Author response v.1

We have addressed the reviewers' comments below and have outlined how we have changed the manuscript since the initial submission.

Reviewer 1 Comments

1. First and foremost, it is very tricky to use retrospective cohort studies to make decisions on therapeutic options. It will be very interesting and welcome to see randomized controlled trials using RCI in sarcoidosis. I have a major concern that this study design, with its inherent high risk of bias, has a high chance of overestimating the efficacy of RCI. This could lead physicians to prescribe more frequently a medication that it is not yet proven to be beneficial in RCTs.

REPLY: Our study is descriptive and exploratory and is aimed at understanding utilization patterns of RCI and concomitant therapies and physicians' assessments of RCI improvement effects on patients' health status in real-world clinical practice. We agree with the reviewer that retrospective studies may present a high risk of bias compared with RCTs and have addressed this in the Limitations section (Page 18, Para 1). Our research model was based on specific retrospective criteria for selection and analysis outlined in our Methods section.

It is important to note the following: RCI is indicated for symptomatic sarcoidosis; it is included in treatment guidelines from the Foundation for Sarcoidosis Research; and, currently, a phase IV, double-blind, randomized, placebo-controlled clinical trial is ongoing to examine the safety and efficacy of Acthar Gel in patients with pulmonary sarcoidosis (https://clinicaltrials.gov/ct2/show/NCT03320070). We believe these points further justify our examination of RCI and have been included in the Limitations section as well.

2. The lack of a control group is problematic here. Ideally we should see a controlled group, with propensity matching (since this is a retrospective cohort), to minimize the risk of bias. An RCT would still be obviously better to answer this therapy question, but a control group with propensity scores would at least improve this study's design.

REPLY: It was an exploratory and hypothesis-generating study, and we did not conduct any inferential statistics. We have addressed this in the Limitations section (Page 18, Para 1).

3. We have no information on prior therapies used in these patients. Were they treated with more standard steroid-sparing agents such as methotrexate, leflunomide, azathioprine, mycophenolate, adalimumab, infliximab?

REPLY: The study design did not address prior therapies in greater detail than described in our Methods section. We addressed this in the Limitations section (Page 19, para 1).

4. We have no information on what was the driver of the decision to treat patients with RCI. Was it used as first line based on disease severity? Was it used after 6, 12 months of treatment failure with other agents?

REPLY: For this study, we did not examine the reasons for treatment decision of using RCI for patients with advanced symptomatic sarcoidosis. Based on our study sample selection criteria and findings, the probable drivers could be advanced stage of the disease and/or lack of improvement in patient's health status on treatments other than RCI. Eighty-six percent of patients had received other medications before RCI therapy, suggesting there might be treatment failure in patients with advanced disease (see Figure 2). We have addressed this in the Limitations section (Page 19, Para 1).

5. There is a very high risk for recall bias here. The physicians were choosing which patients to enter in the database, and also the physicians were entering the outcomes. It is very reasonable to believe that patients with better outcomes while on RCI were more likely to be entered in the database.

REPLY: Patient results were not a screening criterion. We understand the concern of the reviewer, but we did not steer patient selection to those with a positive outcome.

6. Under "Patient Demographic and Clinical Characteristics" it is stated that only 27% of patients with "advanced symptomatic sarcoidosis" had "concurrent use of corticosteroids (≥5 mg/d prednisone equivalent for ≥60 d), nonbiological oral medications (e.g., hydroxychloroquine, methotrexate, azathioprine, leflunomide, mycophenolate, other nonsteroidal oral agents), and biologics"??? This is a very very low proportion of patients, and it doesn't match with the numbers under "Concomitant Medications" and Figure 2.

REPLY: The 27% refers to patients on all 3 medications, whereas the number in Figure 2 refers to any concomitant use (i.e., more than 1 medication but not necessarily all 3). Thus, the two numbers are different, but we can confirm that both are accurate. We have added language to better clarify this on Page 7.

7. Under "Concomitant Medications", however, those numbers are different. But still only 24% of patients were on biologics on the three months before RCI. This percentage is very low for this patient population of "advanced symptomatic sarcoidosis" given the fact that there is one randomized controlled trial showing benefits of biologics in this population. And only 21% of patients were on other immunosuppressants before RCI. This is very low.

REPLY: Our retrospective study was looking back 36 months with no treatment assessment focus or bias. Because of the range of physicians supplying answers, perhaps our cohort of more diverse specialists are lower biologic prescribers than if the respondent population were all pulmonologists.

Further, our study describes the information reported by physicians in terms of concomitant medication use patterns before, during, and after RCI treatment. It is possible that the physicians may be underreporting these estimates; however, this cannot be fully ascertained from the current study. We have addressed this in the Limitations section (Page 18, Para 2).

8. As stated above, recall bias is a big issue here. The 95% improvement rate in the physicians assessment is very likely overestimated due to recall bias.

REPLY: Please see our response to Comment #5. Also, please see note below for Reviewer 2, Comment 1 for the question that was used in the chart review data collection form.

Reviewer 2 Comments

1. Only 5% of "physicians assessments of improvements" following treatment stated not improved. This is such a small figure, because earlier work found 38% improvement after therapy (Baughman 2016). I would like to see/ read how the question was formulated in the questionnaire towards the Physicians. Can this be selection bias?

REPLY: See Table 3, bottom legend statement: †Physicians' responses to the question, "Please select the outcomes below that have improved as a result of RCI treatment." Since respondents could select all options that applied, the sum exceeds 100%.

2. With 100% pulmonary involvement in these patients of which 64% had stage 3-4 sarcoidosis, I'm wondering why only 23% pulmonary physicians were asked. In Europe, sarcoidosis treatment is mainly done by pulmonary physicians. Can you comment on that? Is the situation different in the US? Were there not many pulmonary physicians prescribing the drug in the database? Please add to the discussion that extra pulmonary involvement differs in this study compared to previous work, probably due to selection bias because of the different specialists asked to participate (nonpulmonary).

REPLY: Management of patients with advanced sarcoidosis is complex and may involve multiple organs that are impacted along with co-occurring medical comorbidities. Therefore, this study

reflects the broad range of specialty types reported. We have added this to the Discussion section (Page 17, Para 1).

3. Please keep treatment response more neutral and describe in text as treatment response not as improvement (in Discussion and Table 3).

REPLY: We have edited the text in Table 3 and the Discussion section wherever applicable to make it more neutral.

4. Please note, in table 3, 11% states pulmonary fibrosis is improving. As fibrosis itself will not improve, it should state pulmonary involvement to my opinion. In the same table, size and number of granuloma s are a category. As granulomas can't be seen unless using a microscope, please specify what is meant here: inflammation? pulmonary infiltrates? What does number of granuloma s mean? Pulmonary nodules? Please specify.

REPLY: Per the data collection form, respondents were asked to select the outcomes that have improved as a result of RCI treatment. The selection in the data collection form was described as follows: Size of granulomas (inflamed lumps), numbers of granulomas (inflamed lumps), pulmonary fibrosis (lung scarring). Therefore, no further clinical attributes can be assumed.

5. Overall, the draft reads very well. The tables are simple and easy readable.

REPLY: Thank you.