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Defining the clinical outcome status (COS) in sarcoidosis: results of WASOG Task Force

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Abstract. The clinical outcome of sarcoidosis is quite variable. Several scoring systems have been used to assess the level of disease and clinical outcome. The definition of clinical phenotypes has become an important goal as genetic studies have identified distinct genotypes associated with different clinical phenotypes. In addition, treatment strategies have been developed for patients with resolving versus non resolving disease. A task force was established by the World Association of Sarcoidosis and Other Granulomatous diseases (WASOG) to define clinical phenotypes of the disease based on the clinical outcome status (COS). The committee chose to examine patients five years after diagnosis to determine the COS. Several features of the disease were incorporated into the final nine categories of the disease. These included the current or past need for systemic therapy, the resolution of the disease, and current status of the condition. Sarcoidosis patients who were African American or older were likely to have a higher COS, indicating more chronic disease. The COS may be useful in future studies of sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2011; 28: 56-64)*

Key words: clinical outcome, clinical phenotypes, sarcoidosis

Introduction

The clinical outcome of sarcoidosis can be quite variable (1). In some patients, the disease can resolve within two years of presentation. Other patients may have chronic disease for years, often requiring systemic therapy (2). Many authors have chosen to classify patients as acute or chronic in terms of their clinical outcome. This has been based on the ability to withdraw patients from corticosteroids by two years (2-4). However, some studies have shown that patients withdrawn from corticosteroids after two years will have a relapse of their disease over the next few years (2, 5).

The World Association of Sarcoidosis and Other Granulomatous disease (WASOG) established a

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task force to provide a better definition of clinical outcome in sarcoidosis which takes into account the variable patterns of outcome with/without therapy. We report the clinical outcome status (COS) suggested by the task force.

Methods

Physicians who specialized in sarcoidosis and had sarcoidosis clinics were asked to participate in the task force. Three meetings were held at international pulmonary meetings (European Respiratory Society 2002, American College of Chest Physicians 2002, and American Thoracic Society 2003). A summary was then presented to the World Association of Sarcoidosis and Other Granulomatous disease meeting in 2005. The study was approved by the Institutional Review Board of the University of Cincinnati.

Prior to meeting, the participants were asked to categorize at least 50 patients at their institution using a draft proposal of the clinical outcome score (COS). The original categories were for those with active or resolved disease. The group decided to examine the clinical outcome of patients five years after diagnosis. The meeting reviewed the results of the COS score. The members identified and discussed five issues COS (Table 1). At the end of the meeting, the COS was modified to include patients with minimal activity and to add information regarding past and current systemic therapy. At the next task force meeting, new members of the task force categorized at least 50 patients at their institution using the revised draft proposal of the clinical outcome score. Again, the five issues were reviewed and modifications were made of the COS score. At the final meeting, participants of the first two task forces were asked to categorize at least 50 patients using the modified COS score. The five key issues were then discussed. The protocol was modified for a final time (Figure 1). The results were then presented to the WASOG meeting and comments were

Table 1. Issues regarding clinical outcome score (COS)

How long after the diagnosis?
How to allow for therapy?
How to define resolution or remission?
How to define chronic disease?
Can all patients be classified?

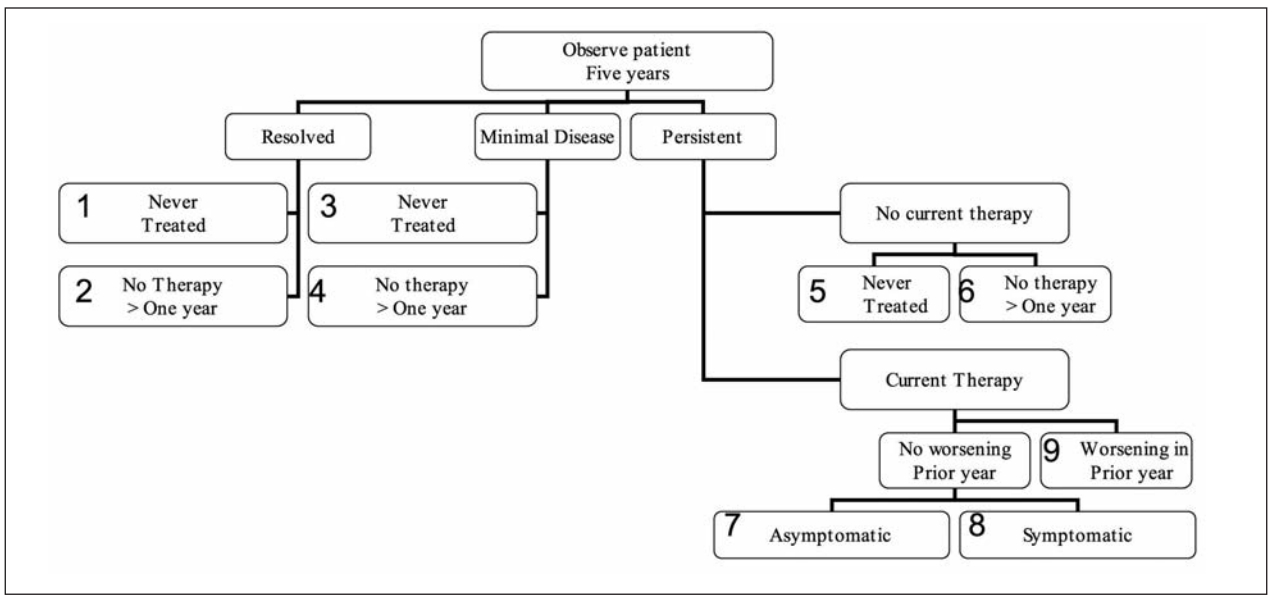

Fig. 1. Schematic of the clinical classifications of sarcoidosis patients. Clinical outcome was determined at a predefined time point. For this report, patients had to be evaluated at least five years after initial diagnosis. Minimal disease was less than 25% of the maximal disease

made by members of the task force and the participants at the meeting. Although the COS was not further changed, the limitations of the COS were highlighted.

For the current evaluation, patients needed to be followed for at least five years after diagnosis. Remission was defined as less than 25% of maximal disease. Organ involvement which was abnormal at time of initial assessment was reevaluated at follow up. This included chest roentgenogram and pulmonary function when these were abnormal. For other organs, the clinician used changes in laboratory tests or size of lesions to assess the change from maximal disease. The use of systemic therapy was classified as never (including patients treated with intermittent corticosteroids for a disease other than sarcoidosis), current, or none in the past year. Patients who received systemic therapy in the past year were considered on current therapy. Patients who had required an increase in their medication in the past year were considered worsening. While not specifically included in this retrospective study, if a patient died during the observation period, their COS would be 9.

Relationships between COS and clinical centers, self reported race, or age were analyzed using a rank sum correlation. A p value of <0.05 was considered significant.

Results

There were a total of 27 physicians who had sarcoidosis clinics, provided clinical outcomes of their patients, and/or had significant input into this report. The physicians and their institutions are listed in the appendix.

Patients were subdivided into the general categories of resolved, minimal disease arbitrarily defined as less than 25% of maximal disease, or persistent disease at five years. For example, for pulmonary disease the most abnormal chest roentgenogram or pulmonary function test has to have improved by at least 75% to be considered minimal disease. Thereafter, the patient was classified based on the use of systemic therapy. These categories comprised: never treated, no therapy in the past year, and current therapy, which included patients treated in the past year. For those on current therapy, the patient could be asymptomatic, symptomatic, or worsening over the past year. This led to a total of nine classifications, summarized in Figure 1.

Ten centers contributed fifty patients each for the final classification. The centers were centered around the following cities: Europe: Essen, Freiburg (both Germany), London (United Kingdom), Maastricht, Nieuwegein (both The Netherlands), and Milan (Italy); North America: Charleston, Cincinnati, Toronto; Japan: Kyoto. The age and self reported race are summarized in Table 2. Although there was no specific protocol for treatment, the patients included in this final classification had their therapy directed by the physicians at each of these specific centers.

Twenty five patients were classified independently by two clinicians at one site (University of Cincinnati) based on the same information from the patients' charts. In only one case was there a difference in classification. In that case, one physician felt the patient was COS=7, the other COS=8.

As noted in the Methods, the decision to use five years was based on the need to include some longitudal observations in the definition of clinical outcome. Table 3 illustrates 50 patients evaluated at one site (Cincinnati) who were classified at two and five years. There was a difference in the number of patients in each outcome at the two time points. Compared to the classification at two years, 12 of the 50 patients were in a different classification after five years. Of these, one patient with minimal disease but no therapy at year 2 (COS=3) had resolved with no therapy at year 5 (COS=1). Two patients with minimal disease but no therapy in the past year (COS=4) at year 2 went to resolved with no therapy in past year at year five (COS=2). At year 2, there were 18 patients on current therapy and worsening

Table 2. Characteristics of patients

Number of Patient	500
Number of Sites *	10
Age, Median (Range), years	44 (12-79)
Female/Male	267/233
Self Reported Race	
Caucasian	344 (68.8%) §
African-American	104 (20.8%)
Japanese	52 (10.4%)

* Fifty patients from each site
§ Number (percent of total)

Table 3. Clinical outcome status of patients after two versus five years followed at the University of Cincinnati

Status	Treatment	Number at Year 2	Number at Year 5
1 Resolved	Never treated	1 (2%) §	2 (4%)
2 Resolved	No therapy for more than one year	2 (4%)	4 (8%)
3 Minimal *	Never treated	2 (4%)	1 (2%)
4 Minimal *	No therapy for more than one year	3 (6%)	1 (2%)
5 Persistent, no current therapy	Never treated	1 (2%)	1 (2%)
6 Persistent, no current therapy	No therapy for more than one year	2 (4%)	5 (10%)
7 Current therapy, Asymptomatic	Therapy within past year	11 (22%)	13 (26%)
8 Current therapy, Symptomatic	Therapy within past year	10 (20%	14 (28%)
9 Current therapy, Worsening ¶	Therapy within past year	18 (36%)	9 (18%)
Change in Classification			12 (24%)

* Minimal is less than 25% of maximal disease
¶ Requiring increase in systemic medication in prior year
§ Number (percent of total)

Table 4. Clinical outcome status of patients

Status	Treatment	Number
1 Resolved	Never treated	59 (11.8%) §
2 Resolved	No therapy for more than one year	44 (8.8%)
3 Minimal *	Never treated	47 (9.4%)
4 Minimal *	No therapy for more than one year	38 (7.6%)
5 Persistent, no current therapy	Never treated	41 (8.2%)
6 Persistent, no current therapy	No therapy for more than one year	54 (10.8%)
7 Current therapy, Asymptomatic		57 (11.4%)
8 Current therapy, Symptomatic		115 (23.0%)
9 Current therapy, Worsening ¶		45 (9.0%)

* Minimal is less than 25% of maximal disease
¶ Requiring increase in systemic medication in prior year
§ Number (percent of total)

in the prior year (COS=9). At year 5, nine of these patients were on therapy and had worsening in the past year (COS=9), three were persistent disease but no therapy in the past year (COS=6), two were current therapy but asymptomatic (COS=7), and three were on current therapy, symptomatic but not recent worsening (COS=8).

In addition, one clinic (Kyoto) provided the rate of resolution of chest roentgenogram of a cohort of 130 patients over a ten year period (6). Many patients had regression of their chest roentgenogram stage by year three. However, there was a difference in the stage of the chest roentgenogram between year three and year five. Of those patients who had an abnormal x-ray at year three, half of them had improvement at year five. The rate of improvement was negligible between year five and ten.

In table 4, we summarize the outcomes for all 500 patients at five years. Of the 500 patients studied, 217 (43%) were still on systemic therapy at least five years after their initial diagnosis. There were no patients who could not be classified using the COS.

We compared the clinical outcome in relation to the various sites. All sites contributed 50 patients. This is shown in Figure 2. There was no correlation between the COS and the clinical site. The clinical outcome was also compared to the three self reported races (Figure 3). There was a significant difference between all three self reported race groups (Chi Square=93.367, $p<0.0001$). There was a weak correlation between the age and COS, with older patients having a higher COS (Rho=0.146, $p<0.005$). There was no difference in COS and sex (Chi square=10.993, $p>0.10$).

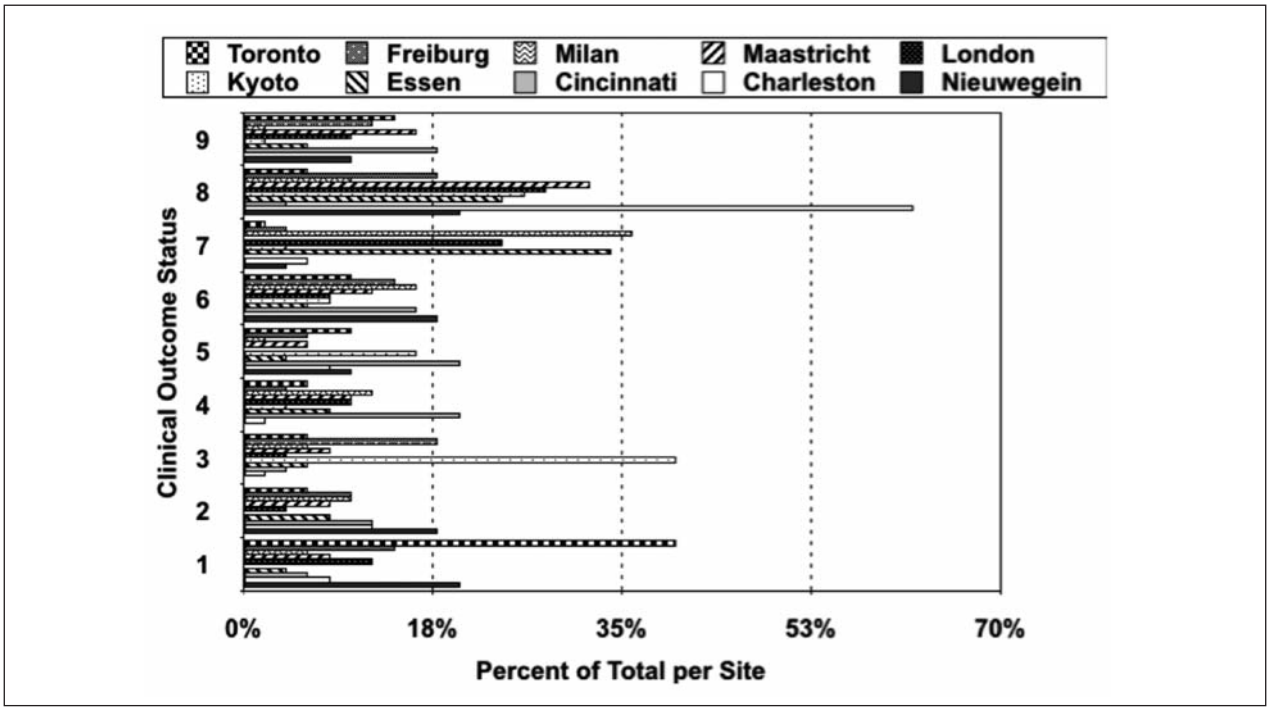

Fig. 2. Comparison of clinical outcome status versus the eight clinical centers (Nieuwegein, Essen, London, Maastricht, Milan, Charleston, Cincinnati, Kyoto, Freiburg and Toronto)

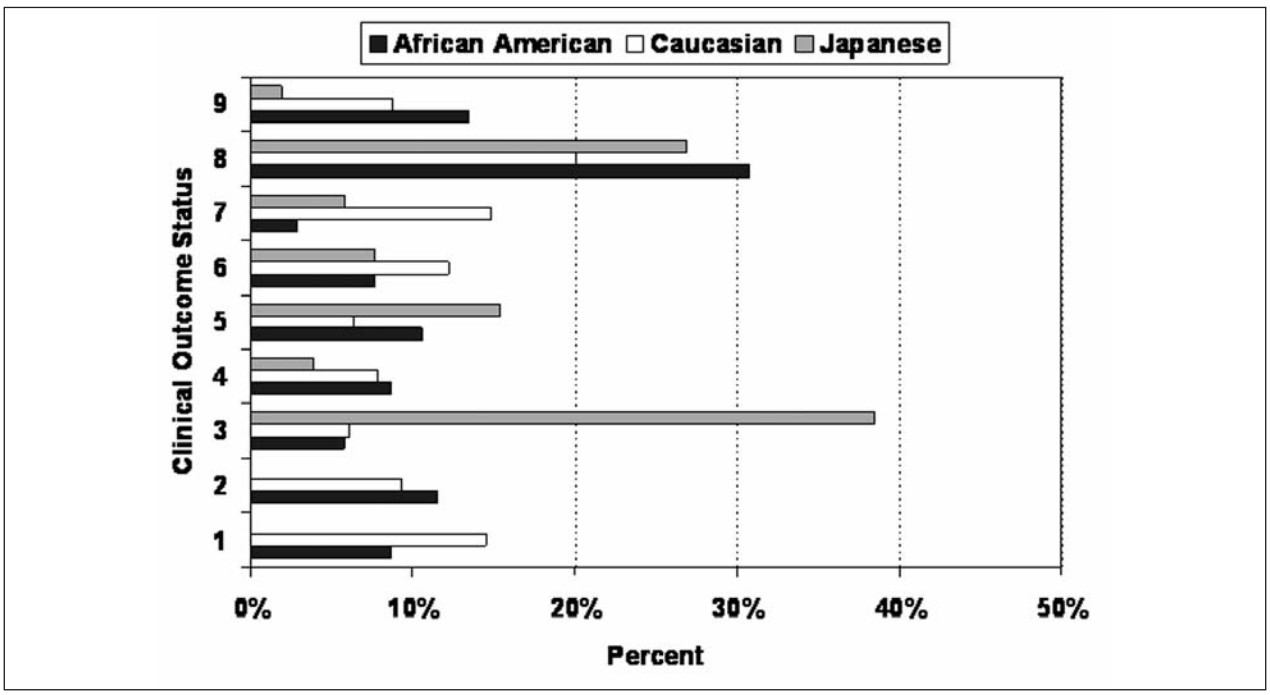

Fig. 3. Comparison of clinical outcome status versus self declared race

Discussion

In order to standardize the clinical outcome description of patients with sarcoidosis, a task force was created by the World Association of Sarcoidosis and Other Granulomatous diseases (WASOG). This task force set out to develop a novel clinical outcome score that incorporated change with time and with/without treatment. The task force did this by answering key questions set out in Table 1.

The final COS scores for all 500 patients are shown in Table 2. While the scores are 11 to 9, this is not a linear score. In fact, one can collapse the different groups depending on the specific question. For example groups 7-9 represent patients still on therapy compared to the other groups. Also, groups 1-4 represent those with minimal or no disease. Also, groups 1,3, and 5 represent those who never received therapy.

How long should the patient be from diagnosis?

The longer the duration of follow up, the more confident one is of the natural history of sarcoidosis. However, the longer the follow up, the larger the drop out of patients. In addition, the more difficult it is to perform timely research. For example, a particular cytokine or cell type in the bronchoalveolar lavage (BAL) fluid may be elevated in some patients with sarcoidosis. However, waiting for ten years to determine the clinical outcome of the patient may make the original observation irrelevant. The duration of time from diagnosis has been the subject of discussion for some time. Neville and James looked at a cohort of patients two years after initial diagnosis (7). Others used two years as a cut off between acute and chronic disease (4). In ACCESS, a cohort of newly diagnosed sarcoidosis patients were seen in follow up two years after initial diagnosis (8). In summary, two years has been a standard time for clinical follow up to determine the outcome.

Longer follow up may provide a clearer cut picture of the resolution of the disease. Nagai et al demonstrated that resolution of hilar adenopathy seen on chest roentgenogram could take up to ten years (Figure 2) (6). In one study, there was a difference in proportions of polymorphisms for patients with resolution of disease in less than 2 years (acute), between 2-5 years (intermediate), and chronic (more than 5 years) (9). Voorter et al reported an association of the allele DQB1*0602 with a severe course of the disease (10, 11). A recent report by Grunewald and Eklund demonstrated the value of long term follow up even in patients who presented with Lofgren's syndrome. Of patients who presented with periarticular arthritis and hilar adenopathy, only one of 87 patients with HLA-DRB1*0301/DQB1*0201 had chronic disease, while 18 of 40 without HLA-DRB1*0301/DQB1*0201 had chronic disease (12).

A particular problem is the possibility of relapse of disease after withdrawal of therapy. In a study by Gottlieb et al, patients were followed at one center (2). For those started on systemic therapy, there was a group who could not be withdrawn from therapy. After two years, approximately half of the treated patients had their therapy withdrawn. Over the next several years, patients would relapse and require reinstitution of systemic therapy. While it could take up to six years after withdrawal of therapy to relapse, the majority of patients relapsed within three years of stopping therapy. This experience would support a follow up of at least five years.

The committee focused on follow up of either two or five years. It was concerned that longer follow up would lose too many of the resolved patients. This could lead to a bias of only chronically ill patients. The committee then examined the COS after two and five years in the same patients seen at one center. Table 3 shows the changes in outcome of 50 patients seen at one institution. Compared to the two year outcome, nearly a quarter of patients had a different clinical outcome after five years. In nine of these patients, the change was from current therapy and worsening (COS=9) to another group. The decision of the committee was to use five years as the follow up period for this report.

The committee pointed out that the COS could be used at any time point from the time of diagnosis. Given the variable nature of the disease, the committee voted for choosing five years, but recognized that two years (or even one year) may be adequate for some studies. Future studies would be useful to determine at what time further follow-up leads to insignificant changes in COS.

How to allow for therapy?

Clearly systemic therapy can affect the clinical presentation of patients with sarcoidosis. Corticosteroid therapy is associated with a significant improvement in chest roentgenogram (13). As noted, the withdrawal of corticosteroids may lead to worsening clinical parameters (2).

The committee decided to divide the history of therapy into three groups: no treatment, no treatment in the past year, and current therapy. Therapy was not limited to corticosteroids, but included all systemic therapies for sarcoidosis except for nonsteroidal anti-inflammatory agents (14). Others have accounted for therapy in assessing the clinical phenotype (3).

How to define resolution or remission?

The committee recognized that complete resolution of disease could occur. For example, the percent of patients with a normal chest roentgenogram two years after initial diagnosis had been described by Neville and James (7). However, there was a group of patients who had minimal disease remaining. Minimal disease was arbitrarily defined as less than 25% of maximal disease. For pulmonary disease, minimal changes could be seen with either chest roentgenogram or pulmonary function studies. While the pulmonary function changes can be easily calculated, changes in chest roentgenogram are subjective (15). Despite this potential limitation, none of the centers had a problem with this classification.

The decision to use 25% residual disease as minmal was based on the oncology literature. In that situation, a partial remission is defined as 25-50% of maximal disease (16, 17). While there is some interobserver variability on using this method (18), this can be minimized when the same reviewer grades both before and after therapy (19). Also, there was better agreement when large differences, such as a 75% reduction, are scored (19).

The committee felt that future studies may be useful to determine the importance of distinguishing between minimal disease and complete resolution. The group did feel that patients with minimal disease were more likely to act like those with complete resolution of disease. This was seen in the five patients with minimal disease at year 2 (Table 2), Three of those patients had complete resolution by year 5 and the other two still had minimal disease.

How to define chronic disease?

Patients who had chronic disease were defined as those with more than 25% of maximal disease after five years. This group included patients who were still on systemic therapy. Patients could have persistent disease, that is more than 25% of their maximal disease, and not be on therapy for the past year. This included patients who had never received therapy (Group 5) and those who had not received therapy in the past year (Group 6). For those who were still receiving therapy (or had received therapy in the past year), the patients were divided into three groups: those with no symptoms (Group 7), those who remained symptomatic (Group 8), and those who had worsened in the past year (Group 9).

Can all patients be classified?

In the follow up study of 500 patients, all patients were classified. There were no examples in the final 5 cases submitted that could not be included in one of nine categories.

This system has several potential problems. After much discussion, it was decided not to add specific organ manifestation. There have been other systems which define organ involvement (20). It has also has been noted that certain manifestations predict clinical outcome (7). However, the clinical outcome of most organ involvements has not been systematically studied. One widely cited manifestation of good prognosis is Lofgren's syndrome (7). However, long term follow up studies have shown that more than ten percent of patients who present with Lofgren's syndrome will have chronic disease (21). The recommended COS is one possible method to report clinical outcome over time and to provide specific information regarding the outcome of these different disease manifestations.

Another issue was the use of treatment to decide classification. The decision of whom and what to treat sarcoidosis patients remains more subjective than objective. The most commonly reported indication is symptoms (1). There is limited evidence based information regarding therapy for sarcoidosis (22).

Some clinicians have recommended prolonged courses of corticosteroids (23). However, withdrawal of corticosteroids was attempted on a regular basis even in that series. Others have reported on the routine attempts to withdraw therapy at their individual clinics (2, 24, 25). The committee felt that the use of treatment was a marker of disease severity, as has been used by others (3, 26). While corticosteroids are the most commonly used class of drugs, other drugs have become more commonly used (27). In particular, biologic agents such as infliximab have been increasingly used. However, these have been used mostly for patients with chronic disease, often because of failure of other medications (28, 29).

There have been two other phenotyping systems proposed in the past few years. In one, the patients were divided into acute and subacute based on the onset of symptoms at the time of diagnosis (3). While this system has advantages in identifying patients with acute onset, such as Lofgren's syndrome (12, 21), it may be hindered by patients who are not diagnosed near the time of onset of disease. In a study of American patients with newly diagnosed sarcoidosis, Judson et al found that there was often a delay in diagnosis of sarcoidosis (30). For example, patients with pulmonary symptoms alone were more likely to be diagnosed 6 months after onset of symptoms compared to patients who presented with skin symptoms. The current scoring system was developed to give a more accurate phenotype based on the true long term outcome of patients. The acute versus subacute presumes that the long term outcome can be predicted by clinical features at the time of presentations. While this is generally true (7), it is clear that some patients may still have a chronic outcome. For example, there was a general agreement that all patients with Lofgren's syndrome had a resolution within one to two years (7). However, recent studies have identified that not all patients have resolution of their disease and in fact there are specific genetic differences in those with resolving versus chronic disease (31).

The other feature of the phenotyping system proposed by Prasse et al was to divide patients into those who required no treatment, treatment for less than one year, and those who required long term treatment (3). This is similar to our final table. However our system allows one to be sure that there were no patients who relapsed after withdrawal of corticosteroid therapy. The rate of relapse after withdrawal of corticosteroids has been reported to be between 50-80% (2, 26). In summary, the Prasse system is more easily applied and does not require follow up for such a long time. On the other hand, the COS is less likely to misclassify resolving versus persistent disease.

Another scoring system reported by Wasfi et al scored patient status using a visual analogue score of sarcoidosis severity (32). This provided a global assessment of disease severity which incorporates the multiorgan nature of the disease. This system is different from the individual organ assessment score used to evaluate therapeutic response (33). One problem with that scoring system was it provides the status of the patient at one point in time. It also was influenced by the individual rater's bias about what constitutes severe disease. This was demonstrated by the lower correlation in the severity score between experts at various institutions (32).

We show the comparative results of the five year COS for each clinical center, self declared race, age, and sex. There was no difference between the proportions of individuals in each COS across clinical site. More of the patients with higher COS scores (6, 7, 8, and 9) were African-American or older. This almost certainly reflects the poorer outcome seen with African American patients. This group has been shown to have a worse clinical outcome after two years (8). In addition, several studies have suggested a higher rate of chronic disease for African Americans (34-36). One striking difference is the requirement for persistent therapy seen in over half of patients from a mostly African American clinic (2) by contrast with a referral American sarcoidosis clinic which comprises mostly Caucasians (24). It has also been observed that patients who are older at time of diagnosis have worse prognosis (8, 37). We did not collect other markers of poor outcome to compare them to the COS. A limitation of comparing COS to race and age was that we collected information from referral centers only. Often these patients have more advanced and chronic disease (38). For example, none of the patients from Kyoto had resolved disease, since patients with resolved disease by year five were usually not followed any further at that clinic.

In conclusion, a proposed clinical outcome of sarcoidosis was developed. It was found that the COS of sarcoidosis was affected by race and age.

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