The Value of a Patient Global Assessment in Management of Sarcoidosis

Robert P. Baughman1,2 · Jacob Kotzin1 · Elyse E. Lower1

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Abstract
The patient global assessment (PGA) is a reported outcome instrument used to gauge the patient’s well-being. We performed a prospective study of patients seen at the University of Cincinnati Sarcoidosis Clinic. Two groups were studied: those at first visit during the time period (initial) and those seen at least one more time by the same physician (follow-up). A total of 1006, including 677 initial, visits occurred during the six-month period. Patients in whom anti-inflammatory treatment was initiated or increased had a significantly lower PGA score (ANOVA \( p < 0.001 \), \( p < 0.05 \) for increased versus all others). There was no significant difference in initial PGA score based on race, sex, or age. The change in PGA was significantly lower for patients in whom treatment was increased (ANOVA \( p < 0.001 \), increased different from all others, \( p < 0.05 \)). The PGA was significantly lower for patients in whom anti-inflammatory therapy was increased; however, there was overlap between groups.

Keywords Quality of life · Sarcoidosis treatment · Prednisone · Visual analogue scale

Introduction

Because patients with multi-organ sarcoidosis often experience a wide array of symptoms, disease assessment and treatment response may involve more than one dimension [1]. For example, forced vital capacity is an objective measure of lung function [2] but fails to provide information regarding other disease aspects and the effect on overall health. Patient reported outcomes (PROs) in sarcoidosis have been developed to provide more comprehensive assessment of the impact of sarcoidosis on the patient’s health [3, 4]. Changes in these instruments have been documented with various treatment regimens for sarcoidosis [5–7].

Although PROs may be important research tools to assess sarcoidosis outcome, these questionnaires may require five to thirty minutes to complete [8]. In contrast, the patient global assessment (PGA) is a ten-point scale with a MCID of two points [9] which can be completed in less than a minute. It is similar to the pain scale, which has been widely adapted to clinical practice [10]. The treatment of sarcoidosis is designed to relieve symptoms and avoid danger [11]. The use of a scale to summarize disease impact by the patient at a clinic visit may facilitate treatment decisions in daily practice.

We report the outcome of employing a PGA as an assessment tool in a sarcoidosis clinic. The results of the PGA were compared to the treatment decisions made at individual clinic visits. The influence of race, gender, age, organs affected, and baseline treatment for sarcoidosis were compared to the PGA results.

Methods

This was a prospective study of all patients seen by either RPB or EEL at the University of Cincinnati Sarcoidosis Clinic from January 1, 2020 to June 30, 2020. Using a Likert scale from 1–10 with 1 the worst and 10 the best; the patient rated how he/she felt regarding sarcoidosis on the day of visit. This PGA has been previously used in sarcoidosis patients [9]. Data collected included race, sex, age, current anti-inflammatory therapy, and organ involvement. Anti-inflammatory therapies and doses captured included glucocorticoids (e.g., prednisone), methotrexate, azathioprine, leflunomide, hydroxychloroquine, infliximab (or biosimilar),...
adalimumab, rituximab, and repository corticotropin injection (RCI). Organ involvement was assessed using WASOG criteria for highly probable or probable disease \[12\]. The information was recorded in an electronic data-capturing database (REDCap) \[13\]. The study was approved by the University of Cincinnati Institutional Review Board and registered on ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02356445).

The decision to change anti-inflammatory therapy was performed by the physician during the clinic visit, and it was captured as increased, decreased, or unchanged. An increase in medications was defined as (1) current anti-inflammatory medication dosage increase, (2) a new anti-inflammatory therapy added with no change in other medications, (3) a new medication was added and another drug (for example prednisone) was reduced or withdrawn, and (4) short course of increased glucocorticoids was prescribed. For cases where treatment was modified, the treating physician recorded the primary reason for increasing or reducing medication as sarcoidosis worsening, an acute infection, or other. For toxicity, it was noted if medication was increased by adding a new agent (such as methotrexate) or current medication was reduced.

Two sarcoidosis groups were studied: patients at first visit (initial) and patients seen at least one more time during the study period by the same physician (follow-up). For follow-up patients, the change in PGA was calculated by subtracting the prior visit score from the current visit.

Statistics

Statistical analysis was performed using MedCalc software (Ostend, Belgium). Comparisons were made between groups using analysis of variance (ANOVA). If the ANOVA analysis found a significant difference between groups, a pairwise comparison was made using the Scheffe test. A \( p \) value of <0.05 was considered significant for the ANOVA and pairwise comparison. To determine the cut-off for PGA scores patients in whom treatment was increased versus no change or reduction of medication, we performed a receiver operator curve (ROC) and calculated the area under the curve (AUC). A \( p \) value of <0.05 was considered significant.

Results

Initial Visit

A total of 1006 sarcoidosis patient visits occurred during the six months of study. In all but 13 (1.3%), complete information was recorded. After exclusion for unclear/missing visit information, full analysis was completed on 677 of 687 sarcoidosis patients with at least one initial visit with complete data. Table 1 depicts the clinical features of these 677 patients. Over a third of patients had medications increased at the visit, and forty percent had no medication changes. A small difference in age was noted between groups (ANOVA \( p < 0.05 \)) with no differences for sex or self-declared race.

Table 2 compares anti-inflammatory change to PGA scores (ANOVA \( p < 0.001, p < 0.05 \) for increased versus all others). There were no significant differences among treatment groups based on age, sex, or self-declared race. The PGA scores for patients in whom treatment was increased were significantly lower compared to the other scenarios. For all but rituximab, there was a significant difference for the PGA scores between the three treatment regimens with no difference between reduced medication and no change in medication. For rituximab, there was no difference between treatment groups but there were only three patient visits where the treatment was increased. There was a significant difference in PGA scores for all organ involvement listed in Table 2. In most cases, the PGA scores for patients in whom treatment was increased were significantly lower than the other three treatment regimens. The PGA score for patients in whom treatment was increased was not significantly different from other treatments for cardiac and spleen involvement. This may have been due to the smaller number of cases with these specific organs affected (less than 80 patients for each).

We compared the PGA scores for changes in anti-inflammatory medication versus the primary reason for changing medication in Table 3. For patients who increased their anti-inflammatory medication or a new medication was added, the PGA score for toxicity was higher (7.44 ± 1.944) compared to patients who increased medication due to sarcoidosis disease activity (5.06 ± 1.991) or acute infection by paired analysis (\( p < 0.05 \)). Using paired analysis, patients who decreased anti-inflammatory medication due to disease activity had lower PGA scores compared to those who reduced for toxicity (\( p < 0.05 \)). At only one visit, anti-inflammatory medication was reduced in the setting of infection. In that case, an antibiotic was prescribed and the dose of prednisone was unchanged but rituximab was held. Patients not on anti-inflammatory medications were ineligible for analysis of medication reduction.

Follow-up Visit

A total of 316 paired visits were evaluable. The PGA score was significantly lower if anti-inflammatory medications were increased (number of visits = 71, change in PGA = −0.58 ± 2.511) compared to having medications reduced (number of visits = 82, change in PGA = 0.74 ± 2.054), no change in medication (number of visits = 159, change in PGA = 0.39 ± 1.942), or not receiving medications...
(number of visits = 4, change in PGA = 3.25 ± 1.893) (ANOVA < 0.0001, p < 0.05 for increased versus each other treatment by paired analysis). No significant differences were noted in change in PGA scores based on gender, race, or age (data not shown).

Receiver operator curve (ROC) analysis determined that a PGA score of 6 or less was associated with a medication increase with a sensitivity of 46% and specificity of 74% (AUC = 0.624, p < 0.005). Medications were increased in more than half of the patients with no change in PGA scores.

**Discussion**

Using the data collected in over 98% of 1006 clinic visits, the PGA was a fast and easy assessment tool for sarcoidosis patients. Significantly lower PGA scores indicated worse...
clinical status for those patients who required increase in anti-inflammatory treatment. In a prospective study, the MCID for PGA was 2 points [9]. In the current study, patients in whom treatment was increased had a PGA scores of 1.94 lower than those whose medications were reduced and 2.2 lower than those without medication change. Furthermore, the PGA scores were significantly lower for patients in whom treatment was increased regardless of race, sex, age, most organ involvement, or therapy. Significant changes in the follow-up PGA scores were identified most frequently in patients in whom treatment was increased compared to other treatment options. There

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was a significant difference in the ages for the various treatment groups (Table 1). However, the mean age differences between the groups were less than three years. When we analyzed race, sex, or age above or below 60, the PGA score was still significantly lower for those who had medications increased versus other treatment subgroups. The average PGA score for patients in whom medication was increased was not significantly different between the various subgroups. Similarly, no change was found in PGA scores for different treatment regimens versus organ involvement (Table 2). These findings support that PGA scores can be useful for most sarcoidosis phenotypes regardless of clinical or demographic features.

The primary reason for changing anti-inflammatory medication was provided by the treating physician at each visit. The most common reasons for increasing medication were increased sarcoidosis activity and acute infection. The most common reason for reducing medication were decreased sarcoidosis activity and toxicity. In some cases, the patient reduced medication for toxicity not detected by the patient, such as an abnormal liver function test or osteoporosis on radiologic imaging. In nine cases, medication was increased for toxicity when the patient was initiated on an additional agent, such as methotrexate or infliximab, with a reduction in prednisone dosage. This may explain the higher PGA scores seen for increasing medication for toxicity compared to other indications.

Although the PGA score performed well for the entire population studied, it was of more limited value for daily decision. Overall, PGA scores of ≤ 6 were associated with increased medication at that visit with a sensitivity of 73% and specificity of 71%. However, no medication change was made in over 20% of patients with a PGA score of 1 or 2.

To enhance the potential value of PGA, we calculated the change in PGA from the previous visit. Patients in whom treatment was increased reported average scores of −0.58, while the average change of 0.74 was found for patients who had medications reduced. Using ROC analysis, a one-point change in PGA was associated with a treatment change but with only a sensitivity of 46% and specificity of 74%. We did not evaluate the change in PGA versus specific changes in anti-inflammatory therapy. Such a study may provide more insight in the impact of specific treatments on the patient’s quality of life.

The limitation of a PRO in daily practice has been noted by others. For example, a study of successful therapy for fibromyalgia found large variability for individual patients, but significant changes for the whole group [14]. The self-reported pain scale has been touted as providing a rapid assessment of pain [15]. This scale reduced the time for initiating analgesia in the emergency room [16, 17]. However, applying the pain scale with an algorithm was associated with higher total amounts of analgesia [16, 18].

In conclusion, this study reveals the ease and clinical applicability of patient global assessment for various sarcoidosis phenotypes and demographics. The lower the PGA score, the greater the likelihood that the patient would increase medication for either sarcoidosis activity or acute infection. This further supports the use of PGA in clinical trials. However, the PGA may not provide additional information for the assessment of individual patients.

**Author Contributions** All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by RPB and JK. The first draft of the manuscript was written by RB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability  Upon request of corresponding author.

Declarations

Conflict of interest  Drs. Baughman and Lower have research grants from Mallinckrodt, Bayer, Genentech, Novartis, Celgene, aTYR. Dr. Baughman has been consultant for Novartis and Mallinckrodt and a speaker for Mallinckrodt. Jacob Kotzin has no conflicts.

Ethical Approval  The study was approved by the University of Cincinnati Institutional Review Board and registered on ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02356445).

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