic rhinitis. Overall, disease-specific tools are recommended when available, while generic questionnaires are useful, especially when comparing different diseases [14•]. The existence of a number of validated questionnaires enables researchers to choose tools pertinent to their study design and population.

Various allergic rhinitis control questionnaires (ARCT, RCAT, CARAT) have also been developed and validated using standardised methods [64]. These vary in the number of questions, as well as the period of evaluation assessed. Of these, only the CARAT score also assesses asthma, which can also coexist in allergic rhinitis patients.

Although the development of these tools is a step in the right direction, the major limitation in assessing allergic rhinitis control, and thus control measure tools, is that unlike other conditions such as asthma, presently there is no universally accepted and validated definition of what constitutes total control. It is therefore difficult to set threshold limits above and below which the degree of control can be classified [12•]. In addition, there are currently no studies comparing these tools in order to identify which of these would be more applicable for clinical trials and/or clinical practice. As previously recommended by the ARIA

guidelines, it is important that methods for measuring severity and control in allergic diseases are uniform [65]. There is also a need to develop control measures applicable to the paediatric population.

Compliance with Ethics Guidelines

Conflict of Interest

Melina Makatsori, Christopher Koulias, and Moises A. Calderon declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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