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Endpoints for clinical trials of sarcoidosis

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Abstract. Over the past few years an increasing number of prospective controlled sarcoidosis treatment trials have been completed. Unfortunately, these studies utilize different endpoints making comparisons between studies difficult. At the recent World Association of Sarcoidosis and other Granulomatous disease (WASOG) meeting, a session was dedicated to the evaluation of clinical endpoints for various disease manifestations. These included pulmonary, pulmonary hypertension, fatigue, cutaneous, and a classification of clinical disease phenotypes. Based on the available literature and our current understanding of the disease, recommendations for clinical evaluation were proposed for each disease category. For example, it was recommended that pulmonary studies should include changes in the forced vital capacity. Additionally, it was recommended that all trials should incorporate measurement of quality of life. *(Sarcoidosis Vasc Diffuse Lung Dis 2012; 29: 90-98)*

Key words: quality of life, forced vital capacity, short form 36, Scadding stage, fatigue assessment scale

Introduction

In the 1950s corticosteroids were first reported beneficial for the treatment of sarcoidosis. Over the next several decades, few alternatives were available to the clinician. Options included the anti-malaria drugs with a few case reports noted benefit for the cytotoxic drugs such as methotrexate and azathioprine (1). In the 1990s, several studies evaluated larger numbers of patients who were treated with inhaled corticosteroids, methotrexate, leflunomide, and azathioprine (2-6). In the past decade, biologic agents, such as infliximab have proven useful in treating certain disease manifestations (7). A current limitation to clinical research in sarcoidosis is that there is no clear agreement on outcome endpoints. As a case in point, the variable study design and outcomes of several double-blind, placebo controlled trials that have been completed in the past ten years (7-11) have hampered comparisons between these studies (12-14).

While initial studies focused on pulmonary disease, recent studies have examined treatment of non-

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pulmonary conditions. In this regard, endpoints of clinical sarcoidosis trials have differed for cutaneous sarcoidosis (15, 16), ocular sarcoidosis (17), sarcoidosis associated pulmonary hypertension (18-20), and sarcoidosis associated fatigue (21, 22).

Unfortunately, the primary end point of each study varied. Although the investigators usually reported multiple measures improved, they were unable to determine the clinical importance of the changes detected except to conclude that the agents were "steroid sparing".

Pulmonary

Currently, the forced vital capacity is the most commonly reported end point in pulmonary trials; however, there is no consensus for what constitutes significant change or how this parameter should be interpreted with other measures such as 6 minute walk time or quality of life indices. In addition, only a few studies have incorporated patient reported outcomes although it generally accepted that sarcoidosis affects patient's health status (23, 24). The lack of a standard assessment has impaired cross study comparison of different potential treatments.

At the World Association of Sarcoidosis and Other Granulomatous disease (WASOG) meeting was held at Maastricht, Netherlands in June 2011, a workshop was devoted to the establishment of clinically important sarcoidosis endpoints. The following summarizes the results of this workshop regarding outcome measures for pulmonary, pulmonary hypertension, fatigue, cutaneous, and classification of clinical sarcoidosis phenotypes.

A discussion of endpoints in sarcoidosis must begin with a simple yet important question: What specifically is desired to be measured? The appropriate endpoint in sarcoidosis is dependent upon whether one wishes to measure the degree of granulomatous inflammation, the physiologic impact of that inflammation, or the effect of physiologic impairment on the patient's quality of life. This is a particularly important distinction in sarcoidosis, where active granulomatous inflammation may not significantly impair physiology or cause significant symptoms. In general, using an endpoint of granulomatous inflammation may be appropriate to assess the effectiveness of an intervention in controlling or eliminating sarcoidosis. However, using such an endpoint to assess an intervention without measuring its effect on physiology and quality of life is unlikely to be useful in determining its benefit to patients. Ideally, a clinically useful intervention in sarcoidosis should demonstrate a reduction in granulomatous inflammation that results in improved physiology and quality of life. Thus, multiple endpoints are likely needed to demonstrate clinical benefit. Useful endpoints were assessed in terms of their validity, reproducibility, specificity for sarcoidosis, cost, and safety on a four point scale (none to 3+) in Tables 1-5. The validation and reproducibility were determined based on sarcoidosis specific as well as non sarcoidosis studies.

In Table 1, we present the potential measures of pulmonary sarcoidosis. It should be stressed that in interstitial lung disease, most recommendations on monitoring are based upon studies of idiopathic pulmonary fibrosis (IPF) (25-27). There are no substantial data in which methods of monitoring pulmonary disease are validated in sarcoidosis. The current view is that serial change is FVC is the best available means of monitoring progression of IPF: in drug trials for IPF, change in FVC is now viewed as the favoured primary end-point. In one large recent placebo controlled study of infliximab therapy in sarcoidosis (7), FVC was the primary end-point. Our choice of serial FVC as the best current primary end-point is based upon ease of measurement, reproducibility and specificity to the interstitium (unlike measures of gas transfer and gas exchange, which are independently influenced by pulmonary vascular events). These advantages apply equally to IPF and to pulmonary sarcoidosis.

However, the essential difference between these two diseases is the substantially lower prevalence of disease progression in sarcoidosis. Furthermore, change tends to be more insidious in sarcoidosis than in IPF and, thus, the amplitude of change in a trial of, say, one year in duration, tends to be lower in sarcoidosis. More often, in sarcoidosis, change does not reach the generally applied threshold of 10% of absolute baseline values (e.g. a change from 2.0L to 1.8L). In the study of infliximab therapy in pulmonary sarcoidosis, changes in FVC of 10% of more were infrequent with no little overall change in FVC values seen in the placebo arm (7). By contrast in a widely cited IPF study, a 10% decline in FVC was

Table 1. Measurements in pulmonary sarcoidosis

	Validated	Reproducible	Sarcoid specific	Low cost	Safe	Quality of life	Tested in sarcoidosis intervention trial
FVC	3+ §	3+	No	Yes	Yes	No	Yes
FEV-1	3+ §	3+	No	Yes	Yes	No	Yes
FEV-1/FVC	3+ §	3+	No	Yes	Yes	No	No
DLCO	3+ §	2+	No	Yes	Yes	No	Yes
6 minute walk	2+ §	1+	No	Yes	Yes	No	Yes
SGRQ	2+ §	3+	No	Yes	Yes	Yes	Yes
Chest X-ray Scadding	No	1+	Yes	Yes	Yes	No	Yes
Chest X-ray Muers	No	2+	Yes	Yes	Yes	No	Yes
HRCT Score	1+	1+	Yes	No	Yes	No	No

*Scale: No, 1-3+, unknown
§ Not validated for sarcoidosis

Table 2. Measurements in pulmonary hypertension

	Validated	Reproducible	Sarcoid specific	Low cost	Safe	Quality of life	Tested in sarcoidosis intervention trial
Pulmonary hemodynamics	3+	2+	No	No	1+	No	2+
6 minute walk test	3+	1+	No	3+	3+	No	3+
Time to clinical worsening	3+	Unknown	No	3+	3+	No	No
NYHA/WHO class	3+	1+	No	3+	3+	No	2+
SF-36	2+	2+	No	3+	3+	Yes	1+
SGRQ	2+	2+	No	3+	3+	Yes	1+
SHQ	2+	Unknown	Yes	3+	3+	Yes	1+
Vital prognosis	-	-	No	3+	3+	No	No
BNP/NT-ProBNP	2+	Unknown	No	2+	3+	No	No
MRI	1+	2+	No	1+	3+	No	1+

*Scale: No, 1-3+, unknown

Table 3. Measurements of sarcoidosis associated fatigue

	Validated	Reproducible	Sarcoid specific	Low cost	Safe	Quality of life	Fatique emphasis	Tested in sarcoidosis intervention trial
TFAS ¶	3+ *	3+	3+	3+	3+	3+	3+	2+
FACIT-F	3+ §	3+	No	3+	3+	3+	3+	2+
FS	1+ §	3+	No	3+	3+	3+	3+	No
SF-36	2+ §	3+	No	3+	3+	3+	1+	2+
SGRQ	2+ §	3+	No	3+	3+	2+	No	2+
SHQ	2+	3+	Yes	3+	3+	3+	No	2+
WHO-QOL BREF	1+ §	3+	No	3+	3+	3+	No	1+

*Scale: No, 1-3+, unknown
¶ FAS: fatigue assessment scale; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; FS: Fatigue Scale; SF-36: short form-36; SGRQ: Saint George Respiratory Questionnaire; SHQ: Sarcoidosis Health Questionnaire; WHO-QOL BREF: World Health Organization-Quality of Life Brief .
§ Not validated for sarcoidosis

seen at one year in 51% of the placebo arm (28).

The lesser progressiveness of sarcoidosis leads to two major problems. Firstly, a 10% change in serial FVC in sarcoidosis is a fundamentally insensitive criterion to detect change. In principle, this problem might be overcome by defining "significant change" as a 5% change in FVC. However, this attempt to deal with the sensitivity problem is severely hampered by Bayesian limitations. The lower prevalence of true decline in pulmonary sarcoidosis, compared

Table 4. Measurements in cutaneous sarcoidosis

	Validated	Reproducible	Sarcoid specific	Low cost	Safe	Quality of life	Tested in sarcoidosis intervention trial
Physician Global Assessment	+3 *	Unknown	+3	+3	+3	No	+2
SASI	+3	+3	+3	+3	+3	No	+3
LuPASI	+3	+1	+3	+3	+3	No	+3
Photographs	No	+2	No	+3	+3	No	+3
Lesion counts	No	Unknown	No	+3	+3	No	+3
Skin biopsies	No	Unknown	+3	+1	+1	No	No

*Scale: No, 1-3+, unknown

Table 5. Measurements in phenotypes/genotypes

	Validated	Reproducible	Sarcoid specific	Low cost	Safe	Quality of life	Tested in sarcoidosis intervention trial
STAI *	No	Unknown	+3 ¶	+3	+3	Yes	No
COS *	+3	+3	+3	+3	+3	No	No
Scadding stage	+3	+2	No	+3	+3	No	Yes
Wasfi	No	Unknown	+3	+3	+3	No	No
Prasse	No	+2	+3	+3	+3	No	No

*STAI: sarcoidosis three-dimensional assessment instrument; COS: clinical outcome score
¶ Scale: No, 1-3+, unknown

to IPF, means that changes of 5-10% from baseline (and indeed changes of 10-15% of baseline) are relatively more likely than in IPF to represent measurement variation.

Given the combined problems of a) insensitivity and b) the confounding effect of measurement variation in serial FVC measurement, the group strongly recommends the use of a composite end-point in trials of pulmonary sarcoidosis. The use of such an end-point allows lesser changes in FVC (of 5-10%) to be taken into account, whilst ensuring that changes of this lower magnitude are not ascribable to measurement variation. The group also recommends that the second variable in a composite end-point should be change in plain chest radiography. Other candidate variables are hampered by lack of validation, lack of specificity to the lung interstitium (measures of gas transfer and gas exchange, exercise variables) or lack of a plausible scoring methodology, validated formally or distilled from widespread clinical experience (serial HRCT).

The group strongly recommended that chest radiographic change should be quantified by means of side by side evaluation of the severity of disease, with change quantified as a three point scale (definitely better, unchanged, definitely worse). This mode of evaluation acknowledges 50 years of clinical experience of the greater accuracy of side by side chest radiographic evaluation. The wish to measure chest radiographic change "objectively" has led some to advocate scoring chest radiographs independently, using profusion scores as developed in the Muers scoring system (29). The difficulty with this "objective" approach is that in some patients, it will be obvious that disease is unchanged, on side by side evaluation, but inter-observer variability will lead to apparent changes in disease extent, based upon changes in profusion scores. In the sole comparison of these scoring methods, the simple side by side estimation of change in disease severity was found to correlate more strongly than changes in profusion scores with serial FVC trends (30). "Objectivity" in scoring is best achieved by asking observers to assess change whilst blinding them to the time sequence of chest radiographs. While a HRCT scoring system has been developed for sarcoidosis (31;32), it has not been widely adapted.

Based upon these considerations, the group recommended that disease progression or regression should be defined, for the purposes of treatment trials, as EITHER a ≥ 15% change in FVC (corresponding to measurement variation of at least three

standard deviations) OR a 5-15% change in FVC in association with a definite change in chest radiographic extent as assessed by a side by side evaluation of serial films.

Pulmonary hypertension

In Table 2, we present the potential measures for pulmonary hypertension (PH) in sarcoidosis. To date, most trials of therapies for pulmonary arterial hypertension have used six minutes distance (6MWD) as the primary endpoint. However, this endpoint has limitations. First, its relevance to clinical efficacy of treatments or survival is unclear. Second, normal values for 6MWD are not well standardized for height and gender. Third, extrapulmonary condtions such as musculoskeletal conditions, cardiac disease, and motivation may affect the test. Sarcoidosis patients frequently have multiple comorbidities apart from PH which adversely affects exercise performance. Finally, the method of performance of the 6MW test is not standardized and may greatly affect results (33, 34). Serum markers of granulomatous inflammation (angiotensin converting ezyme (ACE), soluble interleukin 2 receptor (sIL-2R), etc.) correlate poorly with the severity of PH.

To date, there are a limited number of published retrospective case series (19, 35-37) and prospective intervention trials (18, 38) using specific pulmonary arterial hypertension (PAH) therapies in patients with sarcoidosis-associated PH. Outcome measures have included exercise capacity (most commonly assessed by the 6MWD), hemodynamics recorded at right heart catheterization (mean pulmonary artery pressure, mPAP, and indices of right ventricular function), functional capacity (New York Heart Association -World Health Organization (NYHA-WHO) functional class and quality of life questionnaires (either general health-, respiratory- or sarcoidosis-specific questionnaires, such as the short form-36 (SF-36), Saint George respiratory questionnaire (SGRQ), and sarcoidosis health questionnaire (SHQ)) (39). Additionally, long-term and transplant-free survival was reported in one retrospective series (40).

Future endpoints should include parameters reflecting disease modification such as right ventricular (RV) function. While assessment of pulmonary hemodynamics by right-heart catheterization is a robust endpoint, its invasive nature limits serial measurements. Novel non-invasive measures undertaken by means of magnetic resonance imaging will be of interest in the future. Parameters may include RV end-diastolic and RV end-systolic volumes, RV stroke volume, and RV ejection fraction (RV stroke volume/RV end-diastolic volume). In addition, it is likely that composite endpoints that reflect disease progression will be prioritized in the future. Such composite endpoints may correspond to morbidity/mortality endpoints. Time to clinical worsening (TTCW) will remain a major parameter, but this endpoint must be standardized and validated. Indeed, some components of this composite endpoint may be influenced by national/regional differences such as hospitalization, availability of medical treatments, atrial septostomy and/or transplantation. TTCW may be considered a clinically useful endpoint to identify the effectiveness of medical treatments, provided that a clear and prospective definition is provided and events are adjudicated.

The group recommended selection of appropriate combinations of parameters depending on the severity of PH, size, length and the purpose of the study. For instance, TTCW may be preferred to 6MWD in milder disease due to the ceiling effect of the latter parameter. We also emphasize the importance of adjudication by an expert panel to assess clinical worsening.

Fatigue

Several investigators have identified fatigue as a reported symptom in more than fifty percent of sarcoidosis patients (24, 41-44). However, these diverse multinational studies used a variety of instruments to assess fatigue (Table 3). Endpoints to assess fatigue must incorporate validated, disease specific objective instruments that can be applied to diverse global populations. The Fatigue Assessment Scale (FAS) is a sarcoidosis specific fatigue instrument which has been used in a variety of studies (41, 42, 45, 46), including a clinical trial examining the effectiveness of neurostimulants for sarcoidosis associated fatigue (22). Recently, the minimally clinically difference for the FAS in sarcoidosis has been estab-

lished (47). This will allow the clinical significance of FAS to be evaluated in sarcoidosis patients. Chronic illness fatigue has also been assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) which was developed for oncology clinical trials. This instrument can effectively detect changes in fatigue with drug specific interventions (48). The FACIT-F questionnaire has been used to assess specific drug intervention for sarcoidosis associated fatigue (22). Although the Fatigue Scale (FS) has not been validated for sarcoidosis, it has been used to evaluate sarcoidosis fatigue. The Sarcoidosis Health Questionnaire (SHQ) is a validated sarcoidosis specific health-related instrument (49); however, it is insufficient to evaluate fatigue as it contains only one question regarding this question. The SHQ has provided objective measurement in a drug intervention trials (50). Other general health related quality of life questionnaires, including SF-36, SGRQ, and WHO-QOL, contain fatigue queries. The SF-36 (51) includes an axis for vitality, and the SGRQ contains general information about fatigue which has been studied in drug intervention trials (7, 22). The WHO-QOL questionnaire contains 100 questions and is therefore longer than most of the other questionnaires. A shorter version of this questionnaire (World Health Organization-Quality of Life Brief (WHO-QOL BREF)) has been studied in sarcoidosis (52). While there are some studies measuring cytokines (53, 54) and muscle strength (52, 53, 55) compared to fatigue, there is no consensus for which if any of these should be standardly measured.

Fatigue may be associated with other physical or psychological parameters. Sarcoidosis is frequently associated with an increased risk for sleep apnea (56, 57) and depression (58). Therefore, evaluation and risk for possible treatment cofactors should be considered prior to studying patients with fatigue (22, 24, 56). Instruments to assess depression in sarcoidosis patients can include the Beck Depression Inventory (BDI) (22, 56), and sleep apnea can be screened using the Epworth Sleepiness Scale (56, 59). Cognitive failure has also been associated with fatigue and can be assessed using the cognitive failure questionnaire (CFQ) (60).

Because no perfect disease specific questionnaire for sarcoidosis associated fatigue exists, future intervention studies should evaluate multiple complementary questionnaires. Selection could incorporate disease specific questionnaires such as FAS along with more general health-related quality of life questionnaires such SF-36. Additionally, the investigator should screen for confounding variables for fatigue such as depression and sleep apnea. It is strongly recommended that all clinical sarcoidosis trials should incorporate quality of life assessment.

Skin

Table 4 presents several potential outcome measures for cutaneous sarcoidosis. These include overall global assessment by physician or patient or simply a count of the number of lesions. Alternatively, skin evaluation can involve the extent and characteristics of the lesions such as the area of involvement, erythema, induration, and desquamation using a scoring system such as LuPASI (61). Finally, serial skin biopsies can correlate biomarkers of disease activity with clinical change. Using a Likert score, the physician global assessment was deemed useful in one study (7); whereas, the sarcoidosis activity and severity index has been described and validated in another trial (61). Additionally, a therapeutic intervention trial used this score to confirm effectiveness of the drug (62). Alternatively, skin evaluation can involve the extent and characteristics of the lesions such as the area of involvement, erythema, induration, and desquamation using a scoring system such as the Lupus Pernio Activity and Severity Index (LuPASI) (61). Reproducibility was also tested in an additional study (7). Both retrospective case series and prospective intervention trials have used paired photographs (62, 63). Lesion were counted in one study (15). Although serial skin biopsies can provide useful biomarker information and histology regarding response to drug therapy (64, 65), the high cost and associated complications limit widespread use. Skin disease can be a devastating manifestation of sarcoidosis; however, none of the current endpoints assesses quality of life change during skin treatment. Rather than relying on a single measure, the group recommended studying a combination of parameters which should include objective measurements of quality of life. It was also suggested that non-study agents (e.g. topical agents) should be prescribed using a standard protocol.

Phenotype

A classification for sarcoidosis should be simple, easily applied, reproducible and correlate with disease severity and prognosis. In sarcoidosis the presence and severity of lung and extra-pulmonary involvement must be characterized (66, 67). Different authors have defined chronic sarcoidosis after a variable follow-up time from 2 to 5 years (68). At follow-up the disease manifestations should be classified as absent, stable, or progressive.

Based on pre-defined criteria for severity and outcome, investigators have categorized clinical phenotypes. Wasfi et al scored patients for disease severity using a visual analog scale (69). Prasse et al (70) suggested a classification scheme for lung involvement based on initial onset of symptoms (acute or subacute), need for therapy, and duration of treatment (less than one year or longer). Recently, a similar classification was proposed by the WASOG Task Force, based on clinical outcome status (COS) after a long follow-up period (68).

A phenotype is any observable characteristic that results from the genetic background as well the influence of environmental factors and possible interactions between the two. Different phenotypes can be found in patients with similar disease severity and a particular phenotype can be associated with variable severity of disease (71, 72). The best methods for phenotyping disease make use of unbiased statistical methods, like factorial or cluster analysis (71). These methods do not make assumptions a priori, with the hypothesis being developed after the results. A relatively small recent study evaluated phenotypes in sarcoidosis by factor analysis (73). Similar methods must be applied in larger studies. These phenotypes should be correlated with specific exposures (74, 75), serum and BAL markers, genotypes, and also with treatment and outcomes of disease. At present, the clinical role of sarcoidosis genotyping is limited (68, 76).

Conclusion

This session illuminates the need for universal guidelines for outcome assessment. It is hoped that a specific workshop could facilitate guideline development and consensus for future prospective intervention trials and also assist clinicians in day to day management of sarcoidosis patients.

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