The value of a patient global assessment in management of sarcoidosis

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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 who initiated or increased their anti-inflammatory therapy had a significantly lower mean 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 those who increased medication (ANOVA $P<0.001$, increased different from all others, $p<0.05$). The PGA was significantly lower for patients who increased anti-inflammatory therapy initially or at follow-up, however there was overlap between groups.

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.

The purpose of this study was to determine the feasibility of adapting 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 one the worst and 10 the best, the patient rated how he/she felt regarding sarcoidosis on the day of visit. 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; 4) short course of increased glucocorticoids was prescribed. For cases where treatment was modified, the treating physician recorded the reason as disease worsening, acute infection, toxicity, or other.

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 between groups 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 for increase medication 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

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 increased medications 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 increased treatment 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.

Table 3 lists the PGA scores for those patients changed medications at the initial visit versus the reported indication for change in treatment. For patients who increased the 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 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 was anti-inflammatory medication 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.

A total of 316 paired visits were evaluable. Table 3 reveals PGA score changes from prior visit to current visit compared to concurrent treatment decisions. The PGA score was significantly lower if anti-inflammatory medications were increased (number visits=71, Change PGA -0.58 ± 2.511) compared to reduced medications (number visits=82, Change PGA=0.74±2.054) no change in medication (number of visits=159, Change PGA=0.39±1.942) or not receiving medications (number of visits=4, Change 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 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 an increase in medication with a 73% sensitivity and 71% specificity and AUC of 0.789 ($p<0.0001$). There were 308 paired visits in which patients were receiving anti-inflammatory therapy at the second visit. A decrease in the PGA of 1 or more points was associated with an increase in medications with a sensitivity of 46%, 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 anti-inflammatory treatment increases. In a prospective study, the MCID for PGA was 2 points [9]. In the current study, patients who increased medication had a PGA scores 1.94 lower than those who reduced medications and 2.2 lower than those without medication change. Furthermore, the PGA scores were significantly lower for patients who increased medication regardless of race, sex, age, organ involvement, or therapy.

Significant changes in PGA scores were identified most frequently in patients who increased medications compared to other treatment options. When we analyzed race, sex, or age, the PGA score was still

significantly lower for those who had medications increased versus other treatment subgroups. The average PGA score for patients increasing medication 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 efficacious for most sarcoidosis phenotypes regardless of clinical or demographic features.

Although the PGA score performed well for the entire population studied, it was of more limited value for daily decision. Overall, PGA scores of $\leq$ 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 who increased medication reported average scores of -0.58 while the average change of 0.74 was made for patients who reduced medications. 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%.

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. This further supports the use of PGA in clinical trials. However, the PGA may not provide additional information for the assessment of individual patients.

Declarations

Funding There was no funding for this study.

Conflicts of interest/Competing interests 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.

Availability of data and material upon request of corresponding author

Code availability no code needed

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Robert Baughman and Jeffery Kotzin. The first draft of the manuscript was written by Robert Baughman and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics 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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Tables

Table 1 Demographics and PGA scores for four treatment regimens at initial visit

	Total	Increase medications	Reduce medications	No change in medications	No anti-inflammatory medications
Total number of patients	677	241 (35.6%)	78 (11.5%)	267 (39.4%)	91 (13.4%)
Age (yrs) §		55.7+13.04 *	55.4+11.07	58.5+11.72	57.5+12.60
Age < 60 years	361	127	36	146	52
Age ≥ 60 years	316	114	42	121	39
Proportion of patients					
Female	453	168	50	175	60
Male	224	73	28	92	31
African American	287	101	33	120	33
White	385	138	45	144	58
Asian	3	1	0	2	0
Other	2	1	0	1	0
Organ ¶					
Lung	548	199	64	216	69
Eye	234	85	28	92	29
Skin	195	76	18	77	24
Calcium metabolism	152	53	25	54	20
Neurosarcoidosis	137	46	28	52	11
Liver	97	39	10	38	10
Non thoracic lymph nodes	91	35	9	33	14
Cardiac	75	16	9	38	12
Spleen	70	28	9	27	6
Anti-inflammatory therapy ¶					
Prednisone	283	114	60	109	0
Methotrexate	159	54	28	77	0
Azathioprine	42	16	8	18	0
Mycophenolate mofetil	24	10	4	10	0
Leflunomide	22	5	3	14	0
Hydroxychloroquine	81	21	10	50	0
Infliximab	77	19	17	41	0
Adalimumab	18	4	4	10	0
Rituximab	38	3	8	27	0
RCI	24	8	4	12	0

*Mean ± standard deviation

¶ Patients could have more than one organ involved or more than one treatment

§Difference between groups by ANOVA, $p<0.05$.

Table 2 Demographics and PGA scores for four treatment regimens at initial visit

	Total	Increase medications	Reduce medications	No change in medications	No anti-inflammatory medications
Total number of patients	677	241 (35.6%)	78 (11.5%)	267 (39.4%)	91 (13.4%)
PGA scores					
All †		5.18±1.978 *	7.12+1.844	7.38+1.828	7.89+1.859
Age <60 years †		5.29+1.903	7.19+1.670	7.24+1.836	7.87+2.020
Age ≥60 years †		5.05+2.060	7.05+1.999	7.55+1.812	7.92+1.644
Female †		5.05+2.001	7.00+1.784	7.18+1.950	7.70+1.889
Male †		5.47+1.908	7.32+1.964	7.76+1.507	8.26+1.770
African American †		5.47+2.194	7.21+1.867	7.42+1.930	8.24+1.803
White †		4.96+1.798	7.04+1.846	7.34+1.759	7.69+1.875
Organ involvement ¶					
Lung †		5.10++1.958	7.08+1.846	7.31+1.820	8.00+1.774
Eye †		5.61+2.059	7.11+1.729	7.68+1.644	7.93+2.034
Skin †		5.18+1.923	7.33+1.879	7.48+1.971	7.46+2.166
Calcium metabolism †		5.19+1.922	6.52+1.874	7.43+1.958	7.55+2.012
Neurosarcoidosis †		5.04+2.139	6.61+2.200	7.27+1.548	7.73+2.195
Liver †		4.85+1.710	7.80+1.033	7.45+1.927	7.60+1.776
Non thoracic lymph nodes ‡		6.00+1.831	6.56+1.236	7.55+1.769	9.07+0.997
Cardiac **		5.62+1.857	7.22+2.108	7.13+1.758	7.33+2.461
Spleen §		4.96+1.934	7.56+1.333	7.78+2.189	8.67+0.816
Current drugs ¶					
Prednisone ††		4.90+2.149	7.10+1.829	7.05+1.922	NA§§
Methotrexate ††		4.96+2.018	6.79+1.950	7.48+1.691	NA
Azathioprine ††		4.69+2.024	7.75+1.909	8.11+1.023	NA
Leflunomide ††		4.00+2.000	8.00+1.000	6.64+1.780	NA
Mycophenolate ††		5.30+2.058	7.50+1.000	8.10+0.994	NA
Hydroxychloroquine ††		4.86+2.080	7.70+1.252	7.58+2.043	NA
Infliximab ††		4.84+1.803	7.53+1.875	7.56+1.582	NA
Adalimumab ††		2.50+1.000	6.25+2.986	8.50+1.080	NA
Rituximab		4.67+3.215	6.50+1.852	6.78+1.761	NA
RCI ††		4.38+2.134	8.25+1.708	7.67+1.614	NA

*Mean ± standard deviation

¶ Patients could have more than one organ involved or more than one treatment

†Difference between groups by ANOVA, $p<0.0001$. Those who increased medication were significantly different from other three groups by paired analysis ($P<0.05$).

§Difference between groups by ANOVA, p<0.05.

‡ Difference between groups by ANOVA, p<0.0001. Those who increased medication were significantly different from no change and no anti-inflammatory medications by paired analysis (P<0.05).

** Difference between groups by ANOVA, p<0.01. There was no difference between individual regimens by paired analysis.

†† Difference between groups by ANOVA, p<0.0001. Those who increased medication were significantly different from reduced or no change in medication by paired analysis (P<0.05).

§§ NA=not applicable

Table 3 PGA scores for increasing or decreasing anti-inflammatory medication versus indication for changing medications

		Sarcoidosis	Infection	Toxicity	Other
Increase medication §					
		5.06+1.991 *	4.91+1.771	7.44+1.944	6.33+1.723
	236 †	159	56	9	12
Reduce medication ‡					
		7.74+1.678	9	6.13+1.544	NA **
	75	43	1	31	0

*Mean ± standard deviation

†Number of cases

§ Difference between groups by ANOVA, p<0.001. Those who increased or added new medication for toxicity had a higher PGA than those increased for sarcoidosis or acute infection by paired analysis (P<0.05).

‡ Difference between groups by ANOVA, p<0.001. Those who reduced medication for sarcoidosis had a lower PGA than those who reduced for toxicity by paired analysis (P<0.05).

** NA=not applicable