SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2017; 34; 2-17 DOI: 10.36141/svdld.v34i1.5760

Patient reported outcome measures (PROMs) in sarcoidosis

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Abstract. Patients with sarcoidosis present with a variety of symptoms which may impair many aspects of physical and mental well-being. Traditionally, clinicians have been concerned with physical health aspects of sarcoidosis, assessing disease activity and severity with radiological imaging, pulmonary function and blood tests. However, the most reported symptom of sarcoidosis patients, fatigue, has been shown not to correlate with the most commonly used parameters for monitoring disease activity. Studies have shown poor agreement between physicians and patients in assessing sarcoidosis symptoms. This underlines the importance of patient reported outcomes (PROs) in addition to traditional outcomes in order to provide a complete evaluation of the effects of interventions in clinical trials and everyday clinical assessment of sarcoidosis. We have undertaken a systematic review to identify and provide an overview of PRO concepts used in sarcoidosis assessment the past 20 years and to evaluate the tools used for measuring these concepts, called patient reported outcome measures (PROMs). Various PROMs have been used. By categorizing these PROMs according to outcome we identified the key PRO concepts for sarcoidosis to be Health Status and Quality of Life, Dyspnea, Fatigue, Depression, Anxiety and Stress and Miscellaneous. There is no perfect sarcoidosis-specific PROM to cover all concepts and future intervention studies should therefore contain multiple complementary questionnaires. Based on our findings we recommend the Fatigue Assessment Scale (FAS) for assessing fatigue. Dyspnea scores should be chosen based on their purpose; more research is needed to examine their validity in sarcoidosis. The Modified Medical Research Council Dyspnea Scale (MRC) can be used to screen for dyspnea and the Baseline Dyspnea Index (BDI) to detect changes in dyspnea. We recommend The World Health Organization Quality of Life assessment instrument (WHOQOL-100) for assessing quality of life, although a shorter questionnaire would be preferable. For assessing health status we recommend the Sarcoidosis Assessment Tool (SAT), and have great expectations for this new and promising assessment tool. Supplementary to the WASOG meeting of 2011's recommendation on assessing QoL, we recommend incorporating fatigue, dyspnea and HS assessment in clinical trials and everyday clinical assessment of sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 2-17)*

Key words: sarcoidosis, questionnaires, patient reported outcome, PROM, PRO, clinical trial, clinical assessment

Introduction

Sarcoidosis is a chronic multisystemic granulomatous disease of unknown etiology (1). It mostly affects young and middle-aged adults and is associated with a reduced quality of life (2). Sarcoidosis presents most commonly in the lungs but may involve any organ. Patients may have symptoms related

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to a specific organ involvement but can also have symptoms not attributable to a specific organ, such as fatigue (1).

Traditionally, clinicians have been concerned with physical health aspects of sarcoidosis, assessing disease activity and severity with imaging, pulmonary function and blood tests. However, the patients' concerns may be on other consequences of sarcoidosis: fatigue and social dysfunction, depression and emotional distress, and the impact these consequences exert on quality of life. The most reported symptom of sarcoidosis patients, fatigue, has been shown not to correlate with the most commonly used parameters for monitoring disease activity (3). A study by Cox et al.(4)did show that physicians experienced in treating patients with sarcoidosis had relatively poor agreement with patients in assessing the presence of sarcoidosis symptoms. A recently published study also showed a poor relation between physician global assessment and patient global assessment (5). This underline the importance of patient reported outcomes (PROs) in addition to traditional outcomes in order to provide a complete evaluation of the effects of interventions in clinical trials and everyday clinical assessment of sarcoidosis. Also, a workshop held in Maastricht, Netherlands June 2011 at World Association of Sarcoidosis and Other granulomatous disease (WASOG) meeting concluded that it is strongly recommended that all clinical sarcoidosis trials should incorporate quality of life assessment (6).

This literature review was undertaken to identify and provide an overview of patient reported outcome (PRO) concepts used in sarcoidosis assessment the past 20 years and to evaluate the tools used for measuring these concepts such as PRO instruments, questionnaires, rating scales etc. We will refer to all of these as PROMs in this review.

Methods

A literature search was conducted 10.01.2016 in the databases Medline and Embase using the Embase.com search engine. Search words "sarcoidosis/exp OR sarcoidosis OR 'pulmonary sarcoidosis'/exp" were combined using AND with the search "dyspnoea OR dyspnea OR health status OR 'health status'/exp OR questionnaire OR questionnaires OR fatigue OR 'fatigue'/exp OR 'quality of life' OR 'quality of life'/exp OR measurement OR assessment OR 'outcome assessment'/exp OR 'symptom assessment'/exp OR 'self evaluation'/exp OR 'quality of life assessment'/exp OR 'clinical assessment' OR 'respiratory tract disease assessment'/exp OR 'clinical assessment tool'/exp OR tool OR instrument". The search was repeated 19.08.16 to include articles newly published. Furthermore we performed a snowball search.

Criteria for inclusion were articles in English with an available abstract published after 01.01.95. Filters activated for Language: English; Quick limits: With abstract, Humans; Publication types: Article. We also activated filters to exclude case reports, practice guidelines and systematic reviews.

After removing duplicates, we screened title and abstract or full text articles for eligibility criteria. Selection of papers was based on the following eligibility criteria: 1) the study objective was sarcoidosis and one or more identifiable PROM were used; 2) the study population consisted of only sarcoidosis patients, or included an identifiable and separately analyzed subgroup of patients with sarcoidosis; 3) the article was a full report (no case reports, editorials, poster text, letters or reviews).

Results

After removing duplicates we identified 1216 hits of which we included 117. Seven studies were identified and included through updated search and snowball search (Figure 1). Of the 124 studies included, we found 66 different PROMs (table 1: (3, 4, 7-127)). All PROMs were categorized by concepts. We 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 (table 1). Due to the large number of PROMs, only those used in four or more publications are evaluated in this systematic review (table 2: (3, 4, 7, 8, 10-14, 16-20, 22-24, 26-29, 31-37, 39-107, 110-115, 117, 118, 120, 122-125, 127)). Less reported PROMs are not evaluated any further (table 3: (4, 7-16, 20-32, 38, 41-44, 46, 47, 52, 54, 56, 57, 63, 67, 68, 73, 77, 108-111, 115-121, 126, 128)). Various visual analog scales are not mentioned.

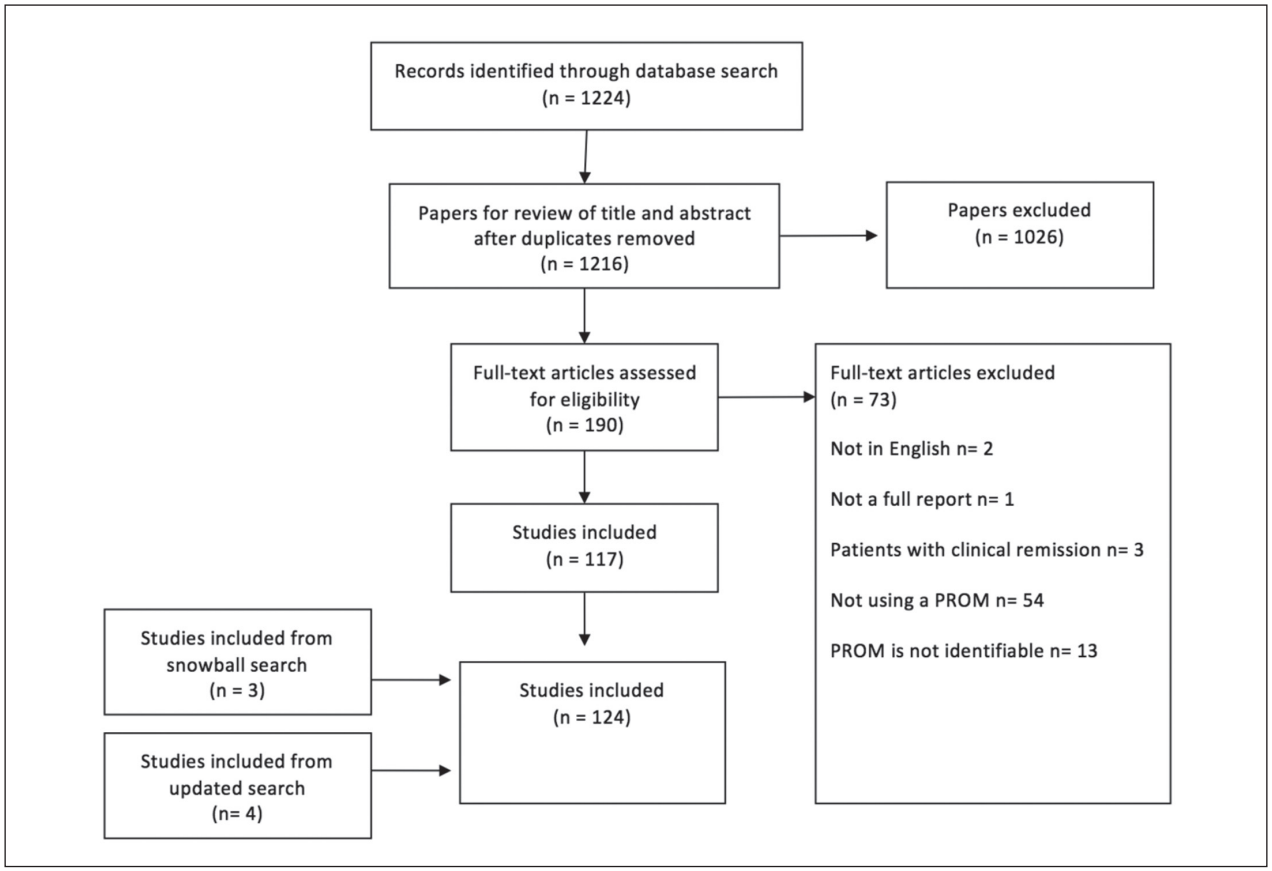

Fig. 1. Search method

PROMs in sarcoidosis assessment

Fatigue

Fatigue is the most reported symptom among sarcoidosis patients in several studies (35, 36, 53, 126) and it is strongly associated with a lower quality of life (35). In a study by Drent et al. no relationship was found between fatigue measured with the WHOQOL-100 energy and fatigue facet and commonly used parameters for monitoring disease activity in sarcoidosis such as S-angiotensin-converting-enzyme (ACE) level, radiographic findings and lung function tests (3). However, patients with fatigue did suffer more frequently from dyspnea and exercise intolerance as self-reported symptoms (3). Other studies neither found a correlation between fatigue measured with FAS and lung function tests (35, 67). This suggests the need for a PROM.

The fatigue-specific questionnaires we found are listed in table 2 and table 3. Apart from the fatigue-specific questionnaires, fatigue was also assessed using the energy and fatigue subscale from the WHO-QOL-100, the health status instruments SHQ, SGRQ and the vitality subscale of SF-36.

The Fatigue Assessment Scale (FAS)

FAS was the most commonly used PROM for assessing fatigue, consistent with findings of de Kleijn et al. in 2009(129). FAS is a one-dimensional 10-item fatigue questionnaire consisting of five questions reflecting physical fatigue and five questions for mental fatigue, developed by Michielsen et al. (130). Each item has a five-point rating scale, ranging from "1-never" to "5-always" and FAS scores range from 10-50. FAS score <22 indicate non-fatigued persons. FAS is a reliable and valid instrument in manage-

Table 1. PRO concepts of sarcoidosis

PRO	Total number of articles	Total number of PROM	References
Health status and quality of life	68	18	(3, 4, 7-10, 12, 14, 16, 23, 24, 28, 29, 31, 33, 35, 36, 38, 40, 42, 44, 47-49, 51, 53-60, 62, 67, 69-73, 77, 80, 82, 87, 88, 91-93, 105, 106, 110-127)
Dyspnea	55	8	(4, 10, 11, 14, 20, 28, 41, 42, 44, 45, 49, 51, 58, 59, 63, 67, 72, 73, 75-111)
Fatigue	42	8	(10, 14, 16, 20, 23, 27-29, 32, 34, 35, 37, 41-43, 50, 52-54, 56-78)
Depression, anxiety and stress	28	11	(4, 7, 8, 13, 16, 19, 20, 23, 27-32, 41-55)
Miscellaneous			
Symptomatology	18	4	(3, 9, 12, 22, 23, 25-28, 32-40)
Personality and cognition	6	5	(13, 27-31)
Pain	6	3	(21-26)
Sleep	5	2	(16-20)
Other	9	8	(7-15)
Total number	124	66	

Abbreviations: PRO: patient reported outcome; PROM: patient reported outcome measure

ment and follow up of patients with sarcoidosis as well as an outcome measure in clinical trials (34, 53, 62). It has been cross-validated in a Croatian sarcoidosis population (34), confirming the high internal consistency (thus reliability) and validity. It has divergent validity regarding depression measured by both Center for Epidemiological Studies-Depression Scale (CES-D) and Beck Depression Inventory (BDI-II) i.e. depression and fatigue measured by FAS are two different concepts and FAS can be used to measure fatigue distinctly from depression (specificity) (53). It is easy to complete and is not time-consuming and can be performed within 1-2 minutes (71). FAS also seems reliable and valid as an indicator for measuring dyspnea, quality of life and exercise tolerance in patients with sarcoidosis (67).

The minimal clinical important difference (MCID) of FAS in patients with sarcoidosis was estimated by de Kleijn et al. (62) in a prospective study of 443 patients of whom 321 completed follow-up. With an anchor-based methodology using the physical quality of life domain of the World Health Organization Quality of Life BREF (WHO QOL BREF), they found the minimal clinical important difference (MCID) to be a change of 4 points. This allows FAS to be used with confidence in clinical trials or in the management of individual patients with sarcoidosis and it has been shown to be responsive to treatment (23).

The Multidimensional Fatigue Instrument (MFI-20)

MFI-20 was used in four articles (table 2). The instrument is one of the most frequently used fatigue questionnaires in Europe and it is widely used in patients with cancer, chronic fatigue syndrome and chronic inflammatory disease(65, 66). Smets et al. developed MFI-20 in 1994 (131). It is a 20-item multidimensional questionnaire consisting of five subscales of fatigue with four items each: general fatigue, physical fatigue, reduced motivation, reduced activity and mental fatigue. It was developed and tested in cancer patients treated with radiotherapy, patients with chronic fatigue syndrome and different groups of healthy volunteers (psychology students, medical students, junior physicians and army recruits). The results show that the instrument has high internal consistency and validity(131). A Swedish study has validated the instrument in two cancer populations, as well as healthy individuals and confirmed that it is reliable (132). Hinz et al. (66) showed that there was a high correlation of the total scores of MFI-20 and FAS, which indicates that both questionnaires measure the same feature. The study showed that MFI-20 had good psychometric properties (reliability and convergent validity) in a sarcoidosis population. Since FAS is more popular and shorter, the authors recommended FAS for further studies.

Table 2. PROMs evaluated in this paper, in concept, with references

PRO	Number of PROMs	PROMs	Number of articles	References
Fatigue	2	Fatigue Assessment Scale (FAS)	34	(10, 16, 23, 27-29, 32, 34, 35, 37, 41, 43, 50, 53, 54, 58-76)
		Multidimensional Fatigue Inventory (MFI-20)	4	(20, 65, 66, 78)
Dyspnea	3	The Modified Medical Research Council Dyspnea Scale (MRC)	36	(4, 10, 14, 20, 42, 44, 45, 49, 51, 58, 67, 72, 73, 78, 92-107)
		Borg Dyspnea Score	23	(11, 28, 41, 42, 44, 58, 59, 67, 72, 75, 76, 83-93, 111)
		Baseline Dyspnea Index (BDI)	7	(14, 67, 77, 79-82)
Health status and quality of life				
Health status	3	The Medical Outcome Study 36-item Short Form Health Survey (SF-36)	27	(4, 10, 12, 16, 23, 24, 47-49, 51, 56, 57, 59, 60, 67, 73, 80, 82, 87, 88, 105, 106, 110, 111, 122-124)
		St. George's Respiratory Questionnaire (SGRQ)	17	(4, 8, 10, 14, 42, 44, 49, 51, 54, 58, 59, 73, 77, 91-93, 111)
		The Sarcoidosis Health Questionnaire (SHQ)	14	(16, 49, 51, 54, 59, 60, 87, 88, 115, 117, 118, 120, 125, 127)
Quality of life	2	The World Health Organization Quality of Life assessment instrument (WHOQOL-100)	9	(3, 33, 35, 36, 40, 53, 55, 113, 114)
		The World Health Organization Quality of Life-BREF assessment instrument (WHOQOL-BREF)	8	(28, 29, 62, 69-72, 112)
Depression, Anxiety, Stress	3	Center for Epidemiological Studies-Depression Scale (CES-D)	10	(4, 7, 19, 27-29, 43, 49-51)
		Beck Depression Inventory (BDI-II)	7	(16, 31, 32, 52-55)
		Hospital Anxiety and Depression Scale (HADS)	8	(8, 13, 20, 44-48)
Miscellaneous	3	Symptom Inventory Questionnaire 43-item (SIQ 43)	8	(3, 32-36, 39, 40)
		The Small Fiber Neuropathy Screening List (SFNSL)	7	(12, 22, 23, 26-28, 37)
		Epworth Sleepiness Scale (ESS)	4	(16-19)

Abbreviations: PRO: patient reported outcome; PROM: patient reported outcome measure

Dyspnea

Dyspnea was the second most reported symptom among patients with sarcoidosis in a study by Wirnsberger et al., with a prevalence of 70% (39). Dyspnea is associated with poorer overall quality of life (36). In a study by Gvozdenovic et al. (14) groups of sarcoidosis patients with pulmonary involvement and pulmonary plus extrapulmonary involvement had significant dyspnea, but normal pulmonary function. This demonstrates the need to assess dyspnea as a PRO and not only as a result of lung function.

Table 3. PROMs not evaluated in this paper in concepts with references

PRO	Number of PROMs	PROMs	Number of articles	References
Fatigue	6	Checklist Individual Strength (CIS)	2	(56, 57)
		Fatigue Scale (FS)	2	(14, 77)
		Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)	2	(16, 54)
		Patient Reported Outcome Measurement Information Systems Fatigue Instrument (PROMIS PFI)	1	(68)
		Fatigue Severity Scale	1	(42)
		Fatigue Scale for Motor and Cognitive Functions (FSMC)	1	(52)
Dyspnea	5	Oxygen Cost Diagram	2	(44, 67)
		The New York Heart Association (NYHA) Functional Classificaion	2	(108, 109)
		University of California San Diego Shorthness of Breath Questionnaire (UCSD-SOBQ)	1	(128)
		Modified Dyspnea Index	1	(110)
		Bath Breathlessnedd Scale (BSS)	1	(63)
Health status and quality of life	12	The Sarcoidosis Assessment Tool (SAT)	3	(10, 120, 121)
		The Dermatology Life Quality Index (DLQI)	3	(73, 115, 117)
		Chronic Respiratory Disease Questionnaire (CRDQ)	3	(47, 111, 116)
		Sickness Impact Profile (SIP)	2	(31, 126)
		National Eye Institute Visual function HRQOL (NEI-VFQ25)	2	(73, 118)
		Vickrey Peripheral Neuropathy Quality-of-Life Instrument-97 (PNQoL-97)	1	(38)
		The EuroQol Group generic measure of health status (EQ-5D)	1	(47)
		The Quality of Well-Being Scale (QWB)	2	(44, 111)
		The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)	1	(119)
		The fifteen-dimensional measure of health-related quality of life (15D)	1	(14)
		The Leicester Cough Questionnaire (LCQ)	1	(9)
		Skindex-29	1	(115)
Depression, anxiety, stress	8	State and Trait Anxiety Inventory (STAI)	2	(28, 43)
		Perceived Stress Scale (PSS)	2	(4, 32)
		Anxiety Sensitivity Index-3 (ASI-3)	1	(46)
		Inventory of Depressive Symptomatology (IDS)	1	(23)
		The Distressed Scale- 14 (DS-14)	1	(29)
		Montgomery-Åsberg Depression Rating Scale	1	(42)
		The 21-item Hamilton Depression Rating Scale (HAM-D)	1	(41)
		Social Readjustment Rating Scale and Life Change Units score	1	(30)
Miscellaneous	18	Patient's Global Assessment of disease activity (Pa-GA)	3	(10-12)
		Brief Pain Inventory	3	(22, 23, 26)
		Pittsburgh Sleep Quality Index (PSQI)	1	(20)
		Pain Coping Cognition List (PCCL)	1	(24)
		The Back Pain Questionnaire	1	(21)
		The Neuropathic Pain Scale (NPS)	1	(25)
		Single-Item Measures of Personality (SIMP)	1	(28)
		Allergy and Asthma Symptom Questionnaire	1	(15)

(continued)

Table 3. PROMs not evaluated in this paper in concepts with references

PRO	Number of PROMs	PROMs	Number of articles	References
		Beliefs about Medications Questionnaire	1	(13)
		Illness Perceptions Questionnaire	1	(13)
		Positive Affect Negative Affect Schedule (PANAS)	1	(31)
		Small Fiber Neuropathy Symptoms Inventory Questionnaire (SFN-SIQ)	1	(38)
		List of Daily Activities (DAL)	1	(14)
		Cognitive Failure Questionnaire (CFQ)	1	(27)
		The Modified Composite Autonomic Symptoms Scale (mCOMPASS)	1	(25)
		The Nijemegen Questionnaire	1	(8)
		The Minnesota Multiphasic Personality Inventory (MMPI) alexithymia scale	1	(30)
		The Cough Hypersensitivity Questionnaire	1	(9)
		Total Health Access Scale	1	(7)

Abbreviations: PRO: patient reported outcome; PROM: patient reported outcome measure

The Modified Medical Research Council (MRC) Dyspnea Scale

MRC was developed by Fletcher et al. in a population of 38 male patients predominantly with chronic bronchitis (133). None had sarcoidosis. It contains a set of five statements about levels of breathlessness during daily activities and the patients select the statement that most closely corresponds to their level of impairment. The five statements are graded 0-4, with 4 being the most severe dyspnea. The MRC does not include the magnitude of effort needed to evoke breathlessness and as a consequence this could theoretically reduce sensitivity in certain populations. Many patients may perform a certain task only by reducing the associated effort and thereby minimize the intensity of breathlessness, e.g. walking up stairs, only slower. This is particularly the case for younger patients with a greater exertional capacity. Modest reduction in exertional capacity might not impair an elderly person, but may have an impact on the daily life of a younger person because of higher occupational demands. The validity of MRC dyspnea scale in a population with Chronic Obstructive Pulmonary Disease (COPD) has been examined by Bestall et al. (134) and was found to be good. However, it has been insinuated that the scale is not sensitive enough to detect changes (135, 136).

The Borg Dyspnea Scale

The Borg Dyspnea Scale was developed in 1982 (137). It is a 10-point scale and the patients select a point on the scale that matches their perception of dyspnea. Scores range from 0 – no impairment to 10 – severe impairment. The Borg Dyspnea Scale is easy to perform and can be administered during exercise (137). It was used together with a six-minute walk test in most of the studies identified in this review.

The Baseline Dyspnea Index (BDI)

BDI describes dyspnea in five steps integrated into three categories: degree of the functional impairment, level of the activity, and the level of effort required to develop dyspnea. Each component is graded on a five-point rating scale from 0 ('extreme impairment') to 4 ('without impairment'); the total BDI score can range from 0 to 12. BDI was developed to detect changes from baseline together with the Transition Dyspnea Index (TDI) (138).

The dyspnea PROMs

In a study by Jastrzebski et al. (67) significant differences in the perception of dyspnea were confirmed between patients with sarcoidosis and healthy

controls in all three dyspnea questionnaires evaluated in this review (MRC, Borg's scale and BDI). In a study by Antoniou et al. MRC and Borg's scale scores were both significantly different in a sarcoidosis population in comparison with healthy controls (44). This adds to the construct validity of these rating scales. They have convergent validity and thus they are sensitive to detect dyspnea in sarcoidosis populations. However evidence is lacking on whether these questionnaires are useful in detecting changes in dyspnea in sarcoidosis patients.

MRC and BDI were both used to measure differences in dyspnea between patients with sarcoidosis with only pulmonary involvement and pulmonary plus extrapulmonary involvement in another study. Only BDI could measure significant differences in dyspnea between the groups(14). Patients with pulmonary and extrapulmonary involvement may be more dyspneic because of more functional limitations. MRC does not include the associated effort necessary to perform a particular activity and this might be the reason why it, opposed to the BDI, was not able to detect the difference between the two groups.

In a study by Baughman et al. including 142 patients with sarcoidosis the range of a six-minute walk test was significantly different for each level of the MRC dyspnea score. The lower the six-minute walking distance, the higher the level of dyspnea ($p<0.0001$) (58). This study also found significant correlations between all three components of the St. George Respiratory Questionnaire and FAS and MRC dyspnea scores ($p<0.0001$ for all correlations). This is also adding to the validity of MRC dyspnea score in a sarcoidosis population.

Health Related Quality of Life (HRQL), Health Status (HS) and Quality of Life (QOL)

HRQL most often refers to HS alone but the term HRQL is also often used on the concepts HS and QOL combined, although these two concepts are different. HS reflects the impact of the disease on patients functioning and QOL reflects the patient's evaluation of functioning (2, 139). QOL can be high in spite of a low level of functioning due to individual expectations of health, ability to cope and threshold of discomfort. In this article we will use the terms QOL and HS. Studies have shown reduced QOL in sarcoidosis patients compared to healthy controls (71). Fatigue is an important negative predictor of QOL (71).

Quality of Life

The World Health Organization Quality of Life assessment instrument (WHOQOL- 100)

WHOQOL-100 is a generic multidimensional measure of QOL. This questionnaire is developed cross-culturally simultaneously in 15 centers around the world and contains six domains 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 scale (from 1-5) (140). The reliability and validity of the instrument was tested in a sarcoid population and was found to be good (40). MCID of the WHOQOL-100 in a sarcoidosis population has not yet been studied. A change in score of 1 on the WHOQOL-100 is proposed as the MCID for women with early-stage breast cancer(141).

The World Health Organization Quality of Life-BREF assessment instrument (WHOQOL-BREF)

This questionnaire is an abbreviation of the WHOQOL-100, consisting of 26 items. It contains 24 questions on four domains and two questions on overall QOL and general health (142). Alilovic et al. have evaluated the usefulness of the WHOQOL-BREF in a sarcoidosis population of 97 patients compared to 97 healthy controls. They concluded that WHOQOL-BREF is not sufficient for the evaluation of QOL in sarcoidosis patients based on the failure to obtain any information regarding fatigue, which is the most significant symptom of sarcoidosis (112).

Health Status

The Medical Outcome Study 36-item Short Form Health Survey (SF-36)

SF-36 is a generic 36-item HS instrument with six domains. Scores are transformed into a 100-point scale, with higher scores indicating better HS (143). There is evidence of reliability and validity for its use among persons with various conditions, including a

population with interstitial lung disease, where 9 patients had sarcoidosis (111). Construct validity of the SF-36 was confirmed by Cox et al. on a population of 120 sarcoidosis patients (4). 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 (144).

St George's Respiratory Questionnaire (SGRQ)

SGRQ is a 76-item respiratory specific questionnaire developed for measuring health in chronic airflow limitation. It contains three domains (symptoms, which measures respiratory symptoms; activities, which measures impairment of mobility or physical activity; and impacts, which measures the psychosocial impact of disease). Scores for each domain and a summary score are on a 100-point scale. Lower scores indicate better HS, the opposite of SF-36 (145). A score of 40 or greater is associated with significant impairment in respiratory health (145). Chang et al. (111) evaluated SGRQ in a population with interstitial lung disease, including sarcoidosis patients, and found good construct validity of this instrument based on correlation with pulmonary function, six minute walking distance, dyspnea rating and other HS-measures such as Quality of Well Being Scale and the Chronic Respiratory Questionnaire (CRQ). The construct validity of SF-36 and SGRQ was confirmed by Cox et al. in a population of 120 patients with sarcoidosis (4). Although SGRQ is a respiratory-specific health status questionnaire, a study by Gvozdenovic et al. (14) showed that patients with pulmonary plus extrapulmonary sarcoidosis had statistically and clinically significant worse health status in terms of SRGQ score than those with isolated pulmonary sarcoidosis.

Sarcoidosis Health Questionnaire (SHQ)

The SHQ is a sarcoidosis specific 29-item health status questionnaire developed by Cox et al. (49) in 2003. It contains three domains: daily functioning, physical functioning and emotional functioning. The responses range from "all of the time" (score of 1) to "none of the time" (score of 7). Higher scores indicate better health status. It takes approximately 10 minutes to complete the SHQ. It is a reliable and validated instrument for assessing health status in sarcoidosis (49, 127), but a MCID is not yet established. The SHQ score is not divided in domains, but provides one total score containing various aspects of sarcoidosis. Therefore, Judson et al. (121) suggests that the SHQ may be insensitive to changes in specific aspects of sarcoidosis related health status such as fatigue or skin changes. This was shown in a randomized controlled cutaneous sarcoidosis trial (117), where treatment did not affect SHQ score - maybe because SHQ only has two questions related to skin symptomatology. The domain fatigue is assessed with only one item: 'Daily Functioning – Felt you were full of energy'. Regarding the measurement of fatigue in sarcoidosis with SHQ, there is no convincing validity and reliability (129).

Depression, Anxiety And Stress

The prevalence of depression in sarcoidosis population was found to be 60% and 66% in two American studies (4, 7) compared to 42% in the American ACCESS study (146). Both fatigue and anxiety are related to depressive symptoms (43). Anxiety is less understood in sarcoidosis. A prevalence of 32% was found in a population of sarcoidosis patients screened with the Hospital Anxiety and Depression Scale (HADS) (13). Anxiety was significantly correlated with symptom severity and was the main covariate of physical symptoms reported by patients with sarcoidosis in a study by Holas et al. (46).

Center for Epidemiological Studies-Depression Scale (CES-D)

CES-D was developed by Radloff et al. in 1977 and was validated for use in general populations (147). It is designed to measure the presence and degree of depressive symptoms. CES-D, originally a 20-item questionnaire, has been shortened to an 11-item version by Chang et al. (7). This 11-item version was also used by Yeager et al. in the ACCESS study (146). Cox et al. (4) used the 11-item version in a sarcoidosis cohort study when validating the Sarcoidosis Health Questionnaire (49). Cronbach's alpha for this 11-item version was 0.83 indicating a good inter-item reliability (7). A cutoff score of 9 or above was used to indicate depression. The 20-item version was used by de Kleijn et al. in two articles (28,

43) and by Ellferich et al. in two other articles (27, 29). A cutoff score of 16 or above was used to screen for depression in all these studies and Cronbach's alpha for the 20-item version was 0.89 (28). Regarding psychometric properties apart from reliability, no information on criterion validation in a sarcoidosis population was found. From the published articles using CES-D it is difficult to draw conclusions about construct validity in a sarcoidosis population.

The Beck Depression Inventory (BDI-II)

BDI-II is a 21-item self-administered measure of depressive illness in adults. Patients have to select the statement from each item that best describes their feelings the past week. Each item has four possible statement responses scored 0 to 3, and the summation score ranges from 0-63 (148). Suggested score ranges for mild depression, moderate to severe depression, and severe depression are 10–19, 20–30, and 31 or higher, respectively (149). For the 21-item version different cutoff-scores were used; 15 (31, 55), 20 (16) and 21 or above (54). The psychometric properties for this self-administered questionnaire have not been investigated fully in a sarcoidosis population.

Hospital Anxiety and Depression Scale (HADS)

HADS is developed by Zigmond and Snaith (150) to detect increased degrees of anxiety and depression in somatically ill patients. It has 7 anxiety and 7 depression items scored on a 4- point scale from 0-3. It provides a sum for both anxiety and depression ranging from 0-21, with higher scores indicating more depression or anxiety. In a review, results of 747 papers using HADS are summarized, and most of them attributing good psychometric properties to the questionnaire (151). In a study by Holas et al. (46) the Cronbach's alpha was found to be 0.86 in a population with sarcoidosis, indicating high reliability. This questionnaire has demonstrated construct validity in a study of sarcoidosis patients where strong correlations between skeletal muscle weakness, HADS score, fatigue and SF-36 were found (47). To draw conclusions on construct validity of this, we need to hypothetically assume that these are the same concepts. There is no evidence for divergent validity (test of specificity) for this questionnaire.

Miscellaneous

The Small Fiber Neuropathy Screening List (SFNSL)

Small-fiber neuropathy (SFN) is recognized as a frequent, chronic, and disabling disorder. The most common symptoms are peripheral pain, dysaesthesia and reduced temperature sensitivity, and there may also be various autonomic disturbances. Sudden death in sarcoidosis might be linked to autonomic dysfunction related to small fiber neuropathy (152). Different PROMs exist for assessing SFN in sarcoidosis such as SFN symptom inventory questionnaire, the Neuropathic Pain Scale and an autonomic symptom assessment. We found that the SFNSL is most used. These instruments are useful in screening patients for SFN but diagnostic confirmations requires a 3 mm skin biopsy and immunohistochemistry to quantify intra-epidermal nerve fiber density (IENFD) (153). SFNSL is a 21-item questionnaire to measure symptomatology related to SFN. It was developed and validated in a sarcoidosis population and the reliability and validity were good (154).

Symptom Inventory Questionnaire 43-item (SIQ 43)

This sarcoidosis specific symptom inventory was developed by Wirnsberger et al. in 1998 (39). It has been used in several studies (table 2) but was most recently used in 2007 (36). It was developed using a population of members of the Dutch Sarcoidosis Society. 1755 completed the questionnaire. It has not been standardized or validated. It was pre-tested in a population of 10 sarcoidosis patients (39). The questionnaire consist of 43 items, including questions concerning current symptoms such as chest pain, arthralgia and fatigue, symptoms at onset of the disease, duration of disease, treatment, diagnostic procedures, medical history and socio-demographic data. Most of the questions are multiple choices, sometimes giving the possibility to tick more than one answer and some of the questions are open-ended.

Epworth Sleepiness Scale (ESS)

We found five studies assessing problems related to sleep quality (table 1); two different PROMs were used (table 1, table 2 and table 3). Assessing sleeping problems may be relevant in sarcoidosis because

prednisolon treatment can lead to sleeping difficulties and sleep apnea can be a symptom of laryngeal sarcoidosis or neurosarcoidosis. Also, sleep apnea might occur as a comorbidity. Sleep apnea can lead to increased daytime sleepiness and is strongly related to fatigue (19, 65, 155). ESS measures the general level of daytime sleepiness as the likelihood of falling asleep in eight different situations. ESS has been proved valid in a population of 150 adult patients with various sleeping disorders (156). More studies are needed to evaluate the psychometric properties of ESS in a sarcoidosis population.

Discussion

In this systematic review we have identified all PROMs used in sarcoidosis the past 20 years (table 2 and table 3). By categorizing these instruments we have identified the most important PRO concepts (table 1). We argue that PROs should be used as endpoints in clinical trials and should also be used for assessing symptom severity and treatment responses in clinical assessment of sarcoidosis patients as many features of sarcoidosis have shown not to correlate with the most commonly used parameters for monitoring disease activity. Our review has shown that there is a lack of agreement on PRO endpoints, which is unfortunate and makes comparison between studies more difficult. We have evaluated the most used PROMs in sarcoidosis and will here provide recommendations for each PRO concept.

The most used, valid and reliable instrument for measuring fatigue is FAS. It has a cutoff score to identify the fatigued and a well-established MCID. It has been shown to be responsive to treatment, is easy to perform and not time- consuming. MFI-20 has shown good reliability and validity in a sarcoidosis population. However, FAS is shorter and more popular, and is therefore recommended.

When assessing dyspnea, the purpose of assessment needs to be clear. MRC can be used for screening, or just to report the symptom. BDI was developed together with the TDI to detect changes. It needs to be investigated whether BDI/TDI can be used in sarcoidosis. The BDI detected more severe dyspnea in functionally impaired patients with pulmonary and extrapulmonary involvement than MRC. This might be explained by the low sensitivity in the MRC or low specificity in the BDI. However, it has been pointed out that the MRC does not include the magnitude of effort needed to evoke breathlessness and many patients may perform a certain task only by reducing the associated effort as may be the case for functionally impaired patients with pulmonary and extrapulmonary involvement. The Borg's Scale is easy to perform during exercise and can be used pre and/or after a six-minute walking test as we found most of the articles did. All dyspnea measurements were sensitive to detect dyspnea in sarcoidosis patients, but we would recommend BDI and TDI for clinical trials and for assessing changes in dyspnea in sarcoidosis outpatients.

WHOQOL-100 seems to have the highest validity in sarcoidosis in assessing QOL although a shorter questionnaire might be valuable for clinical use. Generic, respiratory and sarcoidosis-specific PROMs are available for assessing health status. The generic SF-36 is useful for assessing health status, when all aspects of the disease and possible comorbidities are wanted. SHQ has the ability to differentiate health status based on the degree of organ involvement (49). Although SGRQ is respiratory-specific it has shown to be sensitive to extrapulmonary manifestations of sarcoidosis. Both SF-36 and SGRQ have demonstrated good construct validity in sarcoidosis populations and they have the advantage that domains can be used together or separately. SHQ is shorter, but might be too short to assess all aspects of sarcoidosis involvement. More studies are needed to determine the MCID in HS and QOL PROMs in sarcoidosis in order to make them more useful in clinical assessment and clinical trials Sarcoidosis Assessment Tool (SAT) is a new PROM for measuring HS. It has good construct validity (121) and Cronbach's alpha for each SAT module was at least 0.87, which indicate excellent reliability. It has been shown that the SAT fatigue module (PROMIS PFI) has superior reliability to FAS (68). A MCID is established for each SAT module. The SAT requires approximately 5 to 10 minutes for completion and is thus appropriate for use in clinical settings. Several subscales are organ specific and can be used separately or together to measure patient's assessment of impact of disease and response to therapy.

In conclusion, we would recommend WHOQOL-100 for assessing quality of life, although a shorter questionnaire would be preferable. For as-

sessing HS we would like to encourage the use of the new SAT due to its good psychometric properties, established MCID and convenience in clinical trials and everyday assessment of patients. Initially it can be used together with the generic SF-36 or disease-specific SGRQ in clinical trials to further investigate and enhance its validity.

For PROMs on depression the psychometric properties in a sarcoidosis population is not thoroughly investigated. Evidence for criterion and construct validity is missing, and an evidence based cutoff score is lacking for BDI-II. Both the 11-item and 20-item version of CES- D had good reliability and there was an agreement on cutoff scores. HADS have demonstrated convergent validity with strong correlations between skeletal muscle weakness, fatigue and SF-36, but its specificity needs to be investigated. We therefore recommend CES-D.

Among the miscellaneous PROMs, the SFNSL is worth mentioning. It is a valid and reliable instrument in assessing symptoms related to SFN, which can have a huge impact on the life and health of patients and is important to detect and assess. ESS can be used when screening for sleep apnea.

The WASOG meeting of 2011 recommended that clinical sarcoidosis trials should incorporate QOL assessment. In assessing disease activity, QOL might be biased because it reflects the patient's evaluation of functioning which depend on personal resources and feeling of empowerment and it is therefore less interesting in measuring treatment efficacy in clinical trials. HS might be a better PRO in assessing the impact of the disease on patients functioning. No single PROM can cover all aspects of the disease and we therefore recommend the use of multiple complementary questionnaires when assessing patients with sarcoidosis. We suggest that fatigue, HS and preferable dyspnea should be covered both in clinical trials and everyday assessment. Due to the high prevalence of depression we recommend screening for depression.

Conclusion

Because of the poor correlations between symptoms and traditional parameters of assessing disease activity in sarcoidosis we recommend the use of PROs. Supplementary to the WASOG meetings of 2011's recommendation on assessing QOL, we recommend incorporating fatigue, dyspnea and HS assessment in clinical trials and everyday clinical assessment of sarcoidosis. Our review has shown that there is a lack of agreement on PRO endpoints, which is unfortunate and makes comparison between studies more difficult. We have provided PROM recommendations for each PRO concept. Based on our findings we recommend FAS for assessing fatigue. When screening for confounding variables for fatigue such as depression or sleep apnea, CES-D or ESS can be used. Dyspnea scores should be chosen based on their purpose, and more research is needed to examine their validity in sarcoidosis. MRC can be used to screen for dyspnea and BDI to detect changes in dyspnea. We would recommend WHOQOL-100 for assessing quality of life. For assessing health status we recommend SAT, and have great expectations for this new and promising assessment tool.

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