The Effect of Initiating Corticosteroids on Lung Function and Symptoms in Patients with Active Pulmonary Sarcoidosis

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Declaration

I, Salaheddin Eknewir, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgments indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Date: 29.06.2024

Acknowledgments

I want to thank my supervisor, Professor Richard van Zyl-Smit, who always gave me his time so willingly and worked very hard and supportively with me during this project, I thank him greatly. I shall never forget his outstanding guidance and support. He embodies the standards I aspire to in thoughtfulness, leadership, and compassion. I am privileged to have him as a role model.

Above all, thanks be to God Almighty for giving me the strength and courage to undertake and complete this thesis.

Format

This is a publication-ready format manuscript. We are in the process of submitting it to the South Africa Medical Journal, SAMJ, and African Journal of Thoracic and Critical Care Medicine AJTCCM

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List of abbreviations

6MWT	6-minute walk test
DLCO	Diffusing capacity of the lung for carbon monoxide
DM	Diabetes
FEV1	Forced Expiratory Volume in 1 second
GSH	Groote Schuur hospital
HPT	Hypertension
FVC	Forced Vital Capacity
ICS	Inhaled corticosteroid
mMRC	Modified Medical Research Council
OCS	Oral corticosteroids
SA	South Africa
SATS	South African Thoracic Society
TB	Tuberculosis

PUBLICATION READY MANUSCRIPT

The Effect of Initiating Corticosteroids on Lung Function and Symptoms in Patients with Active Pulmonary Sarcoidosis

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Key Words: Acute pulmonary sarcoidosis, corticosteroid, FVC, FEV1, DLCO

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Abstract

Background: Pulmonary sarcoidosis can lead to significant morbidity and mortality, and the use of corticosteroids is a common treatment strategy[1],[2]. The expected response to corticosteroids with respect to lung function is highly variable and not studied in an African cohort. The primary objective of our study was to investigate the impact of corticosteroids on lung function in patients with active pulmonary sarcoidosis.

Methods: We conducted a retrospective cohort study including all patients with active pulmonary sarcoidosis initiated on systemic corticosteroids documented in the Groote Schuur Hospital respiratory clinic registry.

Patients with histologically proven pulmonary sarcoidosis in whom prednisone therapy was initiated were identified retrospectively from the Groote Schuur Hospital respiratory clinic registry. Data extracted from medical records included patient demographics and clinical characteristics, corticosteroid dosage, duration and recorded side effects, chest imaging, and pulmonary function testing across one year following steroid initiation. We analyzed the effect of prednisone on FVC and DLCO trajectory and reported the serial changes at 3 monthly intervals. Data is presented as mean (± SD) unless otherwise specified.

Results: The study group comprised 42 patients, 30 females (71%) and 12 males (29%), with a mean age of 41.6 ± 9.8 years. The majority of patients (78.5%) were non-smokers. More than two-thirds of patients (69%) were diagnosed with Scadding II sarcoidosis. Routine lung function monitoring at 3 months showed a significant improvement in FVC with steroid therapy from 70.8(26.2) % to 77.5(25.5) % (mean change 6.3(11.3) %, $p<0.001$). Although not statistically significant, the FVC continued to improve numerically between month 3 (77.5%) and month 6, 79.0(23.5%). DLCO improved from 57.6(24.9) % at baseline to 61.0(33.0) % at 3 months to 68.9(28.1) % at 6 months ($p<0.001$) Weight changed over time with a mean (SD) increase of 8.3(7.0)kg at 9 months.

Conclusions: Among patients with acute pulmonary sarcoidosis requiring immunosuppression therapy, prednisone improved FVC and DLCO, with most of the FVC effect occurring within 3 months after initiation. DLCO continued to improve to 6 months Weight gain positively correlated with cumulative prednisone dose over 9 months.

Introduction:

Sarcoidosis is a systemic inflammatory disease characterized by the formation of granulomas in various organs, including the lungs[1]. Pulmonary sarcoidosis can lead to significant morbidity and mortality, and the use of corticosteroids is a common treatment strategy. However, the optimal dosage and duration of corticosteroid therapy for pulmonary sarcoidosis remains unclear.[3],[4],[5]

Corticosteroids are usually used to treat active pulmonary sarcoidosis, which refers to the presence of ongoing granulomatous inflammation. This is typically identified by radiologic progression, worsening lung function, or persistent respiratory symptoms such as cough and dyspnea. In contrast, “burnt-out” or fibrotic sarcoidosis refers to the irreversible scarring phase with no active inflammation. [2]

Studies have shown that corticosteroid use in patients with active pulmonary sarcoidosis can improve lung function and reduce symptoms.[2] This improvement may occur within days to weeks of starting treatment.[6–7] Specifically, corticosteroids have been associated with improvements in FVC ranging from 5% to 15% of predicted values, and a typical symptomatic response is observed within 4 to 8 weeks of therapy initiation.[4–6] Corticosteroids work by reducing inflammation in the lungs, which can help relieve symptoms such as cough, shortness of breath, and wheezing [17]. They may also help prevent the progression of lung damage caused by sarcoidosis. [8–9]

However, corticosteroids have significant side effects, such as weight gain, mood swings, and increased risk of infection.[3],[10] Therefore, the decision to initiate corticosteroid treatment should be made on a case-by-case basis, taking into account the severity of the patient's symptoms and the potential risks and benefits of treatment.[11],[12] Close monitoring of the patient's pulmonary function and symptoms is also important to ensure that treatment is effective and well-tolerated.[3,7]

The primary objective of our study was to investigate the impact of corticosteroids on lung function in patients with active pulmonary sarcoidosis. We aimed to assess their influence on key pulmonary parameters, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and diffusing capacity of the lung for carbon monoxide (DLCO).

Additionally, we aimed to evaluate the effects of corticosteroid treatment on respiratory symptoms and exercise tolerance, and to assess these improvements in the context of potential steroid-induced adverse effects, including weight gain, diabetes, and other metabolic complications.

Methods:

This retrospective cohort study included all patients diagnosed with acute pulmonary sarcoidosis in the interstitial lung disease registry at the E16 Respiratory Clinic, Groote Schuur Hospital (GSH), Cape Town, South Africa, from 1988 to 2023. No sample size calculation was conducted as this was a retrospective cohort study, and all patients identified from those recorded in the registry were included if they fulfilled the inclusion criteria.

Patients with histologically proven disease were identified from the clinic registry. Inclusion criteria were initiation of oral corticosteroids and follow-up for at least 6 months. Exclusion criteria included use of corticosteroids for non-sarcoidosis indications, concurrent immunosuppressive therapy (e.g., methotrexate or azathioprine), or incomplete follow-up data. No formal age restriction was applied, although patient ages ranged from 22 to 64 years in this cohort.

Data from the registry and clinic records were extracted, including demographic data, lung function tests over time, radiologic findings, corticosteroid dosing strategies, clinical outcomes, and adverse effects. Patients were evaluated for a maximum period of 1 year following corticosteroid initiation

Statistical analysis was performed using PRISM OS 10 for Mac Version 10.2.3 (347), April 21, 2024. Categorical data were summarized using numbers (N) and percentages. Descriptive data was summarized using means and standard deviations (SD) or medians and interquartile ranges (IQR) as appropriate

This study was approved by the HREC of the University of Cape Town (reference number 488/2023). The research was conducted in accordance with the Declaration of Helsinki. As this was a retrospective study based on registry data, consent was waived.

Results:

A total of 124 patients with sarcoidosis were identified in the registry. After the exclusion of 82 patients not initiated on steroids, insufficient follow-up, and missing records, a total of 42 patients were included in the evaluation cohort.

The mean (SD) age of the cohort was 41.6(42) and ranged from 22 to 64 years. The majority (n=30, 71%) were female. (Table 1) Due to restrictions on ethical group identification, classifying patients according to race/ethnicity was not possible. The cohort, however, reflects the local Cape Town population of predominantly mixed ancestry and black Africans.

Most patients were classed as having pulmonary stage 2 disease 69% (n=29) (table 1). Multisystem involvement was not common, with 5 (11%) patients having additional eye involvement and 3 (7.1%) or less skin, heart 2(4.8%), and liver 2(4.8%). Pre-existing comorbid diseases such as Diabetes, hypertension, and Previous pulmonary TB occurred in 2 (4.7%), 1(2.3%), and 2 (4.7%), respectively. See Table 1

Baseline lung function measurements showed significant statistical variability, with a mean Forced Expiratory Volume in 1 second (FEV_1) 66.2(26.5) % predicted and a mean Forced Vital Capacity mean FVC = 70.8(26.2)% predicted. Additionally, we had access to baseline measurements of the Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) mean DLCO = 57.6(24.85) % predicted

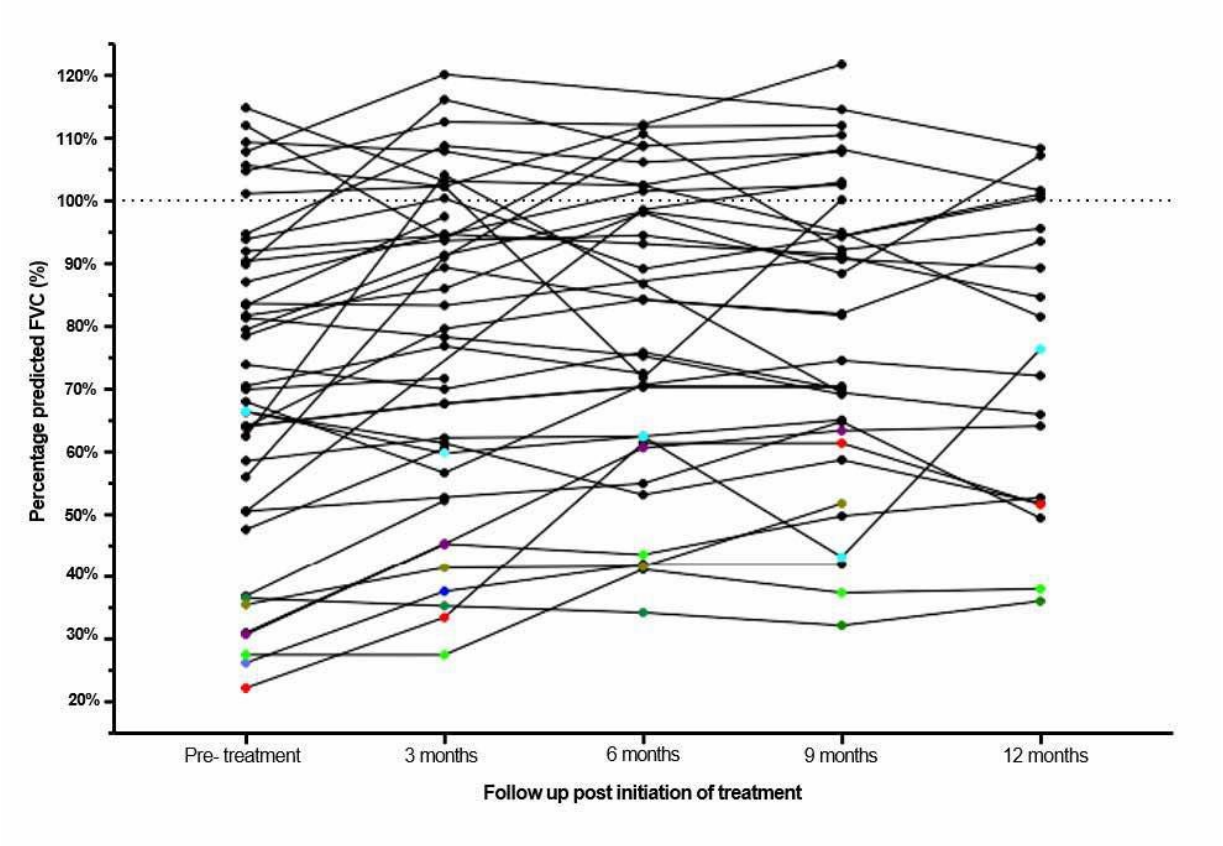
Table 1 Baseline characteristics of patients commenced on systemic oral corticosteroids.	
Patient	**N=42**
Mean (SD) Age	**41.6(42)**
Gender Female	**30 (71%)**
Organ involvement (%)	
Lung	**42 (100%)**
Liver	**2 (4.8%)**
Eye	**5 (11.9%)**
Skin	**3 (7.1%)**
Heart	**2 (4.8%)**
Baseline MMRC	
1	**MMRC I n=5 11%**
2	**MMRC II n=27 64%**
3	**MMRC III n=8 19%**
4	**MMRC IV n=2 5%**
Lung functions	
FVC	**Mean 70.8 ± 26.2**
FEV1	**Mean 66.2 ± 26.5**
Ratio	**Mean 79.9 % SD11.4**
DLCO	**Mean 14.0 ± 5.2**
Sarcoid Lung stage	
I	**4 (9.5%)**
II	**29 (69%)**
III	**4 (9.5%)**
IV	**5 (11.9%)**
Co-morbidities	
Diabetes	**2(4.7%)**
Hypertension	**1(2.3%)**
Previous PTB	**2(4.7%)**
COPD	**1(2.3%)**
HIV	**2(4.7%)**
Smoking	
Current	**3(7.1%)**
Previous	**6(14.2%)**

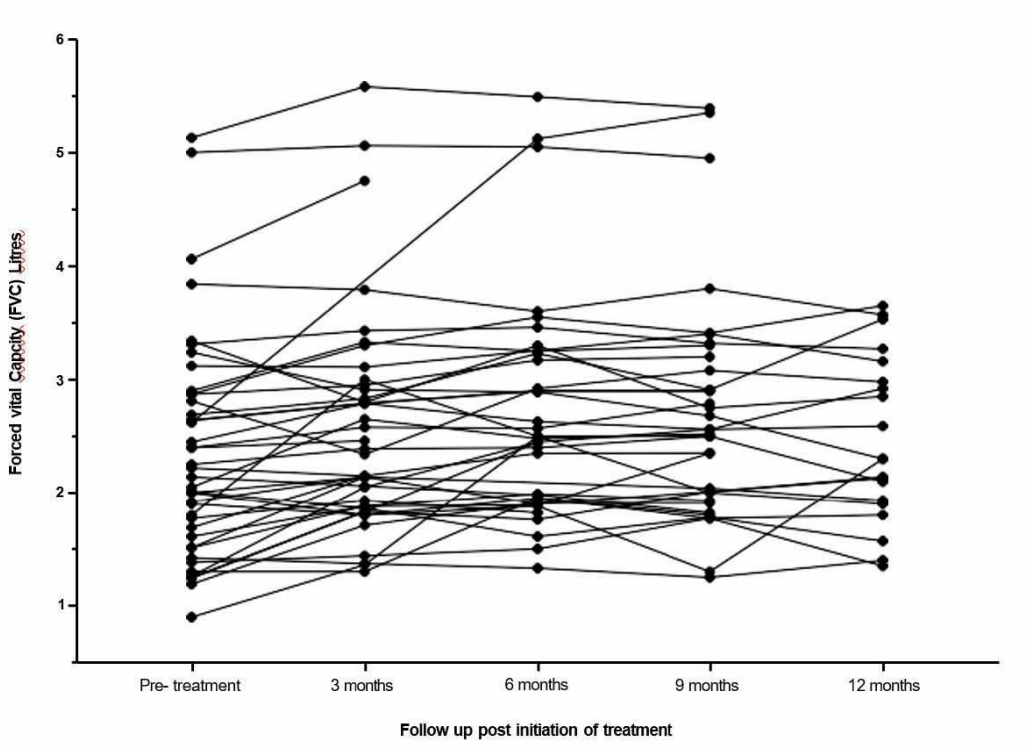
No standard protocol was used to initiate therapy for active pulmonary sarcoidosis. The most common starting dose was 30mg of prednisone with a range of [20mg-40mg] for at least one month, with a tapering reduction of roughly 5mg per week. 90% of patients were on treatment for at least six months. The baseline weight of patients starting oral corticosteroids was a mean (SD) of 72.9(15.7) kg. at 9 months mean (SD) weight was 81.1(16.6) kg with a mean weight gain of 8.3(7) kg. The largest single gain in weight was 23kg (82kg to 105kg)

Lung function

Baseline line lung function was recorded for all patients prior to initiation of corticosteroids. Follow-up lung function was available for 42 patients at 6 months, 38 patients at 9 months, and only 20 at 12 months. Statistical analysis was only performed to 9 months given the less than 50% of the cohort having lung function at 12 months.

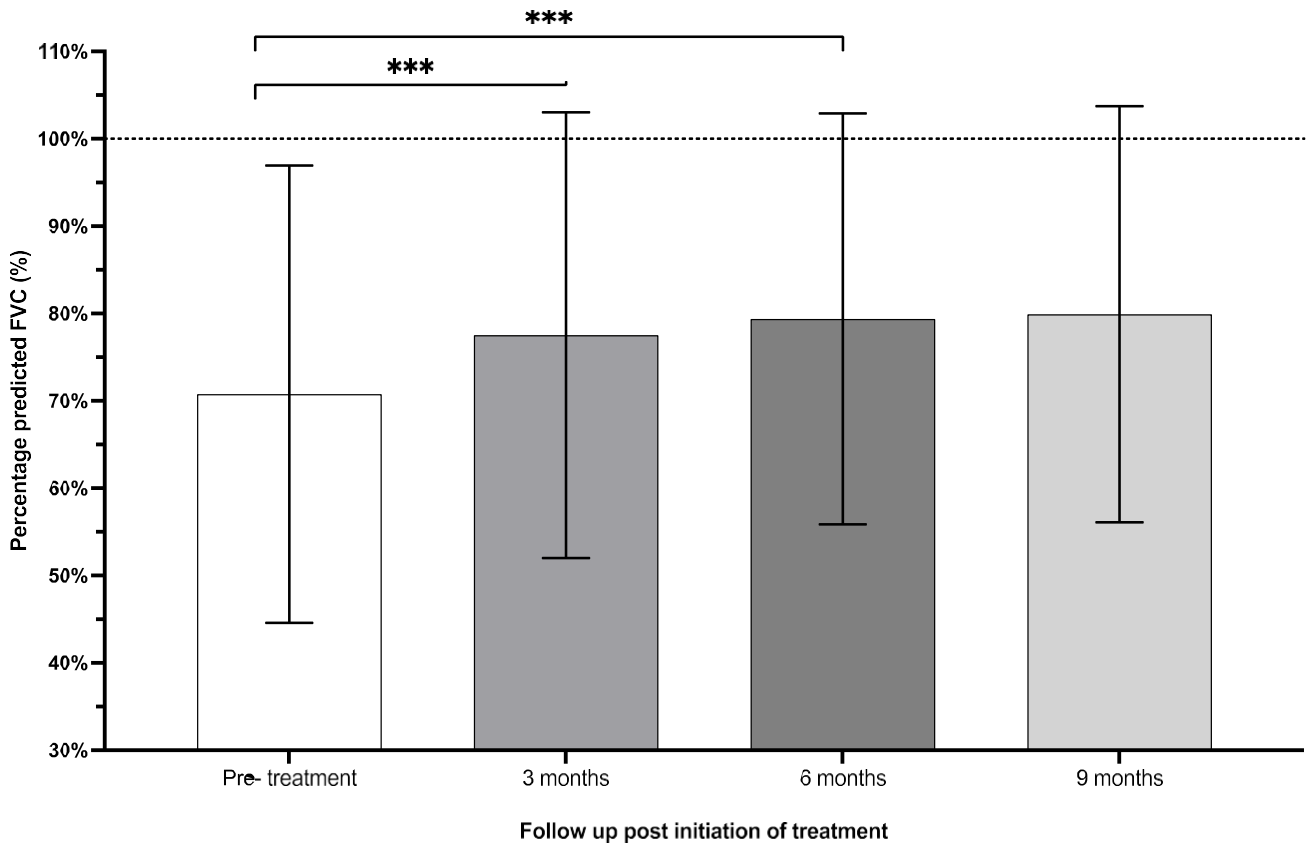
The mean (SD) FVC at baseline was 70.8(26.2) % predicted. Mean baseline DLCO was 14.0 ± 5.2 % of predicted. Overall, the change in lung function was positive for the majority of patients but with significant individual variability. (Figure 1)





(Figure 1 A, B) Individual plots of FVC and % predicted FVC over time for all patients with pulmonary sarcoidosis initiated on treatment with systemic corticosteroids.

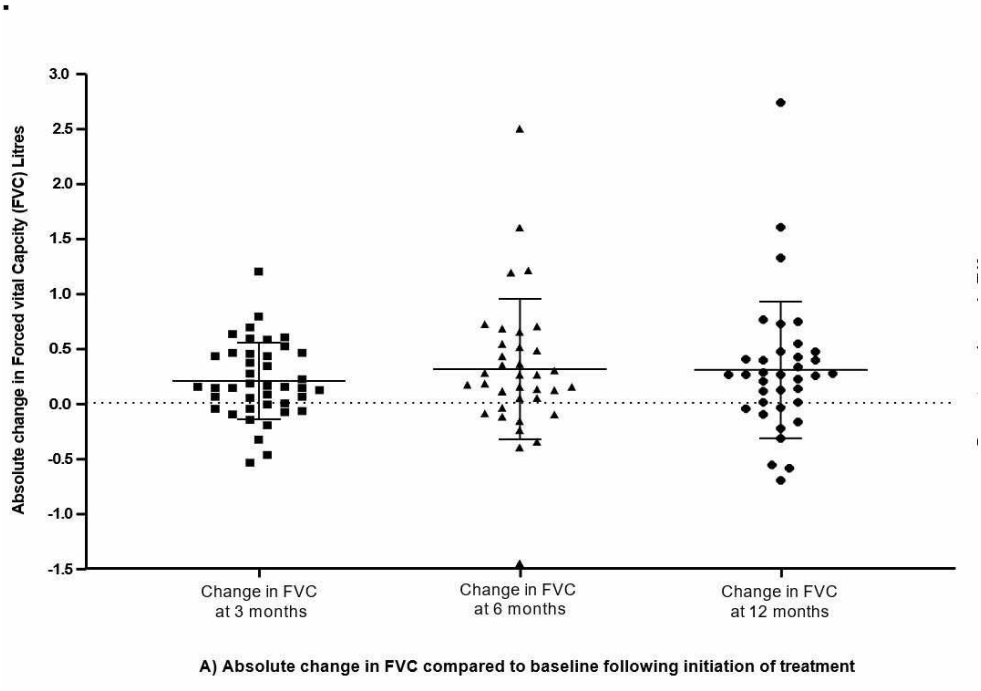
Following initiation of systemic oral corticosteroids, all patients' mean (SD) FVC improved from 2.35L to 2.55L at 3 months, to 2.68L at 6 months, and 2.69L at 9 months.



(Figure 2) Change in Forced Vital Capacity of patients initiating systemic corticosteroids.

*****P<0.001 compared to pre-treatment values**

Following initiation of systemic oral corticosteroids, the mean (SD) change in FVC per patient was + 0.205(0.346) L with a coefficient of variation(cv) of 196% at 3 months; + 0.311(0.639) L, (cv) 206% at 6 months and + 0.303(0.621) L, (cv) 205% at 9 months.



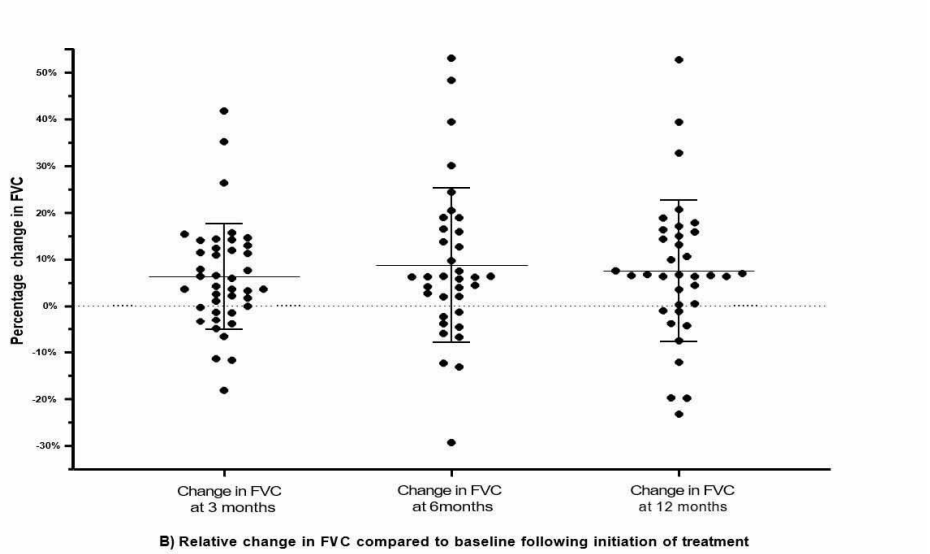


Figure 3 A/B Change in Forced Vital Capacity (absolute Fig A) Percentage predicted (Fig B) from baseline to 3, 6 and 12 months

The mean (SD) change in percentage predicted FVC was 6.3(11.4) % at 3 months, 8.7(15.5)% at 6 months, and 7.5(15.2)% at 9 months.

The DLCO increased from baseline through to 6 months (figure 4). Baseline mean DLCO was 57.6(24.85) % predicted. At three months, this had improved to 61.0(33.0) % and to 68.9(28.1)%

predicted. (p<0.001). Insufficient patients had documented DLCO at 9 months to conduct a meaningful repeated measure ANOVA.

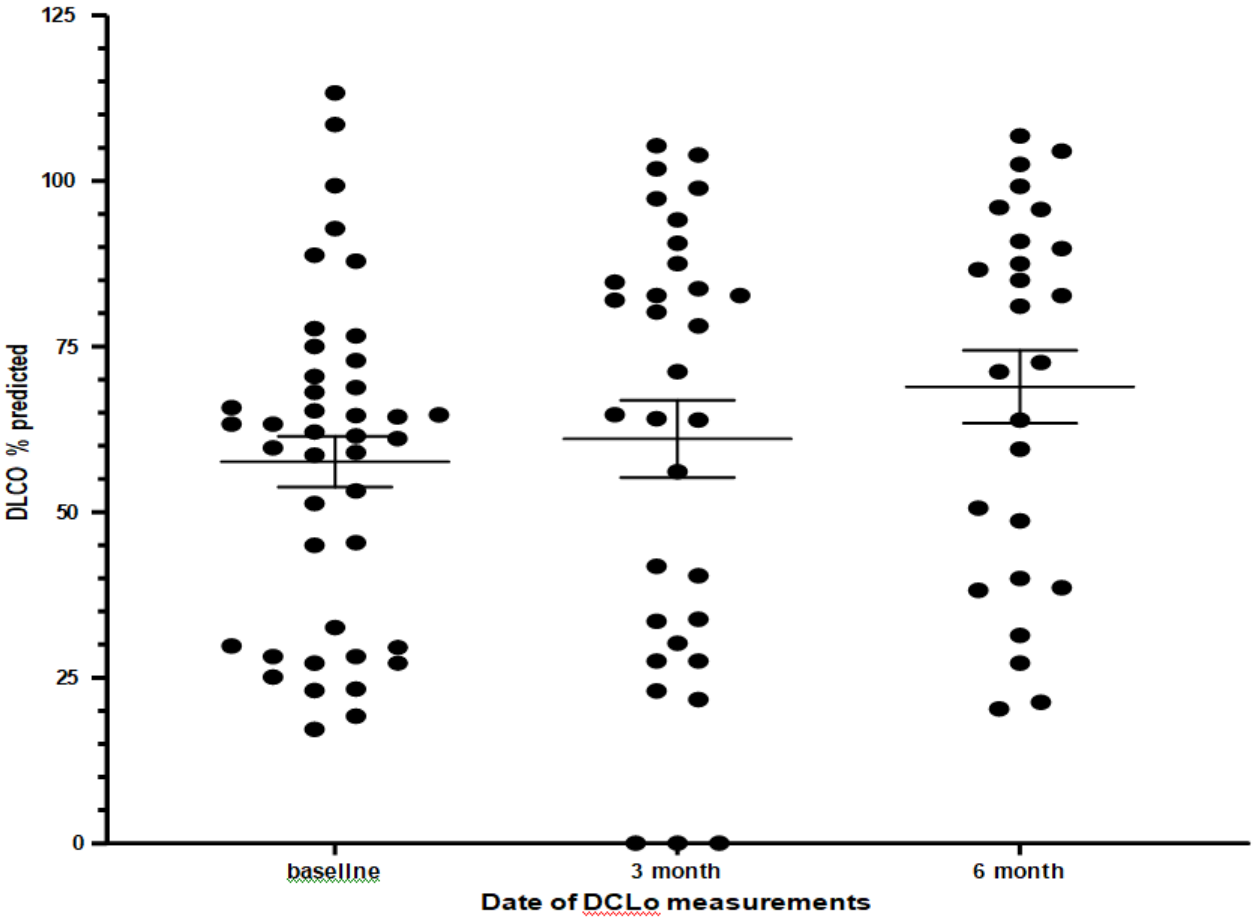


Figure 4 Change in DCLO Percentage predicted from baseline to 3, 6 months. (Mean (SEM))

Discussion

In interpreting these findings, it is important to consider that a clinically meaningful improvement in FVC in patients with interstitial lung diseases, including sarcoidosis, is generally accepted to be an increase of at least 5% of the predicted value. Therefore, the observed changes in FVC in this study may reflect a clinically relevant response to corticosteroid therapy.

This cohort of patients with pulmonary sarcoid showed a modest improvement in lung function with a mean improvement in a Forced Vital Capacity (FVC) of 205ml (mean change 6.3 ± 11.3%, $p<0.001$) at 3 months with significant variability in individual response. Improvement was seen to 9 months, suggesting that prolonging treatment to at least 6 months can result in Forced Vital Capacity (FVC) and DLCO improvement to 9 months. Individual patient responses are highly variable, and further research is needed to understand corticosteroid-related lung function improvement predictors.

It is well-established that patients with early-stage pulmonary sarcoidosis (stage I–III), particularly those with active granulomatous inflammation and preserved lung architecture, are more likely to respond to corticosteroid therapy compared to those with stage IV disease, where fibrosis predominates and reversibility is limited. In our cohort, the majority of patients had radiologic findings consistent with stage II or III disease, with no confirmed cases of stage IV fibrotic sarcoidosis. These patients also demonstrated symptoms and pulmonary function impairment indicative of active inflammation, supporting the rationale for corticosteroid initiation. While this was a retrospective study and no management recommendations are made, these patient characteristics are important when considering the expected treatment response and help inform the clinical relevance of our findings.

Our study showed similar results in a cohort done by Broos C *et al* [10]. In this multicenter, prospective, observational study, conducted to assess the early treatment response to prednisone in newly treated pulmonary sarcoidosis patients, a cohort of 21 treatment-naïve individuals, predominantly diagnosed with Scadding stage II sarcoidosis[10], underwent a 10-week prednisone regimen with a tapering dosage. Results demonstrated a significant improvement in Forced Vital Capacity (FVC), with a maximal mean increase of 9.7% predicted within the initial 24 days, plateauing at this improvement by day 18, consistent with the other studies9.The major increase in FVC occurred during the first month of prednisone treatment. Additionally, in a sub- cohort, the lung's diffusing capacity for carbon monoxide (DLCO) showed a significant increase within the first month, though a slight decrease was observed between months 1 and 3.[13] In our cohort, one–month spirometry was not readily available, and thus, early changes before month three were not identifiable.

There is a significant lack of research on sarcoidosis patients in South Africa. There have been limited studies conducted to examine the complexities of sarcoidosis in this population. In addition, there is a paucity of data originating from Africa and other low-income settings, which limits our complete knowledge of the disease in these communities. This lack emphasizes the urgent need for further comprehensive research efforts focused on understanding the distinct symptoms and difficulties experienced by sarcoidosis patients in these situations.

Few studies have been conducted on South African patients with sarcoidosis *R Morar et al*[14] , *Alwood et al*[15] and *Bentar et al* [16], none of these trials specifically examined the effects of steroids on active pulmonary sarcoidosis. One of the consequences of steroid treatment seen in this particular cohort was significant weight gain. The majority of patients had significant weight gain, with a mean of 8 kg. The potential for diabetes, respiratory infection, and cardiovascular complications were not specifically studied in this group but are of concern, given the prolonged courses of steroids used in patients with sarcoidosis.

In a recent publication, the SARCORT trial led by S. Dhooria et al 4, had Investigated the efficacy of high-dose corticosteroid therapy (40 mg of prednisone) compared to a low-dose regimen (20 mg of prednisone)

in treating sarcoidosis. The mean improvement in FVC at 6 months was 6.3±1.5
% predicted in high dose group (40 mg of prednisone), and 5.2±1.3 % predicted in low dose group (30 mg of prednisone). In our cohort, the mean improvement in FVC at 6 months was 8.7(15.5) %, which is similar to the high-dose group (40 mg of prednisone). In our cohort, no
formal regimen of steroids was used for all patients, and thus, it is difficult to be certain of the magnitude of the effect based on dosing. However, the improvements in lung function of around 5-6% is consistent with this study.

Study limitations

Our study was conducted at a specialized sarcoidosis management center and, although small, is one of the largest cohorts published from a low- middle-income country (LMIC). However, notable limitations exist, primarily related to the retrospective nature of the study and reliance on registry data. This design introduces inherent challenges, such as missing data and loss of follow-up. Oral corticosteroid dosing lacked standardization based on weight, and decision points were not consistently well-documented due to the absence of standardized recording for symptoms and side effects. Additionally, the study did not incorporate adherence measures to verify the consumption of prescribed doses, thus reflecting a pragmatic "real-world" scenario.

Conclusion

Among patients with sarcoidosis requiring immunosuppression therapy, oral prednisone improved FVC and DLCO, with most of the effect on FVC occurring within 3 months after initiation. Weight gain positively correlated with cumulative prednisone dose over 9 months. The optimal duration and dose of corticosteroids remain unclear. Side effects should be weighed up against an expected mean FVC improvement of only 6%.

Acknowledgments

None

Competing Interests

The authors declare no competing interest that may have influenced the study and writing of this manuscript.

Author Contributions

SE overlooked data collection, processed the data, and wrote the manuscript drafts. ME and SE assisted with data collection. RVZS reviewed all the data for the patients and reports. RVZS conceptualized the idea and performed the final review and revision.

Funding Information

Not applicable.

Data Availability

Raw data was generated at Groote Schuur Hospital. The corresponding author makes data derived from the study available upon request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agenda of the authors.

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Human Research Ethics Committee Approval

UNIVERSITY OF CAPE TOWN
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Human Research Ethics Committee

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21 July 2023

HREC REF: 488/2023

Prof R van Zyl-Smit
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Dear Prof van Zyl-Smit

PROJECT TITLE: THE EFFECT OF INITIATING CORTICOSTEROIDS ON LUNG FUNCTION AND SYMPTOMS IN PATIENTS WITH ACTIVE PULMONARY SARCOIDOSIS-LINKED TO R007/2021-MPHIL CANDIDATE-DR SALAHEDDIN EKNEWIR

Thank you for your response letter addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 July 2024.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Salaheddin Eknewir will also be involved in this study.

Please quote HREC REF 488/2023 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies that receive ethical approval the principal investigator **must** obtain appropriate institutional approval, prior to any changes in the study can occur.

Yours sincerely

PROFESSOR M Blo
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research

Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

South African Medical Journal (SAMJ): Author Guidelines

Submission Process

The SAMJ has launched a new submission and tracking system. Authors must **register a profile** on the platform to submit manuscripts.
To submit a manuscript, go to: https://samajournals.co.za/index.php/samj

Note: Manuscripts not conforming to the specified format will be returned for correction, delaying publication.

General Formatting Requirements

- Use **UK English** throughout the manuscript.
- Submit manuscripts in **Microsoft Word** format.
- Use **12-point Times New Roman**, single-spaced, with no text boxes or unnecessary formatting.
- Be concise—even if under the word limit.
- Include **qualifications, full affiliations** (department, school/faculty, institution, city, country), and **contact details of all authors**.
- Spell out **abbreviations** on first use (e.g. 'intravenous (IV)', 'Department of Health (DoH)').
- Include the following sections, as applicable:
    - Acknowledgements
    - Conflict of Interest
    - Author Contributions
    - Funding Sources
      (If none apply, please state "None")
- Use **SI units** for scientific measurements, except for:
    - Blood pressure: mmHg
    - Haemoglobin: g/dL
- Use an **uppercase "L"** for litres (e.g. "mL").
- Insert a **space before units** (e.g. 40 kg, 20 cm), but not before % or °C (e.g. 50%, 19°C).
- Use **proper symbols** (e.g. μ not u; α not a; β not B).
- Group numbers by thousands (e.g. 4 000; 22 160).
- Use **single quotation marks** for quotes: 'The respondent stated:...'
- Use **round brackets** for all purposes, reserving square brackets for insertions in quotes or concentrations.
- For boxed content, indicate in the text; you may use tables—**do not** use borders or fills.

Genetics-Specific Guidelines

- Italicise **gene symbols**, but not proteins/enzymes/hormones.
- Use correct case for genes (e.g. **TP53**, not Tp53).
- Define genetic terms at first use (e.g. "an 11 bp deletion at nucleotide 188").
- Use up-to-date nomenclature from:
    - HGMW
    - HUGO Gene Nomenclature Committee
    - OMIM
    - Bennett et al. (2008) for pedigree nomenclature

Research Articles

Word Limit: 4 000 words

Structure:

1. **Abstract** (Structured, 250–400 words):
    - **Background:** Context and rationale
    - **Objectives:** Study aim
    - **Methods:** Design, participants, interventions, outcomes, analysis
    - **Results:** Start with sample description, present primary results
    - **Conclusion:** Based on findings; include recommendations

      No references in the abstract.

2. **Main Article Sections:**
    - Introduction/Background (max 3 paragraphs)
    - Methods
    - Results
    - Discussion
    - Conclusion
3. **Within these sections, include (as applicable):**
    - **Objectives:** Clear aim and hypothesis/research question
    - **Design:** E.g. prospective, randomised, controlled
    - **Setting:** E.g. primary/secondary care, number of sites
    - **Participants:** Include demographics, eligibility, and exclusion criteria
    - **Interventions:** Detail type, duration, administration
    - **Outcome Measures:** As defined in protocol

Results Section

- Begin with description of study population.
- Include 95% confidence intervals, statistical significance, number needed to treat/harm.
- Prefer **absolute** over relative risks.
- Do **not** duplicate data in tables and text.

Discussion

Structure your discussion clearly:

- Principal findings
- Study strengths and limitations
- Comparison with other studies
- Clinical and policy implications
- Unanswered questions and future research directions
  Subheadings are not required.

Conclusion

This section may be the most read—make it clear and strong.

- State primary conclusions and implications.
- Stay within the bounds of your data.

Illustrations / Images

- Previously published illustrations must have copyright permission.
- Number figures in Arabic numerals (e.g., Fig. 1).
- Include legends for each figure, e.g., *Fig. 1. Description (include abbreviations in full)*.
- Submit high-resolution images in **JPEG or PDF** formats.
- Label all axes in graphs clearly and avoid unnecessary decimal places.
- Use arrows in clinical images/scans to highlight features.
- Upload each figure separately as a ‘Supplementary file’ (not embedded in Word document).

Tables

- Keep tables **simple and clear**.
- Large tables may be published as addenda upon request.
- Embed tables in the manuscript Word file (not separately uploaded).
- Use **editable, cell-based** tables (not tabs or text boxes).
- Number tables (e.g., Table 1, Table 2) and refer to them in order in the text.
- Title each table; use column headings with units.

References

- Use **Vancouver style**.
- Create the reference list **manually**—**do not use EndNote or other citation software**.
- Verify references from original sources.
- Insert citations as **superscript** numbers in square brackets: *e.g., "These findings have been confirmed previously.[1,3]"*
- List references in the order of appearance (not alphabetically).
- Include:
    - Full author names (first 3 + *et al.* if more than 6)
    - Article title, abbreviated journal name
    - Year; Volume(Issue):Page range
    - DOI if available

Examples:

- **Journal:**
  Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. *Stat Med* 1998;289(1):350-355. https://doi.org/10.1000/hgjr.182
- **Book:**
  Jeffcoate N. *Principles of Gynaecology*. 4th ed. London: Butterworth, 1975:96-101.
- **Chapter:**
  Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. *Pathologic Physiology: Mechanisms of Disease*. Philadelphia: WB Saunders, 1974:457-472.
- **Internet:**
  World Health Organization. *The World Health Report 2002 – Reducing Risks, Promoting Healthy Life*. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010)

Publication: Online vs Print

Online:

- The official version with widest reach.
- Indexed in PubMed, SciELO, and academic libraries.
- Full-text articles are published **open access**.
- Include online links, images, data, or video.

Print:

- Not all articles will be selected.
- Selection for print may differ in month from online publication.
- **Only abstracts** of research articles appear in the printed edition.