Health-related quality of life in sarcoidosis

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Purpose of review
The review presents an overview of the scientific publications in the field of health-related quality of life (HRQL) in sarcoidosis.

Recent findings
Literature on HRQL in sarcoidosis is limited. HRQL was mainly used as a primary or secondary endpoint in intervention studies. Moreover, most studies have measured HRQL in sarcoidosis by means of the generic questionnaire 36-Item Short-Form Health Survey. Sarcoidosis-specific questionnaires and computer-adapted testing are innovative approaches to the field.

Summary
HRQL as a primary or secondary outcome in sarcoidosis studies is still scarce. In addition to the proper definition of the concept, the mode of measurement of HRQL remains a matter of debate. Because health-economical evaluations require data on gained quality of life, future studies on sarcoidosis should include HRQL as the study endpoint.

Keywords
computer-adapted test, patient-reported outcome measures, quality-adjusted life years, quality of care

INTRODUCTION

Sarcoidosis is a systemic disorder that is characterized by the development and accumulation of granulomas in different organs. Lungs, lymphatic system, skin and eyes are the most frequently affected; other organs may also be involved. This disease commonly affects young and middle-aged adults. So far, the origin of the disease is unknown and no curative medication exists. Usually, sarcoidosis resolves within 2–4 years, although the disease may become chronic in a small subset of patients [1]. In addition to the functional problems due to the impaired functioning of the affected organs, sarcoidosis patients suffer from a range of nonspecific symptoms of which pain, fatigue and several types of psychological distress are the most reported ones. From a recent survey [2], as well as world-wide clinical experience, it is known that both the functional problems as well as the nonspecific symptoms may afflict patients' quality of life.

Quality of life, health-related quality of life and health status

Quality of life is defined by the WHO as: 'the individuals' 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. It is a broad-ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment' [3,4]. From this definition, it becomes clear that the key factor in quality of life is the perception (or evaluation) by the individual of his functioning.

Since quality of life is a broad concept and may be influenced by numerous factors, the concept health-related quality of life (HRQL) was developed. HRQL focuses on the impact of disease on different aspects of life [5]. In this context, it is wise to bear in mind that patients seeking help in the healthcare system aim to restore not only their health, but foremost their quality of life. Although medical diagnoses and therapy can cure a disease or alleviate

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KEY POINTS

- Sarcoidosis deteriorates the quality of life in the majority of patients.
- HRQL is but scarcely incorporated as an endpoint in clinical trials.
- The use of innovative tools as CATs may improve the assessment of HRQL in the near future.
- The growing importance of health-economical evaluations will make assessment of HRQL imperative.

symptoms, a correct diagnosis and intervention do not automatically induce restoration of quality of life. In HRQL, at least the following domains should be evaluated by the patient: physical health, psychological state and social relationships.

These three domains (physical, psychological and social functioning) are, however, regularly assessed without evaluating the consequences of impairment on patients' life, so without patients' evaluation of his functioning. In these cases, only health status is measured. It may be evident that quality of life is often confused with the health status. Moreover, in daily medical practice, the term quality of life is also habitually incorrectly used to refer to the aforementioned nonspecific symptoms of a disease. However, these nonspecific symptoms (fatigue, general weakness, pain, mood including depressive symptoms and anxiety) should not be regarded equivalent to quality of life. They may only be considered as factors that can potentially influence a patient's quality of life.

Measurement

The impact of disease on quality of life is usually assessed by questionnaires that will be filled out by the patient. Hence, more recently, these questions are referred to as patient-reported outcome measures (PROMs). Although numerous different questionnaires are available, two types of questionnaires can be identified: generic questionnaires and specific questionnaires [5]. Generic questionnaires can be used in all types of diseases and patient groups, and make comparison of HRQL over different groups feasible. Specific questionnaires may be applied in specific diseases, patient groups, or areas of function, for example, respiratory functioning or even more specific – sarcoidosis.

Until now, PROMs have been developed as paper-and-pencil questionnaires. Yet, most of these questionnaires have good psychometric properties, but a range of shortcomings may downsize their usefulness. Major drawbacks are recall bias, redundancy by irrelevant questions in specific patients, impossibility to deal with missing values, labor-intensive calculation of scores and absence of correction for multiplying related scores. As we speak, major efforts are undertaken to develop computer-adapted tests (CATs) using modern test theory or items response theory. CAT is based on the idea that an answer on a specific question (item) predicts the score of the domain. Next, the second item can be selected based upon the first question. After each additional question, the reliability of the predicted score should gain more certainty. Test systems developed with this technology are suitable to be used interactively by computer systems and provide a fundamental solution for the drawbacks of paper-and-pencil questionnaires.

Aim of review

The review presents an overview of the recent scientific publications that describe the impact of sarcoidosis on quality of life, as well as its measurement. Obviously, it may be clear that the actual focus of this review is on health-related quality of life (HRQL) in sarcoidosis.

SELECTION OF STUDIES

Medical scientific literature was identified using: PubMed, Embase, Cinahl, Cochrane, and Google Scholar. The search was limited to English-language articles published in the year 2013. Case reports and reviews were excluded from the current review, but were checked for potentially eligible studies.

The words sarcoidosis, Löfgren, quality of life, health-related, health status, and patients reported were used as MeSh terms or terms to be found in titles or abstracts. The search strategy was reviewed by an informatics librarian to maximize search sensitivity. Titles and abstracts were assessed for relevance, followed by retrieving the original research reports.

ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE

Studies published over the past year have mainly used the Medical Outcome Study – 36-Item Short-Form Health Survey (SF-36) as an instrument to assess HRQL in sarcoidosis [6▪,7▪▪,8▪,9]. The SF-36 [10] (www.sf-36.org) is a generic questionnaire that covers nine different dimensions of HRQL: physical functioning, role limitations due to physical functioning (role functioning-physical), social functioning, role limitations due to emotional functioning

(role functioning-emotional), mental health, vitality, body pain, general health perception, and health change. The SF-36 is validated for the spectrum of medicine, translated and validated in almost all languages and cultures.

Furthermore, also specific questionnaires for measuring HRQL have been used: the St George's Respiratory Questionnaire (SGCQ) [11,12] and the Dermatology Life Quality Index [13]. The latter instrument was applied in an intervention study in cutaneous sarcoidosis. Furthermore, a new and sarcoidosis-specific questionnaire has been launched: the King's Sarcoidosis Questionnaire (KSQ) [14▪]. The KSQ evaluates the general health status in combination with (if applicable) lung, skin, eye and/or medication. The KSQ appeared to be a brief, valid, self-completed tool suitable for clinical and research use.

Nevertheless, in the field of assessment of HRQL in sarcoidosis, choosing the applicable instrument remains a matter of debate [15]. Researchers are using well known questionnaires such as the World Health Organization Quality of Life-abbreviated version [16], whereas new modes of measurement are being developed and tested. Computerized administration in these new approaches is indicated. These new intelligent tools, also called CATs, no longer apply a standard list of items to be scored by the patient, but use an item bank. The patient only answers those domains that are applicable to his situation and condition. For example, in case of sarcoidosis, if a patient does not have skin problems, the items concerning cutaneous sarcoidosis are left out from his personalized assessment. Moreover, selecting the following question based upon the estimated score using the preceding question can limit the number of questions necessary. For example, a patient indicates to be unable to walk 100 yards. From this answer, it may be obvious that the next question 'are you limited by your health to walk more than a mile?' is not applicable. CAT will accurately select only the valid questions in each individual patient. A start of the development and testing of sarcoidosis-specific patient reported outcomes has yet to be made [17▪▪,18]. This innovative approach makes more precise and targeted HRQL assessment feasible. Therefore, CAT seems to be a promising tool.

QUALITY OF LIFE AS STUDY OUTCOME

Quality of life was a matter of study outcome in seven studies. The majority of these studies comprised trials in which the effect of a therapy on quality of life was assessed as a primary or secondary endpoint. The SF-36 was used in two trials as the primary endpoint: both were double-blind, placebo-controlled pilot studies [6▪,7▪▪]. The first trial [6▪] investigated the effect of ARA 290 on HRQL in 22 patients with sarcoidosis and symptoms of small-fiber neuropathy (SFN). A significant change from baseline in the dimensions pain and physical functioning of the SF-36 was observed in the ARA 290 group compared to the placebo group after 4 weeks of treatment.

The other trial tested the effect of armodafinil on HRQL in 15 patients [7▪▪]. In addition to the generic questionnaire SF-36, the Sarcoidosis Health Questionnaire (SHQ) was used as a disease-specific questionnaire. Just in one of the nine dimensions of the SF-36, the vitality score, a significant increase was evinced compared with placebo. Measurement with the SHQ, however, did not detect any differences, neither in total score nor in its individual components consisting of daily, physical, and emotional axes.

Furthermore, HRQL was used as a primary endpoint in one retrospective study. Van Rijswijk *et al.* [8▪] investigated the effect of infliximab on the change in the SF-36 dimension 'physical functioning' in 48 patients with refractory sarcoidosis. In this cohort, infliximab treatment induced a statistically significant improvement in the physical functioning dimension.

Moreover, studies that used HRQL as the secondary endpoint included the effect of a broad-spectrum antimycobacterial therapy [11] and adalimumab [13]. Both studies used specific questionnaires: the SGRQ and the Dermatology Life Quality Index, respectively. Improvement in HRQL was demonstrated in both the studies.

In addition to the intervention studies, two studies have analyzed the impact of specific conditions associated with sarcoidosis on quality of life. The first publication [12] illustrated the correlation of obesity and quality-of-life scores with sarcoidosis. Gvozdenovic *et al.* evaluated 184 sarcoidosis patients and the same number of sex and age-matched healthy individuals. HRQL was measured using the respiratory-specific SGRQ. The study showed that increased BMI ($\geq$25 kg/m^2) and higher total SGRQ scores (indicating reduction of HRQL) were more common among the sarcoidosis patients than among the healthy volunteers.

Additionally, Bakkers *et al.* [9] assessed HRQL in patients with SFN. As SFN is a common feature in sarcoidosis, 36% of the study group (96 out of 265 patients) was identified as sarcoidosis patients. Measurement with the SF-36 in the total study group of SFN patients showed a severe reduction in all dimensions of HRQL. The largest deficits were in the dimensions 'role functioning – physical', 'body

pain', 'vitality' and 'general health perception'. Additional analysis revealed no differences in SF-36 subscale scores between the sarcoidosis group and the patients with nonsarcoidosis cause.

QUALITY OF LIFE-RELATED STUDY OUTCOMES

As mentioned in the Introduction section, the concept of HRQL is intertwined with health status, and in daily medical practice, HRQL is often incorrectly used to refer to the nonspecific symptoms as fatigue, depressive symptoms and anxiety that may accompany sarcoidosis. Also, researchers are confronted with the interchangeability of these concepts when submitting their manuscript to a journal and selecting the appropriate key words during this process. The often used standard key word list regularly forces them to imperfectly choose 'quality of life'. Next, these studies are erroneously retrieved in literature searches for reviews on HRQL. Likewise, in our literature search, three studies appeared that in fact did not assess HRQL, but investigated HRQL-related subjects: fatigue [19], pain [20], sleep and depression [21].

CURRENT SHORTCOMINGS AND FUTURE REMARKS

Even though it was recommended that all trials in sarcoidosis should incorporate measurement of quality of life [15], the number of publications in the field of HRQL in sarcoidosis appears to be limited over the past year. Regularly, the mode of assessment remains to be a matter of debate. Whereas the discussions about choosing the appropriate instrument (generic of specific) prolong, innovative approaches of testing emerge. Development of CAT is very promising for the field of sarcoidosis. Research on CAT should therefore be supported.

Moreover, it is remarkable that no study on quality-adjusted life year (QALY) in sarcoidosis is available. QALY is a measure of disease burden, including both quality as well as the quantity of life lived (www.nice.org.uk/newsroom/features/measuringeffectivenessandcosteffectivenesstheqaly.jsp). Each year of perfect health is assigned with the value of 1.0, whereas death is valued as 0.0. QALY is calculated based on HRQL assessment, commonly the EuroQol-5D (EQ-5D) [22], the SF-36 or its Short Form 6D (SF-6D). Interestingly, neither the EQ5D nor the SF-6D has been used in any of the published studies over the past year. Lack of these data also implies that analysis of cost-effectiveness of the healthcare is not possible. Cost-effectiveness means that the costs of the intervention (e.g. a drug) are recalculated in the light of gaining quality of life. We expect that economic evaluation of healthcare will be of increasing interest and need in the near future. As intervention studies in sarcoidosis often comprise expensive drugs, the evaluation of the effectiveness of the intervention should therefore also include the calculation of QALY. Assessment of HRQL is therefore also in the light of health-economical analysis essential.

CONCLUSION

In conclusion, HRQL remains an intriguing topic of research in sarcoidosis. Clinicians acknowledge the reduction of quality of life in sarcoidosis as a significant and profound problem in their daily practice, whereas patients indicate to experience this in everyday life. Nevertheless, the topic is relatively new and although advised, still rarely used as study outcome. While discussions about the questionnaire of first choice last, CATs will probably improve HRQL assessment in the coming years. Moreover, the increasing importance of economic evaluation of new (and expensive) treatments in sarcoidosis will require standard measurement of HRQL. All in all, these observations generate ample opportunities for expanding the field of HRQL in future studies in sarcoidosis.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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