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REVIEW ARTICLE

Assessment of Patient-Reported Outcomes in Sarcoidosis Patients: A Review

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ABSTRACT

Patient-reported outcomes are standardized reports provided by patients about their own health-related quality of life, health status, their symptoms or functional status associated with the health care or treatment they have received. Patient-reported outcomes are measured by questionnaires that are scientific instruments validated in different clinical conditions. The aim of this review is to provide the updated information on patient-reported outcomes use in assessment of pharmacotherapy effects in patients with pulmonary sarcoidosis. Sarcoidosis is a chronic disease in which treatment decisions for the majority of patients are based predominantly on health-related quality of life measurements. It is a chronic multisystem granulomatous inflammatory disease of unknown origin that is most commonly present in the lungs but may also involve any other organ. Therefore, it is important not only to assess their pulmonary symptoms like dyspnea or cough, but also those that originate from other organs and even constitutional ones, like fatigue or depression.

We separately presented the health-related quality of life and health status, as well as symptom-specific patient-reported outcomes used in sarcoidosis patients that measure fatigue, dyspnea, cough, and depression. Since corelations between objective and subjective disease outcomes in sarcoidosis patients are often mild or moderate or even do not exist at all, a consensus has emerged to use both of these outcomes in clinical trials and routine practice management. Therefore, the World Association of Sarcoidosis and other Granulomatous Disorders recommended that all research studies should incorporate health-related quality of life measurement.

Introduction

The international clinical drug trials include in their design patient-reported outcomes (PROs) as study endpoints to assess the response and efficacy of novel treatments, and their changes during treatment period represent either secondary and exploratory (in phases II or IIIa) or even primary (in phases IIIb and IV) study objectives. Patient-reported outcomes are assessed by questionnaires that are developed and validated in different indications. They can be generic or disease-specific instruments.[1] The United States Food and Drug Administration defines PROs as measurement of any aspect of a patient's health status (HS) that comes directly from the patient, without interpretation of the patient's responses by a physician or anyone else.[2] According to the European Medical Agency Guidelines, PRO is an umbrella term that covers both single dimension and multi-dimension measures of symptoms, health-related quality of life (HRQL), HS, adherence to treatment, patients' satisfaction with treatment.[3] Patient-reported outcomes are increasingly observed as the regulatory authorities' requirement due to specific limitations of some various objective disease related outcomes such as pulmonary function testing or radiographic measurements in respiratory diseases. Moreover, numerous studies have demonstrated that correlations between PROs as subjective outcomes and objective disease outcomes are rather mild or moderate or even do not exist at all.[4,5] Evidence suggests that the correlation between the patient and physician assessment of the health impact of sarcoidosis may be very discordant.[6] Therefore, presently both subjective and objective parameters should be measured in both clinical trials and routine clinical practice.

It has been recognized that the change in PROs' scores had to be defined regarding its significance, i.e. how much they correlate with the clinical improvement or deterioration. As a result, the minimal clinically important difference (MCID) has been established and accepted as an important measurement characteristic of PRO instruments.[7] It represents the smallest difference in a score which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management. The usefulness of any questionnaire in clinical practice and research trials depends on its ability to indicate a likelihood of treatment success during follow-up. The MCID reflects a clinically relevant change of their scores.

Health-Related Quality of Life and Health Status in Sarcoidosis

Health-related quality of life and health status are two distinct, but complementary concepts that are frequently interchangeably used in the medical literature.[8] Health status refers to the disease influence on physical, psychological and social functioning of patients. HRQL is a broader concept that refers to the patients' perception or evaluation of their own functioning,[9] i.e. in what extent they are satisfied or bothered by their functioning. There are some differences between the type of questions and the meaning of HRQL and HS instruments scores. Instruments for the HRQL measurement assess more aspects of life than the HS ones, in such a way that they provide more detailed information about patients' lives. Health status measures only the aspects that are directly associated with health, whereas instruments for HRQL measure a broader range of aspects of patients' lives.[10] Studies have demonstrated inconsistent correlation between improvements in HRQL and HS which can be attributed to various factors, including methodological differences, participant characteristics, and the specific measures used.[11,12]

Sarcoidosis is one of the chronic diseases where treatment decisions for most patients are based predominantly on HRQL issues.[13,14] It is a chronic multisystem granulomatous inflammatory disease of unknown origin that is most commonly present in the lungs but may also involve other organs.[15]

Patients with pulmonary sarcoidosis may have symptoms related directly to the chest such as dyspnea on exertion, chest pain, chest discomfort, cough, and wheeze. Patients may also develop symptoms related to extrapulmonary organ involvement. In addition, complications of sarcoidosis may involve constitutional symptoms such as fatigue, fever, anorexia, weight loss, generalized weakness, and pain that are not attributable to involvement of any specific organ.[16] In their review article De Vries and Drent concluded that the HS and HRQL of sarcoidosis patients are negatively affected by the disease and lead to symptoms that negatively impact their lives.[17]

Obi et al recently reported the results from the US Sarcoidosis Research Institute Survey, where 1018 US sarcoidosis patients responded that their greatest concerns were: 1) fear of worsening disease, 2) fear of sarcoidosis developing in more organs, and 3) fear of sarcoidosis not improving.[18] In addition, these same patients were concerned about poor HRQL, inability to enjoy everyday activities, lack of medical research, disability from sarcoidosis, and pulmonary function status. Lack of physician knowledge and poor physician communication were ranked of lowest concern. Concerns about ineffective medications and cost of medical care were also ranked relatively low.

Disease-Specific Health Status Questionnaires

SARCOIDOSIS HEALTH QUESTIONNAIRE

The first disease-specific HS instrument developed in sarcoidosis is The Sarcoidosis Health Questionnaire (SHQ).[19] It is a 29-item questionnaire with responses ranging from 1 (all of the time) to 7 (none of the time). Higher scores represent better HS. The SHQ requires no investigator supervision, and it requires about 10 minutes for completion. This instrument measures three health status domains: Daily Functioning, Physical Functioning, and Emotional Functioning. Mihailović-Vučinić et al showed that sarcoidosis patients aging 41–50 years experienced the lowest SHQ scores.[20] Unfortunately, this decade of life is often the peak work time, and overall low health status creates a burden for these patients. The overall health status in their study was significantly lower in female patients, and is in

accordance with results of other authors.[8,21,22] In addition, significantly lower SHQ scores in sarcoidosis patients with chronic disease underlines the importance of patients' perceived burden with chronic sarcoidosis, predominantly in the domains of Daily Functioning and Emotional Functioning. They also found single agent methotrexate treatment to be associated with better SHQ scores compared to treatment with prednisone only or prednisone with methotrexate. Total SHQ scores in the US study of Cox et al showed statistically significant differences between symptomatic and asymptomatic patients.[6] In the validation study in Japanese sarcoidosis patients, Tanizawa et al demonstrated that SHQ scores significantly correlate with scores on the generic instrument Short Form 36 (SF-36)[23] and respiratory-specific St Georges Respiratory Questionnaire (SGRQ)[24] health status questionnaires.[25] The SHQ scores also were shown to significantly correlate with serum levels of the soluble interleukin-2 receptor, the percentage of the predicted forced vital capacity (FVC), pulmonary arterial systolic pressure, dyspnea, and depressive symptoms.

A clinically important difference for SHQ has not been established. In addition, the SHQ is not divided into domains and modules so that various aspects of sarcoidosis are lumped together into a total score. Therefore, the SHQ may be insensitive to changes in specific aspects of sarcoidosis-related HRQL, such as fatigue or skin changes.

Treatment can also be associated with significant toxicity which can impair HRQL of patients with sarcoidosis.[26] Patients that received high corticosteroid dose had worse HS as measured by SHQ and Sarcoidosis Assessment Tool (SAT).[27]

KING'S SARCOIDOSIS QUESTIONNAIRE

Another widely used sarcoidosis-specific HS instrument - the King's Sarcoidosis Questionnaire (KSQ) was developed and validated by Patel and coauthors.[28] It is a modular multi-organ HS measure for patients with sarcoidosis for use in clinic and the evaluation of therapies. It consists of five modules: General health status (GHS, 10 items), Lung (6), Medication (3), Skin (3) and Eye (7). The GHS module is intended to be administered to all patients with sarcoidosis. In addition to this, patients also complete organ specific modules if relevant to their condition. The individual module scores are intended to identify the health domains affected. The medication module can be used in isolation or combined with overall lung and skin health status questionnaires but not eye health status. The King's Sarcoidosis Questionnaire is a tool that assesses organ-specific HS and incorporates solely PROs based on pulmonary, eye and skin symptoms since these are the most frequently affected organs in sarcoidosis. It may be possible to assess rarer forms of sarcoidosis such as neurological and cardiac disease with the GHS module since it comprises generic items relevant to most patients.

Baughman et al determined the MCID as the within-patient clinically meaningful change threshold of KSQ general health (KSQ GH) to be 8, and for KSQ lung score to be 4.[29] The best correlations of KSQ scores were seen with the SGRQ, SF-36, and Fatigue Assessment Scale (FAS),[30] which also have established MCID values.

Similar to results noted with SHQ, health status was more deteriorated in females in Serbian population of sarcoidosis patients using the KSQ (GHS and Lung domain scores).[31] However, this was not the case with other HS instruments used, respiratory-specific SGRQ and generic tool – 15D.[32] In addition, women were more dyspnoic as assessed by the Modified Medical Research Council (mMRC) dyspnea scale.[33]

Stjepanovic et al recently demonstrated that KSQ GHS and Lung domain scores were significantly correlated with scores of other administered PROs (SGRQ domains, mMRC, FAS and 15D).[34]

SARCOIDOSIS ASSESSMENT TOOL

Judson and coauthors developed and validetad the Sarcoidosis Assessment Tool (SAT), a sarcoidosis-specific PRO.[27] The Sarcoidosis Assessment Tool is a reliable and consistent PRO that accurately reflects various disparate aspects of the disease. It consists of 8 domains: daily activities, satisfaction with life activities, fatigue, pain, sleep disturbance, lung concerns, skin concerns, and embarrassment over skin appearance. A clinically important difference has been established for the SAT modules, so it should be considered for clinical and research use in sarcoidosis. In other clinical study Judson et al showed that compared to the absence of symptoms at presentation, the presence of symptoms was associated with a greater need for treatment, more organ involvement, and worse HS as measured by the SAT.[35] In addition, it has been shown that the SAT fatigue module has superior reliability to FAS.[36]

Respiratory-Specific Health Status Questionnaire

Several respiratory-specific HS instruments exist, but the most used in sarcoidosis patients is the St. George's Respiratory Questionnaire (SGRQ).[24]

THE ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

The St. George's Respiratory Questionnaire is an instrument that was originally designed to measure the HS of COPD patients.[24] Its validity, reliability and responsiveness were also shown in other pulmonary diseases. The questionnaire consists of 50 items with 76 responses and encompasses three domains of HS: 1) *symptoms*, focusing on distress because of respiratory symptoms, 2) *activities*, measuring decreased mobility or physical activity and 3) *impacts*, measuring the psychosocial influence of disease on the everyday life and patients' well-being. Scores of these domains, as well as the total score, are scaled from 0 to 100, where higher scores represent poorer HS.

Although SGRQ is a respiratory-specific HS questionnaire, it has been shown that patients with pulmonary plus extrapulmonary sarcoidosis had statistically and clinically significant worse health status in terms of SRGQ scores than those with isolated pulmonary sarcoidosis.[37] This was also the case for fatigue and dyspnea.

Another study by Gvozdenovic et al[38] demonstrated that the body mass index and forced expiratory volume in one second (FEV_1) significantly predicted both sarcoidosis patients' HS, as assessed by the SGRQ and 15D, and dyspnea measured by the Baseline Dyspnea Index (BDI)[39].

Žugić et al reported that SGRQ activity scores were significantly lower in male sarcoidosis patients, those with newly diagnosed disease, and in patients with elevated angiotensin-converting enzyme (ACE).[40] Patients with extrathoracic disease had significantly higher scores. Clinical course showed significant correlation with impact and total scores, and the number of relapses with the activity score. The St. George's Respiratory Questionnaire scores significantly correlated with serum IgE and with most spirometric parameters examined.

In the study of Lo et al in patients with symptomatic sarcoidosis SGRQ scores correlated with spirometry parameters FEV_1 and FVC, Borg dyspnea score[41], and Short Form-36 Physical Component Summary (SF-36 PCS) scores both cross-sectionally and longitudinally after 24 weeks of follow up.[42]

Guber and coauthors demonstrated that 12-week pulmonary rehabilitation improves the HS as measured by the SGRQ and dyspnoa assessed via the mMRC scale.[43]

Generic Health Status Questionnaires

Several generic HS questionnaires exist, and the most used in sarcoidosis patients is The medical outcome study 36-item short form health survey (SF-36)[22] and The fifteen-dimensional measure scale of HRQL (15D).[31]

THE MEDICAL OUTCOME STUDY 36-ITEM SHORT FORM HEALTH SURVEY

The SF-36 is a generic 36-item HS instrument with eight different domains: physical functioning, social functioning, limitations in usual role activities due to physical problems (role physical), limitations in usual role activities due to emotional problems (role emotional), mental health, vitality, bodily pain, and general health perception.[22] Scores are transformed into a 100-point scale, with higher scores indicating better HS. There is evidence of reliability and validity for its use among patients with various diseases, including a population with interstitial lung disease, where 9 patients had sarcoidosis.[44] Construct validity of the SF-36 was confirmed by Cox et al on a population of 120 sarcoidosis patients.[6] The domains can be used together or separately. An improvement in vitality score of at least 20 points was found to be the MCID that correlated the best with improvement in other HS-measures in patients with rheumatoid arthritis.[45]

Tanizawa et al reported that three SF-36 domains (general health perception, vitality/energy, and limitations in usual role activities due to physical health problems) had statistically significant associations with a 5-year clinical deterioration in sarcoidosis patients.[25]

Bardakci et al recently demonstrated a significant decrease in HS in sarcoidosis patients using the SF-36.[46] These changes were more pronounced in women and those patients with pulmonary plus exrapulmonary sarcoidosis.

THE FIFTEEN-DIMENSIONAL MEASURE SCALE OF HRQL

The fifteen-dimensional measure scale of HRQL (15D) is a multiatributive instrument that was initially developed and validated in a large Finnish population.[32] The scale consists of 15 different and mutually exclusive health dimensions, each represented by one item. The total questionnaire score ranges between 0 and 1, where 1 signifies the highest level of HS. It was used in different diseases in many different countries. The Serbian version of 15D demonstrated good psychometric measurement properties in sarcoidosis patients.[8,34,37,38]

Total and activity domains of the SGRQ in sarcoidosis patients with pulmonary plus extrapulmonary organs involvement were more impaired than in the isolated pulmonary group.[37] Differences between symptoms and impacts domain SGRQ scores, mMRC dyspnea scores and 15D scores did not reach the statistical significance, although the mean score reflected poorer HS in the former group.

In the cross-sectional study in 145 biopsy proven pulmonary sarcoidosis patients, Gvozdenovic et al demonstrated good correlations between spirometry parameters (FEV_1 and FVC) with 15D and SGRQ (activities, impacts and total) scores.[8] Only 2 out of 7 scores of the HRQL instrument WHOQOL-100[47] correlated with FEV_1 and FVC. In addition, all measured HS and HRQL scores were significantly worse in those patients who had pulmonary plus extrapulomonary disease manifestations.

Body-mass index and FEV_1 proved to be significant predictors of HS in sarcoidosis patients measured by the 15D.[38] In another study,[48] dyspnea measured by the mMRC, fatigue assessed by the FAS and physical domain of the Leicester Cough Questionnaire (LCQ)[49] were significant predictors of HS assessed by the 15D.

Health-Related Quality of Life Instruments

Health-related quality of life instruments that are frequently utilized in sarcoidosis are: The World Health Organization Quality of Life assessment instrument (WHOQOL-100),[47] The World Health Organization Quality of Life-BREF assessment instrument (WHOQOL-BREF),[50] and The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[51]

THE WORLD HEALTH ORGANIZATION QUALITY OF LIFE ASSESSMENT INSTRUMENT

The World Health Organization Quality of Life assessment instrument is a generic multidimensional measure of HRQL.[47] This questionnaire is developed cross-culturally simultaneously in 15 collaborative centers around the world and contains six domains (physical health, psychological health, level of independence, social relationships, environment and spirituality/religion/personal beliefs) covering 24 facets and one general evaluative facet. There are four items per facet producing a total of 100 items. All items are rated on a five-point Likert scale (from 1-5). Studies

among sarcoidosis patients have shown that the questionnaire is reliable and valid.[52]

Using WHOQOL-100, SGRG and 15D PRO instruments, Gvozdenovic et al found that all HRQL and HS scores were better in male sarcoidosis patients, with the highest differences seen between the SGRQ Activity domain scores and the Level of independence domain of WHOQOL-100.[8] Significant differences were demonstrated between the patients with isolated pulmonary sarcoidosis and those who had pulmonary plus extrapulmonary disease manifestations for all HRQL and HS scores – patients with extrapulmonary sarcoidosis had worse both HRQL and HS. The highest difference was between the scores of Level of independence domain of WHOQOL-100.

Hoitsma et al addressed the importance of pain in sarcoidosis patients as the factor that influences their low HRQL.[53] The total amount of experienced pain categories was associated with the WHOQOL-100 domain Level of Independence and the facet Energy and Fatigue. As Wirnsberger et al reported, the WHOQOL-100 is a sensitive instrument to measure fatigue, one of the most common symptoms in sarcoidosis, which otherwise is difficult to assess objectively.[54]

THE WORLD HEALTH ORGANIZATION QUALITY OF LIFE-BREF ASSESSMENT INSTRUMENT

The World Health Organization quality of life-BREF assessment instrument is the questionnaire that is an abbreviation of the WHOQOL-100, consisting of 26 items. It contains 24 questions on four domains (physical health, psychological health, social relationships, and environment) and two questions on overall HRQL and general health.[50] Alilovic et al have evaluated the usefulness of the WHOQOL-BREF in a sarcoidosis population of 97 patients compared to 97 healthy controls.[55] They concluded that WHOQOL-BREF is not sufficient for the evaluation of HRQL in sarcoidosis patients based on the failure to obtain any information regarding fatigue, which is the most significant symptom of sarcoidosis.

Marcelis et al showed that the physical training in sarcoidosis patients improved the psychological health domain of the WHOQOL-BREF as well as their fatigue using the FAS and dyspnea mMRC scores.[56] Drent et al reported that fatigue and exercise capacity predicted the scores for the WHOQOL-BREF physical health domain at baseline and follow-up (after 2 years).[57]

THE QUALITY OF LIFE ENJOYMENT AND SATISFACTION QUESTIONNAIRE

The Quality of Life Enjoyment and Satisfaction Questionnaire is a self-report instrument used to assess the degree of enjoyment and satisfaction experienced by subjects in eight areas, including: physical health/activities (13 items), feelings (14), work (13), household duties (10 items), school/course work (10 items), leisure time activities (6 items), social relations (11 items), and general activities (14 items).[51] The three areas of work, household duties, and school/course work are filled out by the respondent only if applicable. Items are rated on a 5-point scale. Higher scores denote higher levels of satisfaction. There are two additional items which explore medication satisfaction and life satisfaction and contentment over the last week. The Italian version of the Q-LES-Q has been validated by Rossi et al in outpatient setting of patients with anxiety disorders.[58] Goracci et al reported significant correlations between spirometry parameters (FEV_1 and FVC) and several domains of the Q-LES-Q in sarcoidosis patients.[59] Those with multi-systemic involvement, with asthenia and with a more severe radiographic stage and patients receiving steroids, reported a poorer HRQL.

Symptom-Specific Patient-Reported Outcomes Instruments Used in Sarcoidosis

Thunold et al identified five key PRO concepts in sarcoidosis: 1) Fatigue; 2) Dyspnea; 3) Health Status and Quality of Life; 4) Depression, Anxiety and Stress and 5) Miscellaneous (symptomatology, personality and cognition, pain, sleep, other).[60] There are currently a high number of validated symptom-specific PROs instruments used in sarcoidosis patients worldwide and more comprehensive list of them are well described in the review article from Obi at al.[61]

FATIGUE

Fatigue is the most frequently described and disabling symptom in sarcoidosis patients that often leads to a decreased HRQL. We describe here two frequently used questionnaires in sarcoidosis patients – The Fatigue Assessment Scale (FAS)[30] and The Fatigue Scale (FS).[62]

The Fatigue Assessment Scale

The Fatigue Assessment Scale is a one-dimensional 10-item self-report fatigue questionnaire consisting of 5 questions reflecting physical fatigue and other five for mental fatigue.[30] The response option is a 5-point Likert scale (1 never to 5 always). Total scores can range from 10 to 50, with high scores indicating more fatigue. FAS total score < 22 indicates no fatigue. The psychometric properties (reliability and validity) of the FAS are good, and it was also shown in sarcoidosis patients.[63,64]

The Fatigue Assessment Scale appears to be a reliable and valid tool to use as an indicator for measuring dyspnea, HRQL and exercise tolerance in patients with sarcoidosis.[65] De Kleijn et al determined that the MCID for the FAS is a 4-point difference on its score.[66] This MCID can be used in the follow-up of fatigue (FAS) in clinical trials and in the management of individual sarcoidosis cases.

Bardakci demonstrated a statistically significant, positive, low-level relationship between FAS and sarcoidosis duration, as well as FEV_1 (% predicted).[46] Contrary to them, Jastrzębski et al did not find the correlations between FAS and spirometry or diffusing capacity.[65] In their study fatigue correlated with all dyspnea domains of BDI and mMRC scales, as well as with HRQL scores of the SF-36.

Mihailovic-Vucinic et al reported that granulomatous inflammation detected by 18-FDG PET scan correlates with Total and Physical fatigue FAS scores.[67] However, it was not the case with its mental fatigue scores. On the

other side, the Total FAS score ≥22 has been shown to be the best independent predictor of depressive symptoms, depression and anxiety. [68,69]

The Fatigue Scale

The Fatigue Scale contains 14 questions and distinguishes mental fatigue (with six items) that describes cognitive difficulties, and physical fatigue (eight items). A total fatigue score is also calulated. Each fatigue score ranges from 1 to 4. Higher scores correspond with more severe fatigue. The scale was found to be both reliable and valid[62] and has shown sensitivity to treatment changes.[70]

Gvozdenovic et al reported higher FS–Total scores in patients with sarcoidosis compared to control group of gender and age matched healthy individuals.[4,71] In addition, fatigue was worse in females both in the sarcoidosis and in healthy control group.[71] The correlations between the FS scores and spirometric parameters: FVC and FEV_1, were statistically significant.

Fatigue assessed by the FS is more severe in those sarcoidosis patients who apart from pulmonary has also other organs involved.[37] Using the same scale it has been shown that BMI, clinical course of disease (chronic vs. acute) and FEV_1 are significant predictors of sarcoidosis related fatigue.[38]

DYSPNEA

Dyspnea may be present in sarcoidosis patients even when pulmonary function tests and chest radiographs are normal. Dyspnea reflects more than pulmonary impairment alone in sarcoidosis, as it is more severe in sarcoidosis patients with pulmonary plus extra pulmonary sarcoidosis than in those with isolated pulmonary sarcoidosis.[37,72] This demonstrates the need to assess dyspnea as a PRO and not only as a result of worsened lung function.

The most frequently used dyspnea instruments in sarcoidosis patients are mMRC,[33] Borg dyspnea scale[41], and BDI/TDI.[39]

The modified medical research council dyspnea scale

The Modified Medical Research Council Dyspnea Scale classifies subjects into one of five categories according to their degree of dyspnea when performing certain activities.[33] Scores range from the 0 to 4, with the higher scores indicating more severe dyspnea. It has been widely used in patients with sarcoidosis.[8,34,38,48,65,73,74] It has been suggested that the scale is not sensitive enough to detect changes.[75] It has been demonstrated that dyspnea measured by the mMRC and BDI represents a significant predictor of sarcoidosis patients' HS assessed by the SGRQ.[76]

The Borg Dyspnea Scale

The Borg dyspnea scale[41] is an 11-point scale on which dyspnea is graded from 0 (nothing at all) to 10 (maximum). It is widely used in clinical trials in different respiratory and cardiovascular diseases. It was also frequently administered in studies with sarcoidosis patients.[34,48,73]

It has been shown that the Borg category scale can best detect the presence of increased dyspnea that largely correlates with fatigue presence in sarcoidosis patients.[74] In addition, dyspnea measured by Borg scale as well as sACE were strong predictors of cough-specific HRQL in sarcoidosis patients.[48]

Borg dyspnea scale is frequently used together with the six-minute walk test (6MWT) assessment. Gupta et al reported that 6MWD significantly correlated with initial Borg score, as well as with the FAS in patients with sarcoidosis associated pulmonary arterial hypertension.[77]

There are several drawbacks of mMRC and Borg dyspnea scales – neither the mMRC nor the Borg scale specifically addresses the functional impairments resulting from dyspnea.[39] In addition, evidence is lacking on whether these measures reliably quantify changes in dyspnea over time in sarcoidosis patients.[37,60] Therefore, further instruments are needed for measurement of dyspnea in this patient population.

The Baseline Dyspnea Index and Transition Dyspnea Index

The Baseline Dyspnea Index (BDI) and Transitional Dyspnea Index (TDI) evaluate dyspnea at a single baseline state (BDI), and as a change from baseline (TDI) across three components: degree of the functional impairment, magnitude of task and magnitude of effort that evokes dyspnea.[39] Functional impairment (BDI_Function) assesses the impact of dyspnea on the ability to carry out activities, magnitude of task (BDI_Task) reflects the type of task that produces dyspnea, and magnitude of effort (BDI_Effort) quantifies the level of effort that causes dyspnea. Each component is graded on a five-point rating scale from 0 ('extreme impairment') to 4 ('without impairment'). Therefore, the total BDI score can range from 0 to 12. Changes in dyspnea from baseline on each of the three components (TDI) are rated on a seven-point scale from -3 (major deterioration) to +3 (major improvement) for a TDI_Total score of -9 to +9.

The scores of BDI-TDI have been validated for the measurement of dyspnea and change in dyspnea over time in COPD patients and have been shown to correlate with measures of HRQL in that population.[78,79] A 1-unit change in TDI has been determined to be the MCID in TDI for COPD patients.[78,79]

The Baseline Dyspnea Index has been widely used in sarcoidosis patients.[8,37,73] Statistically significant differences in BDI dyspnea scores were demonstrated between the isolated pulmonary group and the pulmonary plus extrapulmonary group of sarcoidosis patients.[37] Patients with additional organs involvement were more dyspnoic.

Obi at al reported that BDI scores significantly correlate with pulmonary function parameters (FVC and FEV_1), 6MWD, FAS and other dyspnea measures (mMRC and Borg scales).[73] On the other side, TDI scores did not correlate with changes in pulmonary function or other dyspnea measures.[73]

COUGH

More attention has been paid to the cough in sarcoidosis during the last several years, since it is a common and significant symptom in these patients.[80] There is a validated tool – Leicester Cough Questionnaire (LCQ) for measuring this important symptom.[49] It is a 19-item specific HRQL measure of cough over the period of previous two weeks. The Leicester Cough Questionnaire is a valid outcome to assess the intra-individual impact of cough on HRQL and to detect large changes in quality of life mainly in a short-term clinical trial setting.[81] Its scores can be calculated in 3 domains covering physical (8 items), psychological (7 items), and social (4 items) aspect of chronic cough, in addition to the total score. It evaluates the impact of cough on patients' HRQL. Scores are calculated by domain (range from 1 to 7) and then added to obtain the total score (range from 3 to 21), with higher scores indicating a better HRQL.

The Leicester Cough Questionnaire has been validated for different diseases, like chronic cough itself, cystic fibrosis including affected children, bronchiectasis, COPD,[82-84] and also for sarcoidosis.[48,85]

It has been demonstrated that dyspnea measured by Borg scale and sACE were strong predictors of all LCQ domains.[48] Mental aspect of patients' fatigue was significantly correlated with all domains except with psychological LCQ domain. It is important to measure both cough-specific and generic HRQL in sarcoidosis patients since they measure different health aspects, and their predictors can be different. Physical domain of LCQ is significant predictor of generic HRQL measured by the 15D.[48]

DEPRESSION

The prevalence of depression in sarcoidosis patients was found to be 60% and 66% in two American studies[6,86] compared to 42% in the American ACCESS study.[87] Both fatigue and anxiety are related to depressive symptoms.[88] The most frequently used depression questionnaire in sarcoidosis patienst is The Center for Epidemiologic Studies - Depression Scale (CES-D)[89].

The Center for Epidemiologic Studies - Depression Scale

The Center for Epidemiologic Studies - Depression Scale[89] was initially developed to measure the current level of the respondent's depressive symptoms in epidemiological studies in the general population and primary care, and it has also been extensively used in other chronic conditions,[90,91] and even as a stand-alone depression diagnostic measure.[92] It has also been used in sarcoidosis patients.[69, 88,93] The scale contains 20 items related to symptoms occurring the week before the interview with response options from 0 to 3 that refer to the frequency of the symptoms. The Center for Epidemiologic Studies - Depression Scale score ranges from 0 (best possible) to 60 (worst). A cutoff score of 9 or above is used to indicate depression.

Using the CES-D scale, Gvozdenovic at al reported that measuring the contribution of low serum 25-hydroxyvitamin D and the impact of persistent dry cough on depressive symptoms in patients with sarcoidosis may be crucial in deciding whether to use vitamin D_3 alone or with antitussive therapy before the psychiatric diagnosis of depression with antidepressant therapy initiation.[69]

The aim of this review is to provide the updated information on patient-reported outcomes use in assessment of pharmacotherapy effects in patients with pulmonary sarcoidosis

Methods

A search using the PubMed database was performed with the keywords sarcoidosis, quality of life, patient-reported outcomes and therapy. This resulted in 37 articles. Twelve review articles were immediately excluded from the analysis, while 15 original articles were excluded for various reasons: 1) the study population did not consist exclusively of patients with sarcoidosis (N = 11); 2) there was no pulmonary sarcoidosis and/or the therapy was not related to pulmonary sarcoidosis (N = 3); and 3) the study population did not have sarcoidosis patients (N = 1). Therefore, only 10 studies were retained in our analysis.

Culver et al demonstrated a significant improvement in PROs (SAT lung, KSQ lung, KSQ general health and FAS) in the group of sarcoidosis patients who administered investigated treatment (Efzofitimod) after 24 weeks compared with placebo, which corresponds to a significant but small improvement in FVC % predicted and diffusion capacity of the lung for carbon monoxide (DLco) % predicted.[94] In the PREDMETH study it was planned to monitor changes in FVC % predicted and DLco % predicted, as well as changes in FAS, SAT, mMRC and KSQ scores, over time in sarcoidosis patients for up to 2 years.[95] Preliminary results have been published only regarding the safety of the treatment with prednisone and methotrexate, i.e. the occurrence of side-effects during the treatment.[96] Recently presented final results by Kahlmann et al indicated that methotrexate was noninferior to prednisone regarding the improvement in FVC % predicted.[97] Both medications improved KSQ General Health and Lung scores as well as FAS scores. Sharp et al emphasized the importance of monitoring therapeutic adherence simultaneously with important PROs (measured by KSQ and SGRQ) in addition to spirometric parameters.[98] In their study higher medication adherence was associated with better HRQoL. Baker at al tested sarilumab in 15 glucocosricosteroid-dependent sarcoidosis patients and did not observe the improvement due to the small sample size.[99] However, they noticed the improvement in the visual analogue scale and score of the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F)[100] after 16 weeks of treatment. In other pharmacotherapy studies in sarcoidosis patients, in addition to health-related quality of life, fatigue[26,101,102] and cough[103,104] were mainly monitored.

Incorporation of PROs is very important in designing of the clinical trials protocols, especially in chronic diseases like sarcoidosis where objective outcomes cannot fully direct treating physicians in therapeutic decision making and follow up of their patients. Sarcoidosis has a substantial impact on patients' HS and HRQL that are

differently related to the conventional disease outcomes. Because of the differencies between the two concepts, they should not be used interchangeably, since HS instruments may be inappropriate for measuring HRQL, and vice versa. Therefore, evaluations of the effectiveness of medical treatment may differ depending on whether HS or HRQL is the study outcome. We can advise use of both HS and HRQL instruments in assessment of PROs in sarcoidosis and recommend future research in the development and standardization of new tools for their measurement. This also applies to the symptom-specific PROs used in sarcoidosis patients that measure fatigue, dyspnea, cough, and depression. Incorporating real-time electronic modifications and actively engaging patients in the co-creation of PRO instruments ensures that clinical trials remain both scientifically rigorous and patient-centric.

In 2011, the World Association of Sarcoidosis and other Granulomatous Disorders recommended that all research studies should incorporate HRQL measurement.[105]

Limitation of this review is in the fact that it could not list all PROs used in sarcoidosis, especially those that are not frequently used in both clinical trials and routine practice.

Conclusion

We conclude that from clinical trials to real-world environment, patient-reported outcomes are central to evaluating the effectiveness of interventions and ensuring that treatments align with patients' lived experiences. Our understanding of diseases continues to grow, and healthcare evolves with advancements in early disease detection and a deeper understanding of its progression, so the relevance and applicability of many existing patient-reported outcomes measures are increasingly questioned. This is also applicable for sarcoidosis as a multisystem disease that can negatively impact health status and health-related quality of life across generic (e.g., physical, social and emotional wellbeing) and disease-specific (e.g., pulmonary, ocular, dermatologic) domains. Therefore, their regular assessment is very important in determining the best instruments for particular indications and even diseases' phenotypes. In comparison to the preceding decade, the last ten years have seen a marked improvement in the incorporation of patient-reported outcomes in pharmacotherapy studies of patients with sarcoidosis.

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