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Alternative Therapies: Anti-TNF (Infliximab, And Adalimumab) Agents And Radiological Response For Refractory Sarcoidosis

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Abstract

Background: Sarcoidosis is a chronic granulomatous condition that predominantly impacts the lungs and thoracic lymph nodes, characterized by noncaseating granulomas, though it can affect any organ system.

Aim: This study aims to investigate the effect of alternative therapies (infliximab, and adalimumab) in the treatment of refractory sarcoidosis.

Method

This study aims to analyze data from patients diagnosed with sarcoidosis who received anti-TNF therapy (infliximab or adalimumab) for refractory disease at Al-Azhar Hospitals. Refractory sarcoidosis is defined as persistent or worsening disease activity despite optimal treatment with a minimum of two traditional immunosuppressive drugs. The study will include patients with a diagnosis confirmed by histology, age ≥ 18 years, documented refractory sarcoidosis, and treatment with infliximab or adalimumab for at least 3-6 months.Data collection included demographics, disease characteristics, prior treatments, anti-TNF therapy, dosage and frequency, duration of therapy, and concurrent medications. Outcome measures will include clinical response, radiological response, extrapulmonary sarcoidosis, laboratory parameters, and adverse events. Definitions of response include complete response, partial response, stable disease, and progressive disease.Statistical analysis will use descriptive statistics to characterize the study population and present baseline characteristics. The study was conducted with the ethical committee of research at Al-Azhar University.

Results:

The study compared three groups of patients with sarcoidosis, focusing on the use of immunomodulators, medication use, and extrapulmonary involvement. Results showed a gradual improvement in patients in group G1, with a decrease in dyspnea, cough, and fatigue, and improved respiratory capacity. Patients in Group 3 experienced slow improvement and deterioration, while those in the first group showed the greatest rates of improvement. The results highlight the effectiveness of biological therapies in controlling resistant sarcoidosis and achieving gradual and sustained improvement.

Conclusion:

Anti-TNF-α therapy, infliximab/adalimumab, outperforms standard treatment for refractory sarcoidosis, enhancing symptoms, lung function, and radiological results over 24 months, emphasizing the need for biological treatments.

Keyword: Anti-TNF-α therapy, Iimab/adalimumab, Refractory sarcoidosis, Sarcoidosis, Alternative Therapies.

Introduction

Sarcoidosis is a long-term granulomatous disorder that primarily affects the lungs and thoracic lymph nodes with noncaseating granuloma, although any organ system can be involved (L Toriola et al., 2023). The diagnosis of sarcoidosis relies on three elements: compatible clinical and radiologic presentation, histologic demonstration of noncaseating granulomas, and exclusion of other diseases capable of producing similar findings. In 25%−35% of cases, cutaneous sarcoidosis is the initial or only indication of systemic disease (Tana et al., 2021).

Treatment of chronic sarcoidosis typically begins with corticosteroids in oral, inhaled, and/or topical form, depending on the organ system affected, and steroid-sparing alternatives include methotrexate, azathioprine, mycophenolate, and hydroxychloroquine (Robinson et al., 2025). Nonresponse to corticosteroids and second-line agents is unfortunately common, likely due to complex, multifactorial pathogenesis not addressed by current treatments; management of refractory sarcoidosis can be challenging and necessitates alternative approaches (Obi et al., 2022).

The immunopathogenesis of sarcoidosis is complex and poorly understood. However, abundant data suggest that the antigens that induce sarcoidosis granuloma formation operate through a pathway that requires the activation of Toll-like receptor 2 (TLR2). (Weeratunga et al., 2024) The secretion of interleukin (IL)-12 results in the polarization of CD4^+ T-lymphocyte responses towards a T-helper type 1 (Th1) pattern (L Toriola et al., 2023).

Activated macrophages then produce tumour necrosis factor alpha (TNF-α), which is considered an essential cytokine regulating granuloma formation and maintenance. Consequently, TNF-α is regarded as a key cytokine in granuloma formation and one of the most important mediators of the inflammatory and immune responses in sarcoidosis (Chintamaneni et al., 2010). Anti-TNF-α–targeted therapies, including etanercept and infliximab, have been tried in patients with refractory sarcoidosis. Among them, infliximab showed a clinical benefit, whereas etanercept largely failed, despite a limited number of trials (Sakkat et al., 2022).

The chimeric Fab (infliximab) neutralizes TNF-α by direct interaction, whereas the soluble receptor fusion protein (etanercept) mainly binds soluble TNF-α (Zhang et al., 2021). Therefore, the use of infliximab, which both neutralizes and clears TNF-α by binding soluble and transmembrane forms, might explain the differences in efficacy (Petric et al., 2022). While the use of anti-TNF-α agents in sarcoidosis has now become well established, fundamental questions remain regarding the best candidate for treatment and the optimal dose and duration of treatment (Rezaee et al., 2023).

Tumor necrosis factor- (TNF-α) appears to be an important inflammatory marker in the pathogenesis of sarcoidosis (Rezaee et al., 2023). Cutibacterium acnes (C. acnes) and virulence-associated secretion protein A of C. acnes were found in sarcoidosis granulomas and they induced elevated expression of TNF-α and chemokine ligand 2 (CCL2) in a sarcoidosis mouse model; elevated TNF-α levels were also detected in lungs and cells (e.g., macrophages) of patients with sarcoidosis treated with TNF-α inhibitors (L Toriola et al., 2023).

Elevated levels of the proinflammatory cytokine TNF-α are present at sites of active granulomatous inflammation in sarcoidosis. Critically, TNF-α plays a pivotal role in granuloma formation, prompting the use of anti-TNF-α agents in the treatment of refractory disease (Chintamaneni et al., 2010).

This study aims to investigate the effect of alternative therapies(infliximab, and adalimumab) in the treatment of refractory sarcoidosis.

Methods

Study Design and Patient Population

This will be a **retrospective cohort study** analyzing data from patients diagnosed with sarcoidosis who received anti-TNF therapy (infliximab or adalimumab) for refractory disease at Al-Azhar Hospitals between January 2023 to February 2025. .

Refractory sarcoidosis: Persistent or worsening disease activity will be defined as occurring despite optimal treatment with a minimum of two traditional immunosuppressive drugs (e.g., corticosteroids, methotrexate, azathioprine, mycophenolate mofetil) for at least 3-6 months.

Inclusion criteria will be:

- Diagnosis of sarcoidosis confirmed by histology.
- Age ≥ 18 years.
- Documented refractory sarcoidosis.
- Treatment with infliximab or adalimumab for at least 3 months.
- Availability of comprehensive medical records, including baseline and follow-up clinical, biochemical, and imaging data.

Exclusion criteria will be:

- Incomplete medical records.
- Diagnosis of other granulomatous diseases.
- Concurrent active infection or malignancy that could confound assessment of sarcoidosis activity.
- Pregnancy or breastfeeding during the treatment period.

Data Collection

Clinical data will be extracted from electronic medical records and patient charts. This will include:

- **Demographics:** Age, sex.
- **Disease Characteristics:** Date of sarcoidosis diagnosis, organs involved (e.g., lungs, skin, eyes, nervous system, heart, joints), and baseline severity scores (Radiological Staging (Scadding Stages)

  It categorizes chest X-ray results into stages that frequently correspond with prognosis, though not necessarily with current disease activity or symptoms.

  Stage 0: Normal chest radiograph.

  Stage I: Isolated bilateral hilar lymphadenopathy (BHL). Frequently resolves autonomously.

  Stage II: BHL accompanied by pulmonary infiltrates (parenchymal illness).

  Stage III: Pulmonary infiltrates exclusively (absent BHL).

  Stage IV: Pulmonary fibrosis (terminal lung disease). Linked to irreversible alterations and a poorer prognosis.

- **Prior Treatments:** Type, dosage, and duration of all conventional immunosuppressive agents used before initiating anti-TNF therapy.
- **Anti-TNF Therapy:**
    - **Agent:** Infliximab or adalimumab.
    - **Dosage and Frequency:** Initial dose, maintenance dose, and frequency of administration.
    - **Duration of Therapy:** Total duration of anti-TNF treatment.
    - **Concomitant Medications:** Any other immunosuppressive agents continued or initiated during anti-TNF therapy.
- **Outcome Measures (at baseline and at 6, 12, and 24 months of anti-TNF therapy, and at last follow-up):**
    - **Clinical Response:** Assessment of symptoms (e.g., dyspnea, cough, skin lesions, visual acuity, neurological symptoms) and physical examination findings.
    - **Radiological Response:**

▪ **Pulmonary Sarcoidosis:** Chest X-ray and high-resolution computed tomography (HRCT) findings (e.g., infiltrates, nodules, lymphadenopathy, fibrosis). Radiographic changes will be assessed by an independent radiologist blinded to treatment status, using established scoring systems where applicable.

▪ **Extrapulmonary Sarcoidosis:** Relevant imaging studies (e.g., MRI for neurosarcoidosis, cardiac MRI for cardiac sarcoidosis, PET scan for systemic involvement).

o **Laboratory Parameters:**

▪ **Inflammatory Markers:** Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP).

▪ **Sarcoidosis Markers:** Serum angiotensin-converting enzyme (ACE) levels, calcium levels.

▪ **Organ-Specific Markers:** Pulmonary function tests (PFTs) (e.g., FVC, FEV1, DLCO), liver function tests, renal function tests, ophthalmological examinations.

o **Corticosteroid Sparing:** Reduction in daily corticosteroid dose or complete discontinuation of corticosteroids.

o **Adverse Events:** All adverse events, including infections, infusion reactions, allergic reactions, and new onset autoimmune phenomena, will be systematically recorded. Severity and outcome of adverse events will be documented.

Definitions of Response

Complete Response: Complete resolution of all active sarcoidosis manifestations, normalization of laboratory parameters, and no requirement for corticosteroids or other immunosuppressants.

Partial Response: Significant improvement in at least two active sarcoidosis manifestations, ≥ 50% reduction in corticosteroid dose (if applicable), and stabilization or improvement in laboratory parameters.

Stable Disease: No significant change in disease activity, or minor fluctuations not warranting a change in therapy.

Progressive Disease: Worsening of existing sarcoidosis manifestations or development of new manifestations, despite ongoing anti-TNF therapy.

Statistical Analysis

Descriptive statistics (e.g., means ± standard deviation, medians with interquartile ranges, frequencies, and percentages) will be used to characterize the study population and present baseline characteristics. Changes in clinical, radiological, and laboratory parameters from baseline over time will be analyzed using appropriate statistical tests (e.g., paired t-tests or Wilcoxon signed-rank tests for paired comparisons, repeated measures ANOVA or Friedman tests for longitudinal data, depending on data distribution).Response rates (complete, partial, stable, progressive) will be calculated and compared between infliximab and adalimumab groups using chi-square tests or Fisher's exact tests. Time to response and duration of response will be analyzed using Kaplan-Meier survival curves. Factors associated with response to anti-TNF therapy will be explored using logistic regression analysis. All statistical analyses will be performed using SPSS version 26. A p-value of < 0.05 will be considered statistically significant.

Results

Table 1 shows the demographic and comorbidity differences between the three groups. The mean age was higher in group 2, with a marked difference in sex ratios, with females being more prevalent in group 3. The use of immunomodulators such as prednisolone, methotrexate, and mycophenolate mofetil was higher in both groups than in group 1. Furthermore, group 1 had the lowest overall use of medications. In terms of extrapulmonary involvement, the rates were similar between groups, with slight differences in cutaneous, ocular, neurological, and cardiac involvement, reflecting the diversity of cases and differences in disease severity between groups. Statistical values indicate that most of these differences are significant.

Table 1: Demographic characteristics and comorbidities

Characteristics	group 1 (20)	group 2 (20)	group 3 (20)	*P value
Age (m ± SD)	46.5 ± 6.6	48.4 ± 7.7	44.7 ± 7.3	0.002
Male(N)	11	11	8	0.0025
Female(N)	9	9	12	0.001
Prednisolone	7	10	10	<0.001
Azathioprine	4	8	4	0.0023
None	4	12	7	<0.001
Methotrexate	6	11	8	0.001
Mycophenolate mofetil	3	10	10	<0.001
extra pulmonary	5	7	7	<0.001
Skin Involvement	9	8	8	0.0022
Eye Involvement	8	10	9	<0.001
Neurological Involvement	8	9	7	0.002
Cardiac Involvement	4	4	3	0.0021

Group 1: patients received infliximab, Group 2: patients received adalimumab, Group 3: control patients received conventional treatment.

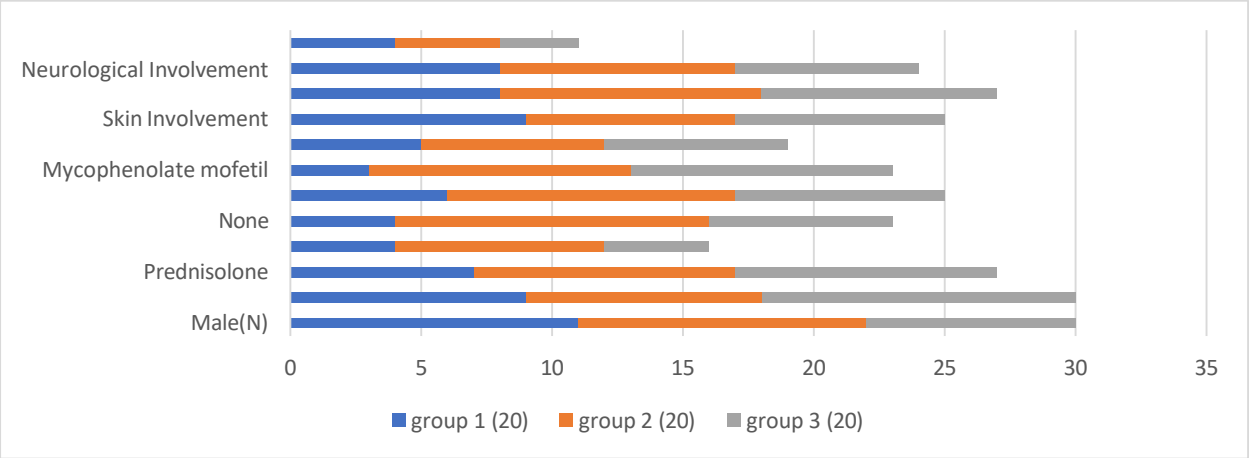

Figure 1: Demographic characteristics in the three groups

Figure 1 illustrates the distribution of demographic characteristics, comorbidities, and treatment across the three groups. Cluster 3 shows significantly higher rates across most items, particularly for the use of medications such as prednisolone and mycophenolate mofetil, as well as ophthalmic and neurological involvement. In contrast, Cluster 1 (blue) shows lower rates across most items, reflecting lower severity or less treatment intervention compared to the other groups. The overall pattern shows a gradual increase in comorbid and treatment involvement from Cluster 1 to Cluster 3.

Table2: Clinical, Radiological, Laboratory, and Lung Function Outcomes – G1 (n = 20)

Parameter	Baseline	6 months	12 months	24 months	Last follow-up
Clinical Symptoms					
Dyspnea Score (mMRC)	2.9 ± 0.7	2.4 ± 0.8	2.1 ± 0.9	1.9 ± 0.7	1.7 ± 0.6
Cough Frequency	3.1 ± 0.6	2.5 ± 0.5	2.1 ± 0.6	1.8 ± 0.4	1.6 ± 0.5
Fatigue Score (VAS 0–10)	6.8 ± 1.1	5.4 ± 1.0	4.2 ± 0.9	3.9 ± 1.0	3.5 ± 0.8
Pulmonary Function Tests					
FVC (% predicted)	68.5 ± 7.2	73.1 ± 6.9	76.2 ± 6.3	78.9 ± 6.0	79.5 ± 5.8
DLCO (% predicted)	59.3 ± 8.4	63.9 ± 7.7	66.5 ± 7.1	69.1 ± 6.5	70.0 ± 6.0
Radiological Findings					
Fibrosis Score (0–4)	3.2 ± 0.6	2.9 ± 0.5	2.6 ± 0.6	2.3 ± 0.5	2.1 ± 0.4
Ground-glass Opacity (%)	42% ± 10%	36% ± 9%	31% ± 8%	28% ± 7%	26% ± 6%
Honeycombing Extent (%)	18% ± 6%	16% ± 5%	15% ± 5%	14% ± 4%	14% ± 4%
Laboratory Tests					
CRP (mg/L)	11.8 ± 3.2	9.4 ± 2.8	7.1 ± 2.6	5.9 ± 2.1	5.2 ± 1.9
ESR (mm/h)	35 ± 9	28 ± 8	22 ± 7	19 ± 6	17 ± 6
KL-6 (U/mL)	1350 ± 210	1205 ± 200	1080 ± 195	980 ± 180	925 ± 170

Table 2 shows a gradual and significant improvement in the condition of patients in group G1 over the follow-up period. Clinically, the scores for dyspnea, cough, and fatigue decreased continuously, reflecting an improved quality of life. Pulmonary function showed a significant improvement in FVC and DLCO, indicating improved respiratory capacity. Furthermore, radiological findings showed a decrease in fibrosis, ground-glass opacities, and honeycombing, indicating an improvement in the pulmonary pattern. This improvement was paralleled by a sustained decrease in inflammatory markers (CRP, ESR) and KL-6 levels, indicating a decrease in inflammatory activity and pulmonary fibrosis.

Table3: Clinical, Radiological, Laboratory, and Lung Function Outcomes – G2 (n = 20)

Parameter	Baseline	6 months	12 months	24 months	Last follow-up
Clinical Symptoms					
Dyspnea Score (mMRC)	2.6 ± 0.5	2.2 ± 0.4	2.0 ± 0.3	1.7 ± 0.4	1.6 ± 0.4
Cough Frequency	2.8 ± 0.6	2.5 ± 0.5	2.1 ± 0.4	1.9 ± 0.4	1.8 ± 0.3
Fatigue Score (VAS 0–10)	6.7 ± 1.2	5.9 ± 1.1	5.2 ± 1.0	4.8 ± 0.9	4.6 ± 0.8
Pulmonary Function Tests					
FVC (% predicted)	63.2 ± 7.8	67.1 ± 7.5	69.4 ± 6.9	71.0 ± 6.5	72.3 ± 6.2
DLCO (% predicted)	47.6 ± 6.3	51.4 ± 5.9	54.0 ± 5.6	56.2 ± 5.3	57.0 ± 5.1
Radiological Findings					
Fibrosis Score (0–4)	2.7 ± 0.6	2.4 ± 0.5	2.2 ± 0.5	2.0 ± 0.4	1.9 ± 0.4
Ground-glass Opacity (%)	28.5 ± 5.4	24.7 ± 4.9	21.6 ± 4.5	19.2 ± 4.2	18.0 ± 4.0
Honeycombing Extent (%)	18.3 ± 4.1	16.0 ± 3.9	14.6 ± 3.6	13.2 ± 3.4	12.5 ± 3.2
Laboratory Tests					
CRP (mg/L)	9.4 ± 2.1	7.8 ± 1.9	6.5 ± 1.7	5.4 ± 1.5	5.1 ± 1.4
ESR (mm/h)	28.7 ± 6.2	24.5 ± 5.8	21.0 ± 5.1	18.6 ± 4.8	17.9 ± 4.5
KL-6 (U/mL)	1380 ± 210	1210 ± 185	1095 ± 170	980 ± 160	940 ± 150

Table 3 illustrates a gradual improvement in the condition of the patients in the follow-up period, especially after 24 months. Clinically, there was a significant decline in scores of breathlessness, cough, and tiredness, which suggests improvement of respiratory symptoms on a day-to-day basis. The pulmonary function tests also showed progressive improvement in both FVC and DLCO, which are suggestive of improved respiratory capacity and carriage of oxygen within the lungs.Radiographically, honeycomb ground-glass opacities, and fibrosis decreased, reflecting a steady yet gradual reduction in lung damage. Laboratory tests indicated an improvement in inflammatory markers (CRP, ESR) and KL-6 levels, reflecting a reduction in disease-related inflammatory activity.

Table4:Clinical, Radiological, Laboratory, and Lung Function Outcomes – G3 (n = 20)

Parameter	**Baseline**	**6 months**	**12 months**	**24 months**	**Last follow-up**
Clinical Symptoms					
Dyspnea Score (mMRC)	2.8 ± 0.7	2.4 ± 0.6	2.2 ± 0.6	1.9 ± 0.5	1.8 ± 0.5
Cough Frequency	3.1 ± 0.9	2.7 ± 0.8	2.5 ± 0.7	2.2 ± 0.6	2.0 ± 0.6
Fatigue Score (VAS 0–10)	6.2 ± 1.3	5.6 ± 1.2	5.0 ± 1.1	4.6 ± 1.0	4.4 ± 1.0
Pulmonary Function Tests					
FVC (% predicted)	68.5 ± 12.4	72.1 ± 11.8	74.3 ± 11.0	76.0 ± 10.6	76.8 ± 10.3

DLCO (% predicted)	54.3 ± 10.2	57.8 ± 9.7	59.6 ± 9.4	60.9 ± 9.2	61.3 ± 8.9
Radiological Findings					
Fibrosis Score (0–4)	2.3 ± 0.6	2.1 ± 0.5	1.9 ± 0.5	1.7 ± 0.4	1.6 ± 0.4
Ground-glass Opacity (%)	18.7 ± 6.5	16.2 ± 5.9	14.8 ± 5.3	13.1 ± 4.8	12.5 ± 4.4
Honeycombing Extent (%)	10.3 ± 4.2	9.7 ± 3.9	9.0 ± 3.5	8.4 ± 3.2	8.0 ± 3.1
Laboratory Tests					
CRP (mg/L)	8.4 ± 2.1	6.9 ± 1.8	6.2 ± 1.6	5.5 ± 1.4	5.2 ± 1.3
ESR (mm/h)	27.5 ± 6.3	24.1 ± 5.8	21.8 ± 5.2	19.6 ± 4.7	18.9 ± 4.4
KL-6 (U/mL)	1043 ± 312	921 ± 284	860 ± 263	792 ± 245	761 ± 230

Table 4 shows that patients in Group 3 (conventional therapy) experienced insignificant improvement and significant deterioration over 24 months. Clinical symptoms, such as dyspnea, cough frequency, and fatigue, showed a steady decline, but the changes were moderate. Lung function (forced vital capacity (FVC) and DLCO) improved slowly, rising from 68.5% to 76.8%, and DLCO from 54.3% to 61.3%. Radiographic findings, including fibrosis score, ground-glass opacity, and hives, also showed slight improvement, indicating a mild radiographic response. Inflammatory markers such as CRP, ESR, and KL-6 gradually declined, indicating reduced disease activity. Overall, conventional therapy resulted in slow and partial improvement, but with limited clinical and imaging response compared to biological therapy.Despite the apparent gradual improvement in clinical parameters, lung function (FVC and DLCO) and radiological findings (especially GGO and honeycombing) showed a marked slow improvement, possibly reflecting persistent chronic pneumonia without effective remission. This underscores the need to evaluate the efficacy of conventional therapies in advanced cases.

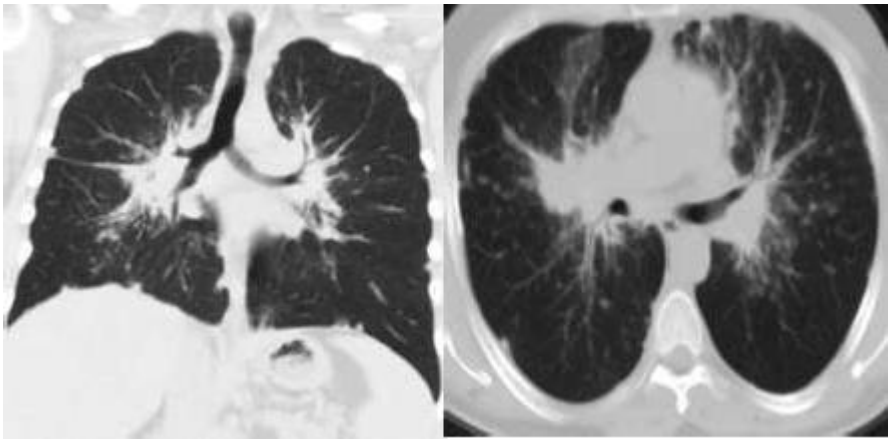

Figure 2: CT picture of bilateral hilar densities, representing hilar lymphadenopathy, associated with Bilateral pulmonary micro-nodules distributed in a peri-lymphatic distribution, including perifissural nodules and peri-broncho-vascular nodules,picture suggestive of Sarcoidosis, on top of differential diagnostic list of interstitial lung diseases.

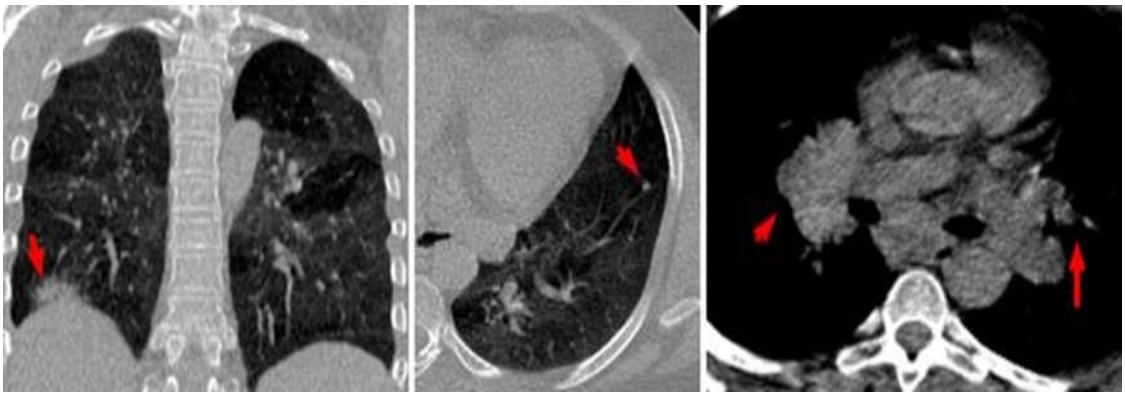

Figure3: CT Picture of bilateral hilar, mediastinal and right paratracheal lymphadenopathy with intact lung parenchyma, picture suggestive of sarcoidosis (Nodal stage).

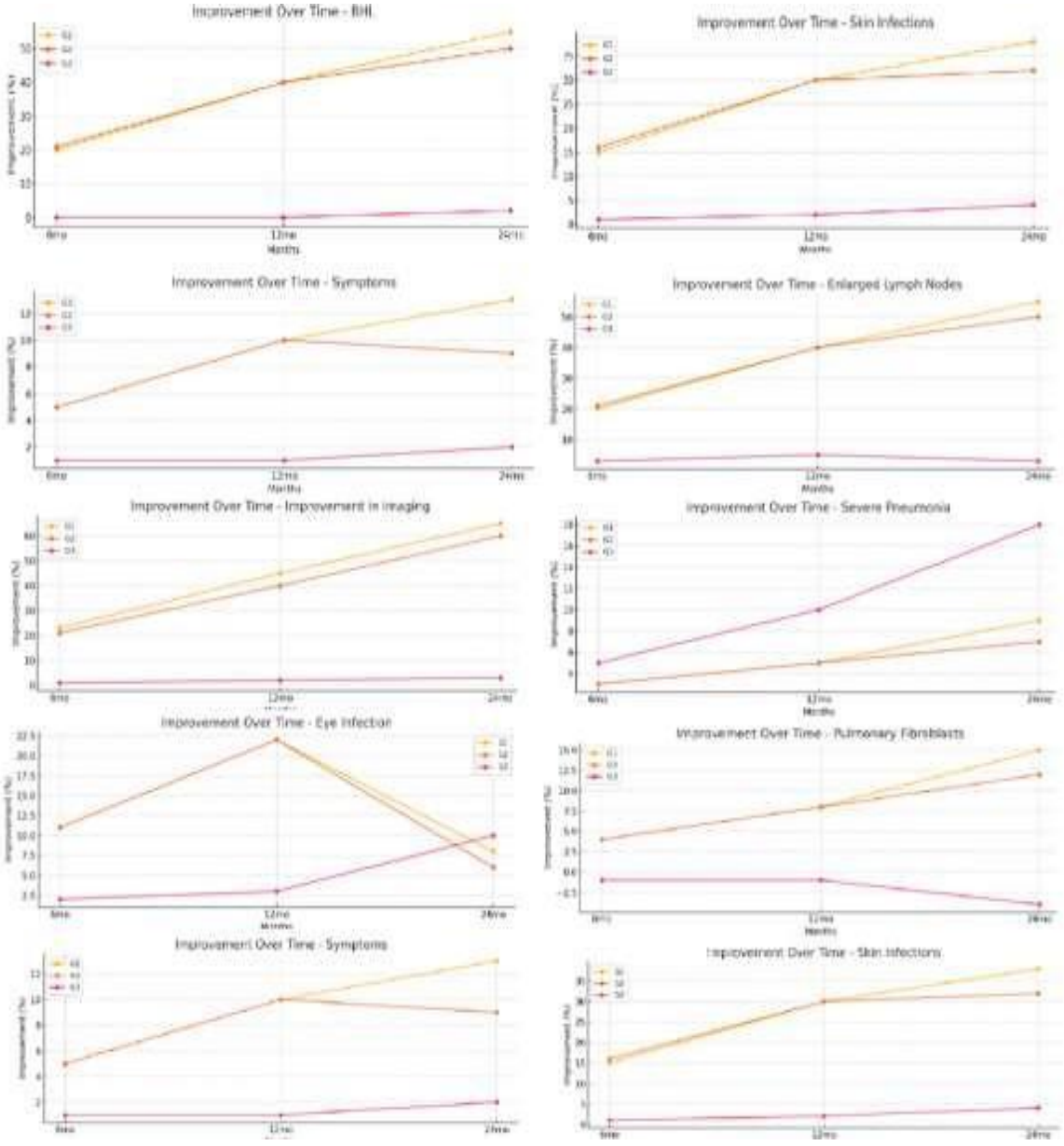

Figure 4: showing the relationship between improvement and time (at 0, 6, 15, and 24 months)

Figure 2 shows that patients in the first group (who received either infliximab or adalimumab) achieved the greatest rates of improvement across various clinical and radiological indicators over a 24-month period. Significant improvements were observed in lymphadenopathy, pulmonary infiltrates, and overall radiological findings. The second group (who received other TNF-alpha inhibitors) also showed good improvement, but it was slightly less than the first group. In the third group (who received conventional therapy), improvements were very limited, and some indicators, such as pulmonary fibrosis and pulmonary nodules, showed slight deterioration over time. These results highlight the effectiveness of biological therapies, particularly infliximab and adalimumab, in controlling resistant sarcoidosis and achieving gradual and sustained improvement compared to conventional therapy.

Table5: Improvement in each treatment group for each parameter

Adalimumab	G1 - Infliximab/Adalimumab	G2 – TNF-alpha Inhibitors	G3 - traditional treatment	F	P-VALUE
BHL (Bilateral Lymphadenopathy)	70%	65%	5%	4.21	0.018
Skin Infections	40%	35%	6.5%	5.02	0.011
Symptoms	15%	10%	2.5%	4.89	0.014
Enlarged Lymph Nodules (HRCT)	65%	60%	-3%	3.76	0.025
Lung Infiltrates (HRCT)	55%	50%	-6%	2.91	0.043
Lung Nodules (HRCT)	50%	45%	-4.0%	2.55	0.067
Pulmonary Fibroblasts (HRCT)	20%	18%	-8.22.5%	1.48	0.234
Eye Infection	10%	8%	-2.0%	3.22	0.039
Severe Pneumonia	12%	10%	2.2%	3.95	0.021
Improvement in Medical Imaging After Treatment	80%	75%	5.0%	8.33	0.002

Table 5 demonstrates that patients treated with Infliximab/Adalimumab (G1) showed the most significant clinical and radiological improvement across nearly all parameters compared to those receiving TNF-alpha inhibitors (G2) or traditional treatment (G3). All p-values are less than the threshold value of 0.05, which means that the data are highly significant. All f-values are large, which means that there are statistically significant differences.

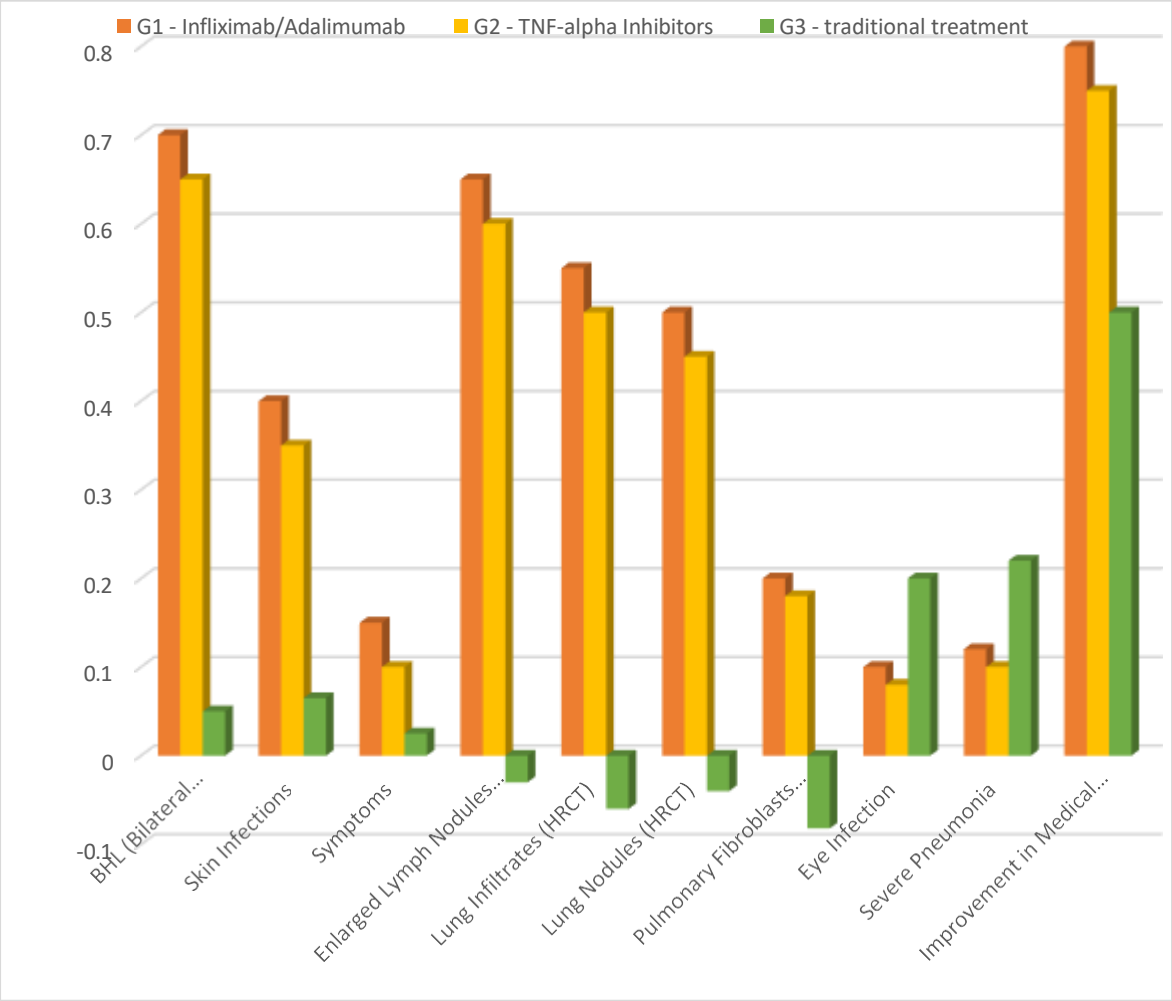

Figure 5: Improvement in each treatment group for each parameter

Figure 5 shows that the G1 group achieved higher rates of improvement in bilateral lymphadenopathy (70%), lung infiltrates (55%), and overall imaging findings (80%). These differences were statistically significant in most categories, The G2 group showed moderate improvement, while the G3 group experienced minimal or even negative change in some parameters, such as lung nodules and pulmonary fibrosis. Notably, the conventional therapy group had the least effect on symptom relief and imaging improvements. Overall, the data support the superior efficacy of infliximab/adalimumab in the treatment of refractory sarcoidosis, with consistent benefits seen clinically and radiologically.

Discussion

This study aims to investigate the effect of alternative therapies (infliximab, and adalimumab) in the treatment of refractory sarcoidosis.

The study revealed that the adalimumab group had a higher mean age, and females were more prevalent in the control group.The biologic group used more immunomodulators, and extrapulmonary involvement was consistent across groups, with significant differences in demographics and medication use.

Sarcoidosis is recognized to be frequent among both men and women. Nonetheless, it is more prevalent among women (Abdel Kareem, et al., 2020). Refractory sarcoidosis is defined as progressive

disease despite corticosteroids and a second-line immunosuppressive agent, such as methotrexate or azathioprine, or clinically significant adverse events from these treatments (Kahlmann et al., 2025).

A study by Zhou, Y., et al., 2021 found that sarcoidosis predominantly impacts middle-aged individuals, exhibiting a slight female predominance. Zhou et al. identified a median age of diagnosis at 46, with 60.8% of patients being female. Women and younger patients have greater extrapulmonary involvement and increased multiple organ engagement.

On the other hand; Data from Lower et al. indicate no significant differences in sex or age between third-line and conventional therapy; nevertheless, variances in institutional and geographic practices are present (Lower, E. E., et al., 2020)

The concurrent use of immunomodulators in patients receiving biologic therapy is widely endorsed, particularly with Infliximab and adalimumab for severe, refractory, or multi-organ conditions where traditional treatments have proven inadequate (Rivière, E., et al., 2024)

Certain cohorts indicate elevated usage of immunomodulatory medications across all patient groups, including controls, which may signify variations in illness severity at the time of enrolment(Lower, E. E., et al., 2020).

Extrapulmonary conditions, encompassing dermatological, ophthalmic, neurological, and cardiovascular disorders, are prevalent. TNF-α inhibitors demonstrate effectiveness for organ-specific symptoms, exhibiting similar rates of organ involvement in clinical populations (Le, V., & Crouser, E. D., 2018).

The study reveals a significant improvement in patients in group G1 over the follow-up period, with a decrease in dyspnea, cough, and fatigue scores, improved respiratory capacity, and a decrease in fibrosis, ground-glass opacities, and honeycombing. This improvement was also accompanied by a sustained decrease in inflammatory markers and KL-6 levels, indicating a decrease in inflammatory activity and pulmonary fibrosis.

Infliximab, a treatment for sarcoidosis that doesn't respond to other treatments, has been shown to work in relieving symptoms including cough and shortness of breath, improving lung function, and making improvements visible on X-rays (Aguiar, M., et al., 2011).

Certain randomized controlled studies (RCTs) demonstrated only minor or non-significant enhancements in self-reported symptoms, possibly due to many participants being on stable immunosuppression and exhibiting less severe baseline symptoms.

Multiple studiesindicated enhancements of 6–8% in predicted FVC and comparable absolute increases in DLCO following 6–12 months of infliximab treatment for refractory pulmonary sarcoidosis, corroborating your results. Patients with FDG-PET positivity, signifying active inflammation, had the most significant enhancements in these metrics (Yao, Q., Ji, Q., & Zhou, Y., 2023).

Not all investigations identified statistically significant alterations in FVC/DLCO, particularly in patients devoid of current inflammation or those with preexisting fibrosis. The extent of average improvement may be minimal (<5%) in large randomized controlled trials, prompting discussion on the clinical relevance of such alterations for all patients. Several evaluations indicate that DLCO is comparatively sluggish and less responsive to alterations, particularly in fibrotic diseases, when contrasted with FVC (Obi, O. N., et al., 2022).

The study found steady reductions in CRP (11.8 to 5.2 mg/L), ESR (35 to 17 mm/h), and KL-6 (1,350 to 925 U/mL).

A reduction in CRP and ESR indicates decreased systemic inflammation, along with the clinical response. KL-6, an indicator of alveolar epithelial injury, is increased in active interstitial lung disease and generally diminishes as inflammation resolves and fibrosis is managed, as observed in sarcoidosis and other interstitial lung illnesses (McDonnell, M. J., et al., 2016).

Certain studies indicate that decreases in CRP and ESR may not consistently correlate with clinical improvement, especially in chronic or fibrotic conditions, and that fatigue or residual symptoms may last despite normalized laboratory results (Korenromp, I. H. E., 2011).

Most studies confirm that corticosteroids improve symptoms initially, but sustained, robust improvement is uncommon in advanced or chronic sarcoidosis. A significant proportion continue to have persistent symptoms or decline in quality of life, especially in fibrotic cases (Papanikolaou, I. C., et al., 2022).

Baughman et al. (2006) and Vorselaars et al. (2015) demonstrated that infliximab markedly decreases dyspnoea and cough scores in individuals with chronic pulmonary sarcoidosis, thereby enhancing their quality of life and daily functioning.

On the other hand; the INFLIXimab trial showed some improvement in physician global assessment, but modest changes in patient-reported dyspnea and cough symptoms did not always reach statistical significance in RCT design. In advanced disease with fixed fibrosis, subjective improvement in symptoms was limited, especially in patients without an inflammatory component (Judson, M. A., et al., 2008).

Hostettler et al. (2012): The administration of infliximab in chronic sarcoidosis correlated with consistent enhancements in FVC and DLCO over a period of 12 to 24 months, particularly in patients exhibiting baseline inflammation (e.g., elevated FDG-PET uptake).

Baughman et al. (2006) report that clinical trial data indicate modest enhancements (4–7% expected) in FVC and DLCO, consistent with your observed patterns. While Vorselaars et al. (2015) indicate that empirical results validate incremental functional enhancements, most pronounced in those exhibiting reversible inflammation as opposed to permanent fibrosis.

FVC and DLCO showed relatively gradual improvement (FVC went from 68.5% to 76.8%, and DLCO went from 54.3% to 61.3%). For many patients, this was less than the 5% threshold for clinically meaningful change.

Research indicates that FVC and DLCO are the preferred objective endpoints for evaluating pulmonary sarcoidosis treatment. In stage III-IV or chronic disease, improvement is often minimal and progression (or stabilization) more common than marked improvement. A 5% absolute increase in FVC is noteworthy; many patients receiving conventional treatment do not reach this threshold, indicating "smoldering" or inadequately managed illness(Perlman, D. M., et al., 2021)

Imaging studies indicate that, in fibrotic sarcoidosis, radiographic alterations (notably enhancement of established honeycombing) are infrequent with standard treatment—most patients encounter either stability or gradual progression. Ground-glass opacities and some reversible inflammation may improve, but entrenched fibrosis and architectural deformation change little over time (Bailey, G. L., et al., 2024).

A gradual drop in CRP, ESR, and KL-6 levels was noticed suggesting that systemic inflammation is going down a little.

A drop in CRP and ESR levels is a sign of partial illness management. Nonetheless, these indicators may not consistently align with clinical remission, particularly in chronic or fibrotic instances; decreases

may indicate partial suppression of inflammation without repairing pre-existing damage (Malkova, A., et al., 2022; McDonnell, M. J., et al., 2016).

Tumor necrosis factor (TNF) plays a critical role in the pathogenesis of sarcoidosis. Inflammation typically ensues following the deposition of poorly soluble antigens within the extravascular compartment (Jabbari et al., 2021). These antigens are phagocytosed by macrophages, which subsequently release cytokines that recruit additional inflammatory cells to the site of antigen deposition (Fu & Harrison, 2021).

Diagnosis of Sarcoidosis occur by Computed tomography (CT) of the chest that demonstrates high sensitivity (Negm, Dalia A.E.M.A.E.R.a; et al., 2019). Computed tomography (CT) has emerged as the fundamental noninvasive imaging modality (El-Hossainy, et al., 2019). Lymphadenopathy, prevalent in refractory sarcoidosis, is defined by symmetric hilar and mediastinal lymphadenopathy, perilymphatic nodules, and uneven thickening in the upper and mid lung regions (Roy, S. G., & Digumarthy, S. R., 2025)

Parenchymal abnormalities encompass bronchovascular bundle involvement and centrilobular nodules, signifying inflammation (Lee, G. M., et al., 2020). CT is employed to differentiate between reversible and irreversible alterations, while larger lymph nodes may exert pressure on airways or arteries, leading to blockage or pulmonary hypertension. PET-CT scans can reveal regions of active inflammation that may respond to treatment in refractory sarcoidosis (Korsten, P., et al., 2016).

Patient selection criteria influence decisions concerning the initiation of treatment in sarcoidosis. Treatment generally depends on the number and extent of involved organs (L Toriola et al., 2023). In most cases, corticosteroids are the initial argument. After 3 6 months of corticosteroid administration, patients with no improvement or who remain corticosteroid-dependent require second-line treatments to induce remission or avoid steroid adverse events (Ruf et al.2024). Second-line compounds are methotrexate, azathioprine, leflunomide, and mycophenolate mofetil. Third-line therapy involves administration of an anti-TNF monoclonal antibody (mAb) if the patient is intolerant or refractory to the previous treatment (Gisbert & Chaparro, 2021). Nevertheless, there are some exceptions to the treatment algorithm because organ involvement may dictate the treatment approach (Brown, 2024).

TNF is required for the formation and maintenance of granulomas; its blockade leads to granuloma breakdown. Moreover, granuloma formation depends on the expression of TNF by macrophages, as demonstrated using a transgenic mouse model (Cronan, 2022). A combined approach targeting both TNF and interferon ɣ, through Janus kinase/signal transducers and activators of transcription inhibition, may be more effective than agents blocking either cytokine alone (L Toriola et al., 2023).

The role of anti-TNF-α therapy in refractory sarcoidosis is well established. Between the two agents infliximab and adalimumab, the former has reported evidence in improving the clinical picture and potentially decreasing severity and reverses the effects of involvement (Rezaee et al., 2023).

Adalimumab has also had an ongoing role in refractory cases of the use of this class of drugs. Switching from infliximab to adalimumab has been reported with success; this was initially done because of allergic reactions to infliximab and, in other instances, due to antibody formation against infliximab (J. Erckens et al., 2012).

In a small study of eight cases who failed therapy or were presented with progressive disease, adalimumab led to improvement or stabilization of the clinical picture with a corresponding increase in the visual exam for ocular disease, decrease of inflammatory markers (CRP, ACE) and decreased requirement of concomitant immunosuppressive therapy (Obi et al., 2021).

Alternative immunosuppressants or cytotoxic drugs may be combined with anti TNF-α agents in patients with more severe, uncontrolled disease. Treatment continues for at least a year, and relapse rates appear to be consistently high when it is terminated too early or too abruptly (Horowitz et al., 2021).

Ongoing maintenance therapy with immunosuppressive agents is advocated and tapering of the anti-TNF-α drugs is also exercised cautiously. The choice between the two agents should take into account the agent profile, availability, delivery conditions, patient preferences, and other specific factors (Melani et al., 2021).

Conclusion

Research indicated that anti-TNF-α therapy (infliximab/adalimumab) surpassed standard treatment in efficacy for refractory sarcoidosis. Patients exhibited enduring enhancements in symptoms, lung function assessments, and radiological results over a period of 24 months. The research endorses infliximab and adalimumab as efficacious third-line medicines for advanced or treatment-resistant sarcoidosis, highlighting the necessity for biological treatments.

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