Usage of Tofacitinib as a Steroid-Sparing therapy in Pulmonary and Cutaneous Sarcoidosis

Abstract

Background: Sarcoidosis is a multisystem, granulomatous & chronic illness which typically affecting lymph nodes & lungs also any organ system. We aimed to evaluate the tofacitinib effectiveness as cutaneous & pulmonary sarcoidosis steroid-sparing treatment.

Methods: This prospective cohort observational research was performed on 45 cases aged from 20 to 65 years old, both sexes, a forced vital capacity (FVC) >50%, histology consistent with sarcoidosis, pulmonary sarcoidosis definition by association for Sarcoidosis and other Granulomatous Disorders (WASOG) & disease progression or symptoms necessitating 15-30 mg/day prednisone (or comparable corticosteroids) as a consistent dose of for at least 4 weeks before enrolment. The definition of Steroid-dependent disease was the necessity for steroids for disease symptoms or progression control, but pulmonary impairment on pulmonary function testing was not required. Additionally, all instances with a history of failed attempts to reduce corticosteroid doses, and their treating physicians urged steroid-sparing therapy.

Results: Pulmonary function tests (FVC, FEV1, FEV1/ FVC ratio) were significantly improved after treatment compared to baseline (P value <0.001). 41 (91.1%) patients showed pulmonary improvement. The last evaluated CSAMI activity score was significantly lower compared to baseline CSAMI activity score (6.38 ± 2.7 vs. 39.51 ± 14.1, P <0.001). The mean CSAMI activity score decrease was 33.13± 11.4 %.

Conclusions: Tofacitinib is a promising strategy for of cutaneous & pulmonary sarcoidosis treatment

Keywords: Tofacitinib , Steroid-Sparing therapy ,Pulmonary ,Cutaneous ,Sarcoidosis

Introduction:

Sarcoidosis is a multisystem, granulomatous & chronic illness that typically affecting lungs & lymph nodes also can affect any organ system. It is believed that 35 / 10 000 black Americans & 10 / 10 000 African Americans and are affected by the disease [1, 2].

Nonetheless, up to 80% of cases will need treatment, and around 50% of those needing systemic treatment will remain needing treatment 5 years after diagnosis. Since 1951, corticosteroids have been the treatment of choice for cases with progressive & symptomatic illness. Despite its short-term efficacy, its utilization as a long-term treatment has been limited via dose-dependent side effects & an absence of evidence that it positively affects the natural course of progressive disease [3, 4]. When an unknown antigen is handled by antigen-presenting cells and introduced to T-lymphocytes as major histocompatibility complex class II surface components, sarcoidosis pathogenesis is initiated. The link initiates an inflammatory response with a strong Th1 bias, recruitment of inflammatory cells & noncaseating granulomas formation [5, 6].

Recent evidence suggests that Th17 immunological pathways have a role in sarcoidosis granulomas formation & maintenance. According to the popular view, antigen persistence causes inflammatory cascade intensification & prolongation (with tumor necrosis factor increase), while stoppage of the inflammatory cascade and disease remission occur following the antigen clearance [7].

Sarcoidosis is a T-helper cell-mediated granulomatous immunological response to an unknown antigen as showed by the current knowledge, although the precise pathophysiology is unclear. Polycythemia vera is an acquired myeloproliferative neoplasm result in excessive erythrocyte production caused by Janus kinase 2 (JAK2) signaling mutations [8, 9].

It can be difficult to cure sarcoidosis. Glucocorticoids, which have numerous side effects, are a therapy staple. In granulomatous disorders as granuloma annulare & sarcoidosis, Janus

kinase–signal transducer & transcription activator (JAK-STAT) signaling has been found to be constitutively active [10]. We postulate that JAK-STAT activation in sarcoidosis is a result of cytokines increased production, as interleukin 6 (IL-6) & interferon- γ (IFN- γ), by macrophages & T cells, leads to. Tofacitinib, a JAK1 & JAK3 inhibitor, was recently shown to induce remission of refractory cutaneous sarcoidosis in 3 consecutive individuals. In these cases, tofacitinib resulted in normalization JAK-STAT signaling in the blood and skin & histologic remission of granulomatous skin inflammation [11, 12]. In 6 cases of thoracic sarcoidosis, 2 from lymph node biopsies & 4 from lung biopsies, As in cutaneous sarcoidosis, a similar pattern of phosphorylated-STAT1 (p-STAT1) and phosphorylated-STAT3 (p-STAT3) activation was observed, as well as high p-STAT1 & p-STAT3 levels [13]. Also, mostly cutaneous sarcoidosis treated with JAK inhibitors improvement have been demonstrated by several case reports & 1 case series [14]. JAK-inhibitors effect on pulmonary sarcoidosis is poorly understood however, pulmonary disease is the most prevalent sarcoidosis treatment indication, and there is few prospective research with pulmonary outcomes [15]. This research aims to evaluate the efficacy of tofacitinib (a selective JAK-1 and JAK-3 inhibitor) as a cutaneous & pulmonary sarcoidosis steroid-sparing treatment.

Meterials and Methods:

This prospective cohort observational research was performed on 45 cases aged from 20 to 65 years old, both sexes, a forced vital capacity (FVC) >50%, histology consistent with sarcoidosis, pulmonary sarcoidosis definition by association for Sarcoidosis and other Granulomatous Disorders (WASOG) [16], and disease progression or signs necessitating a 15-30 mg/day prednisone (or comparable corticosteroids) as a consistent dose for at least 4 wks. before enrolment. Steroid-dependent illness was characterised by the steroids need for disease development or symptoms control, but pulmonary impairment on pulmonary function testing

was not necessary. Additionally, all instances had a history of failed attempts to reduce corticosteroid doses, and their treating physicians urged steroid-sparing treatment.

Among the exclusion criteria were malignancy history, the immunosuppressive medicine utilization other than methotrexate within the previous 8 wks., or an opportunistic infection within the previous 6 months.

Methods:

All cases underwent a full history taking (age, sex, BMI), laboratory investigation & general examination. After 4 weeks of tofacitinib treatment, corticosteroids were reduced in accordance with the protocol. Despite earlier therapy, all patients exhibited persistent, aggressive skin illness.

Assessments:

Chest x-ray were assessed at baseline & week 16. Monthly monitoring was conducted for safety labs, adverse events, spirometry, the Saint George Respiratory Questionnaire (SGRQ) & WASOG organ involvement [17, 18]. X-rays were done & a granuloma existence grading system was applied. Two experienced radiologists read the X-rays without knowledge of the patient's condition, assigning a number score (0–4) to the granuloma infiltration and infiltrates evaluation for the size & length (0 normal, 1 about 25 %, 2 up to 50 % , 3 up to 75 % , and 4 virtually the whole lung field affected). Only slight variations in score classification were revealed by repeated assessments on 2 separate dates. A colorimetric technique utilized for ACE measurement that expressed as Kat/L using taken serum samples [14].

22 μM 4-methylumbelliferyl-β- was used for CTO assessment, the condition was monitored by X-rays, and at diagnosis time, after approximately 6 months, & at the treatment end (remission), inflammatory cytokines were measured in the serum. Remission consisted of the lower CTO levels than the initial values, absence of ACE, symptoms, & indicators of active

disease. The number of months till remission was determined for each patient. Additionally, assessment of number of patients with disease recurrence.

Our outcomes was a ≥50% reduction in corticosteroids at week 16 with no substantial impairment in respiratory symptoms as determined by the SGRQ or pulmonary function (>15% decline in FEV or FVC compared to baseline). Patients were excluded from the research if they needed a prednisone dosage increase of > 30 mg / day or their sarcoidosis worsened in any other organ system. The primary outcome-achieving patients were invited to participate in a 1-year extension. Respiratory symptoms & adverse events were followed throughout the 1-year extension, while other diseases were monitored according to the treating physician's instructions.

Treatment protocol

Tofacitinib Treatment lasted between 4 - 9 months (mean: 6.4 months) with daily dose ranged from 2.5 to 16 mg (mean: 9.0 mg). Tofacitinib dosage was adjusted based on tolerability & response. Additionally, patients got prednisone (15-25 mg) at the onset of treatment, which was reduced over 6 weeks. The activity section of the Cutaneous Sarcoidosis Activity and Morphology Instrument (CSAMI) was utilized for effectiveness evaluation [15].

Statistical analysis

SPSS v26 was used for the statistical analysis (IBM Inc., Armonk, NY, USA). It was determined whether or not the data followed a normal distribution by using the Shapiro-Wilks test and examining the histograms. Parametric quantitative data were shown as means and standard deviations. Frequencies & percentages were used for qualitative data. In order to compare two associated population means, a paired sample t-test was used. A statistical significance was defined as a two-tailed P value of less than 0.05.

Results:

The mean age of the studied patients was 45.76 ± 9.18 years. 26 (57.78%) males and 26 (57.78%) females were involved. The mean weight was 82.36 ± 12.67 Kg. The mean height was 1.66 ± 0.07 m. The mean BMI was 29.32 ± 5.52 kg/m^2. The mean Hb level was 11.96 ± 1.63 gm/dL. The mean PLT count was 258.6 ± 72.51 *10^3 cells/dL. The mean WBC was 8.12 ± 1.79 *10^3 cells/dL.

Table 1: Baseline characteristics and laboratory data of the studied patients (n = 45)

		Patients (n = 45)
Age (years)		45.76 ± 9.18
Sex	**Male**	26 (57.78%)
	Female	19 (42.22%)
Weight (Kg)		82.36 ± 12.67
Height (m)		1.66 ± 0.07
BMI (kg/m^2)		29.32 ± 5.52
Hb (gm/dL)		11.96 ± 1.63
Platelet count (*10^3 cells/dL)		258.6 ± 72.51
WBCs (*10^3 cells/dL)		8.12 ± 1.79

Data are presented as mean ± SD or frequency (%). BMI: Body mass index, Hb: hemoglobin, WBCs: White blood cell

The mean of period passed since sarcoid diagnosis was 33.93± 15.15 months. The mean of the Maximum daily tofacitinib dosage was 9.23± 3.68 mg. The mean prednisone dose was 19.73± 3.58 mg. The mean of Treatment duration was 6.31± 1.76 months, and the mean duration of steroid use was 8.69± 3.43 months.

Table 2: Clinical data of the studied patients (n = 45)

	Patients (n = 45)
Months since sarcoid diagnosis	33.93± 15.15
Maximum daily tofacitinib dosage (mg)	9.23± 3.68
Prednisone dose (mg/day)	19.73± 3.58
Treatment duration (months)	6.31± 1.76
Duration of steroid use (months)	8.69± 3.43

Data are presented as mean ± SD or frequency (%).

Pulmonary function tests (FVC, FEV1, FEV1/ FVC ratio) were significantly improved after treatment compared to baseline (P value <0.001). 41 (91.1%) patients showed pulmonary improvement.

Table 3: Pulmonary function tests of the studied patients (n = 45)

		Patients (n = 45)	P value
FVC	**Baseline**	80.91 ± 2.87	**<0.001***
	After	88.38± 4.6	
FEV1	**Baseline**	66.96 ± 4.59	**<0.001***
	After	80.27± 5.66	
FEV1/ FVC	**Baseline**	0.83 ± 0.06	**<0.001***
	After	0.91± 0.09	
Pulmonary improvement		41 (91.1%)	**---**

Data are presented as mean ± SD or frequency (%). *: statistically significant as P value <0.005, FVC: Forced vital capacity, FEV1: Forced expiratory volume in the first second.

Regarding the Cutaneous sarcoidosis among the studied patients, Annular Cutaneous sarcoidosis occurred in 16 (35.6%) patients, Papular Cutaneous sarcoidosis occurred in 20 (44.4%) patients and Photo-aggravated Cutaneous sarcoidosis occurred in 9 (20%) patients. The last evaluated CSAMI activity score was significantly lower compared to baseline CSAMI activity score (6.38 ± 2.7 vs. 39.51 ± 14.1, P <0.001). The mean CSAMI activity score decrease was 33.13± 11.4 %.

Table 4: Cutaneous sarcoidosis and CSAMI activity score of the studied patients (n = 45)

		Patients (n = 45)	
Cutaneous sarcoidosis	**Annular**	16 (35.6%)	
	Papular	20 (44.4%)	
	Photo-aggravated	9 (20%)	
CSAMI activity score	**Baseline**	39.51 ± 14.1	P value **<0.001***
	Last evaluated	6.38 ± 2.7	
CSAMI activity score decrease %		33.13± 11.4	

Data are presented as mean ± SD or frequency (%). *: statistically significant as P value <0.005, CSAMI: Cutaneous Sarcoidosis Activity and Morphology Instrument

Discussion

Sarcoidosis is a multisystem condition defined by the noncaseating epithelioid cell granulomas formation that can affect any organ, with the lung being the most commonly afflicted region. Although it is a rare condition, it is found all over the world, with a higher

prevalence in African American & northern European individuals [19, 20]. There are currently no authorised steroid-sparing sarcoidosis therapies. The lung is the most often affected organ in sarcoidosis, and there is a huge unmet need in the treatment of pulmonary affected individuals [21]. The JAK-STAT signalling system is crucial for haematopoiesis as well as adaptive & innate immunity [22]. Recently, JAK inhibitors have emerged as a promising treatment class for a growing range of inflammatory cutaneous conditions, as atopic dermatitis, vitiligo, alopecia areata & psoriasis [23]. In addition, the signalling pathway of JAK-STAT is considerably differentially expressed between sarcoidosis cases & healthy individuals and that the sarcoidosis severity was associated with a severity score produced by the gene signature discovered as reported by a recent gene expression research [24]. These findings imply that JAKSTAT signalling may play a role in sarcoidosis aetiology. JAK-STAT pathway appeared to be involved in the pathogenesis [25]. A JAK inhibitor as a steroid-sparing treatment in pulmonary sarcoidosis is the subject of a limited prospective trial, as far as we are aware. In a recent case series of 5 Tofacitinib treated patients by 5 mg twice daily, it was determined that all patients' pulmonary function was stable, with all variations falling within the 10% margin of inter-test variability. All SGRQ scores improved by clinically significant margins over the course of the research. 2 patients' chest x-rays improved while 2 patients remained constant [26].

In an open-label trial of tofacitinib, conducted by Damsky et al. [27] and examined its effeciency in 10 cutaneous sarcoidosis cases. In all cases, the disease control offered by a tofacitinib-based regimen was superior to that of the previous immunotherapeutic regimen, especially in terms of skin involvement. Four out of five prednisone users in the research were able to cease or considerably reduce their prescription. Tofacitinib significantly inhibits IFN-γ, a key cytokine that is a major contributor to sarcoidosis as suggested by the mechanistic analysis. Their finding is consistent with previous research indicating that in

sarcoidosis cases, IFN-γ correlated with disease activity and elevated in the tissues and blood, which makes sense given IFN-γ fundamental basic in granuloma formation, classical macrophage activation, & protection against Mycobacterium tuberculosis [28, 29].

In sarcoidosis, tofacitinib appears to be an efficient method for IFN-γ inhibition , which signals via JAK1/2. Also, other cytokines activity as TNF (JAK-independent), IL-12 (JAK2/ TYK2), IL-6 (JAK1/2), GM-CSF (JAK2) & IL-15 (JAK1/3) is also observed. In autoimmunity, monocytes differentiation into inflammatory macrophages enhanced by GM-CSF, IL-6 is involved as a potential sarcoidosis treatment & CD4+ T cell effector responses reinforced by IL-15 &, [30, 31]. However, a clinical trial utilising ustekinumab, an inhibitor of p40 (both IL-12 and IL-23), was ineffective in treating pulmonary sarcoidosis, IL-12 has been previously linked to sarcoidosis. Multiple cytokines can be suppressed directly and simultaneously, which could be a benefit of JAK inhibition over TNF inhibition [32].

This is consistent with a previous trial that shown a better response of extensive sarcoidosis to tofacitinib 10 mg twice absence as compared to 5 mg twice daily. Throughout IFN-γ activity suppression, a higher dose of tofacitinib could be administered to some patients, or other focused JAK inhibitors, as JAK1- or JAK1/2-specific inhibitors evaluation [33].

Conclusions and limitation

The strengths of this research involve its prospective design, its emphasis on pulmonary illness, the most prevalent sarcoidosis therapy indication, chest imaging and close monitoring of respiratory symptoms & spirometry. Tofacitinib is a promising strategy for treatment of pulmonary and cutaneous sarcoidosis.

This study limitations is placebo or control group absence & small sample size. Measures of global quality of life & glucocorticoid toxicity were also omitted due to brief research duration & the small sample size. For further research JAK-inhibitors for pulmonary sarcoidosis, a randomised, placebo-controlled, multicentre study is necessary.

Ethical Approval and Consent:

An informed written consent was taken from the patients. The research was performed after approval from the Ethical Committee Tanta University Hospitals.

Financial support and sponsorship: Nil

Conflict of Interest: Nil

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