Original Research Article

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

Abstract

Background: Sarcoidosis is a chronic, multisystem granulomatous disorder that commonly involves the lungs and lymph nodes but can involve all other organ systems. We aimed to determine whether tofacitinib (a preferential JAK-1 and JAK-3 inhibitor) may be an effective steroid-staringtherapy in pulmonary and cutaneous sarcoidosis.

Methods: This prospective cohort observational study was carried out on 45 patients aged from 20 to 65 years old, both sexes, Association for Sarcoidosis and other Granulomatous Disorders (WASOG) definition of pulmonary sarcoidosis,histology consistent with sarcoidosis, a forced vital capacity (FVC) >50%, and 4) symptoms or disease progression requiring a stable dose of 15-30 mg/day prednisone (or equivalent corticosteroids) for ≥4 weeks prior to enrolment. Steroid dependent disease was defined by the need for steroids to control disease progression or symptoms but did not require evidence of pulmonary dysfunction on pulmonary function testing. In addition, all patients had a history of failed attempts to taper their corticosteroids to lower doses and had been recommended for steroid-sparing therapy by their treating physicians.

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

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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 treatment of pulmonary and cutaneous sarcoidosis

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

Introduction:

Sarcoidosis is a chronic, multisystem granulomatous disorder that commonly involves the lungs and lymph nodesbut can involve all other organ systems. The disease is thought to affect 10 per 10 000 white Americans and 35 per 10 000 African Americans[1, 2].

Yet, up to 80% of patients will require treatment, and nearly half those who require systemic therapy will still require therapy 5 years after the diagnosis. Since 1951, corticosteroids have been the first line of therapy for patients with symptomatic and progressive disease, but its use, although effective in the short-term, has been limited as a long-term therapy by dosedependent side effects and a lack of evidence that it favorably alters the natural history of progressive disease[3, 4].

Sarcoidosis pathogenesis begins when an as of yet unidentified antigen is processed by antigen-presenting cells and presented to T-lymphocytes in the context of major histocompatibility complex (MHC) class II surface molecules. The interaction leads to the activation of an inflammatory response with a decidedly Th1 bias, the recruitment of inflammatory cells, and the formation of non-caseating granulomas[5, 6].

More recently, there is compelling evidence for a role for Th17 immune pathways, in the generation and maintenance of sarcoidosis granulomas. The prevailing hypothesis is that antigen persistence leads to augmentation and persistence of the inflammatory cascade (with increased tumor necrosis factor), whereas antigen clearance is followed by termination of the inflammatory cascade and disease remission[7].

Current understanding suggests that sarcoidosis represents a helper T cellmediatedgranulomatous immune response to an unidentified antigen, but the exact pathogenesis remains unknown. Polycythemia vera (PV) is an acquired myeloproliferative neoplasm characterized by mutant Janus kinase 2 (JAK2) signaling leading to erythrocyte overproduction[8, 9].

Sarcoidosis can be difficult to treat. Glucocorticoids, which have many adverse effects, are a mainstay of treatment. It has shown beenthat Janus kinase–signaltransducer and activator of transcription (JAK-STAT) signalingis constitutively active in sarcoidosis as well as granulomaannulare, another granulomatous disease[10].

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We hypothesizethat JAK-STAT activation in sarcoidosis is a result of increasedproduction of cytokines, such as interferon-γ (IFN-γ) and interleukin 6 (IL-6), by T cells and macrophages, respectively.We recently reported remission of refractory cutaneous sarcoidosis during treatment with tofacitinib, a Janus kinase 1 (JAK1)and JAK3 inhibitor, in three consecutive patients. In thesepatients, we showed that tofacitinib resulted in histologic resolution of granulomatous inflammation in the skin as well as normalization of JAK-STAT signaling in the skin and blood[11, 12]. In sixcases of thoracic sarcoidosis, four from lung and two from lymphnode biopsies, we showed not only a similar pattern of phosphorylated-STAT1 (p-STAT1) and p-STAT3 activation but also elevatedlevels of p-STAT1 and p-STAT3 as in cutaneous sarcoidosis[13].

In a direct extension of these data, several case reports and 1 case series have shown improvement of primarily cutaneous sarcoidosis treated with the Janus protein tyrosine kinase (JAK) inhibitors[14]. However, pulmonary disease is the most common reason fortreatment of sarcoidosis. Little is known about the effect of JAK-inhibitors onpulmonary sarcoidosis, and prospective studies with pulmonary endpoints are lacking[15].

Thepurpose of this prospective cohort study is to determine whether tofacitinib (a preferentialJAK-1 and JAK-3 inhibitor) may be an effective steroid-staring therapy in pulmonaryand cutaneous sarcoidosis.

Patients and Methods:

This prospective cohort observational study was carried out on 45 patients aged from 20 to 65 years old, both sexes, Association for Sarcoidosis and other Granulomatous

Disorders(WASOG) definition of pulmonary sarcoidosis[16], histology consistent with sarcoidosis, a forced vital capacity (FVC) >50%, and symptoms or disease progression requiring a stable dose of 15-30 mg/day prednisone (or equivalent corticosteroids) for ≥4 weeks prior to enrolment. Steroid dependent disease was defined by the need for steroids to control diseaseprogression or symptoms but did not require evidence of pulmonary dysfunction on pulmonary function testing. In addition, all patients had a history of failed attempts to taper their corticosteroids to lower doses and had been recommended for steroid-sparing therapy by their treating physicians. An informed written consent was obtained from the patient or relatives of the patients. The study was done after approval from the Ethical CommitteeTanta University Hospitals (approval code:).

Exclusion criteria included the use of an immunosuppressive drug other than methotrexate in the preceding 8 weeks, history of malignancy, or opportunistic infection in the last 6 months, among others.

Methods:

All patients were subjected to full history taking (age, sex, BMI) , general examination and laboratory investigation. After four weeks on tofacitinib,corticosteroids were tapered according to a present protocol. All patients had persistent, active cutaneous disease despite previous treatment.

Assessments:

Chest x-ray was evaluated atbaseline and week 16. Spirometry, safety labs, adverse events, WASOG organ involvement,and the Saint George Respiratory Questionnaire (SGRQ)[17, 18]were monitored monthly.X-rays were taken and a grading scheme for the presence of granuloma was used as described previously.The X-rays were read by two experienced radiologists, unaware of the status of the patient, grading granuloma infiltration according to

a numerical score (0–4) and judging the size and extension of the infiltrates (0 normal, 1 about 25% of lung field involved, 2 up to 50%, 3 up to 75%, and 4 virtuallythe whole lung field involved). Repeat evaluations on two successive occasions showed only minor deviations in the score classification.Serum samples were taken, and ACE was determined using a colorimetric method and expressed as μKat/L[14].

CTO was determined using 22 μM 4-methylumbelliferyl-β-The disease was monitored using X-ray, and inflammatory cytokines in serum were determined at the time of diagnosis, after about 6 months, and at the end of treatment (remission). Remission comprised absence of symptoms, signs of active disease and ACE, and CTO lower than the initial values. Time till remission in months was determined for all subjects. In addition, the number of patients with arecurrence of the disease was determined.

Our outcomes where the primary endpoint was a ≥50% reduction in corticosteroids at week 16 with no significant worsening in pulmonary function (>15% decline in FVC or FEV1 relative to baseline) or respiratory symptoms measured by the SGRQ. Patients were withdrawn from the study if they developed worsening sarcoidosis in any other organ system or required a prednisone increase to more than 30mg/day prednisone. Patients who met the primary endpoint were invited to enroll in a 1-year extension. During the 1-year extension respiratory symptoms and adverse events were monitored; other disease monitoring was per treating physician.

Treatment protocol

Tofacitinib dose ranged from 2.5 to 16 mg daily(mean: 9.0 mg), and treatment duration ranged from4 to 9 months (mean: 6.4 months). Tofacitinib wastitrated according to response and tolerability. Patients also received prednisone (15-25 mg)at treatment onset,tapered over

6 weeks. Efficacy was assessed by usingthe activity portion of the Cutaneous Sarcoidosis Activity and Morphology Instrument (CSAMI)[15].

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Armonk, NY,USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD). Quantitative non-parametric data were presented as median and interquartile range (IQR). Qualitative variables were presented as frequency and percentage (%). Paired sample t-test was used to compare two population means that are correlated.A two-tailed P value < 0.05 was considered statistically significant.

Results:

The mean age of the studied patients was 45.76 ± 9.18 years. 26 (57.78%) males and 26 (57.78%) females were included. The mean weight of the studied patients was 82.36 ± 12.67Kg. The mean height of the studied patients was 1.66 ± 0.07 m. The mean BMI of the studied patients was 29.32 ± 5.52kg/m^2. The mean Hb level was 11.96 ± 1.63gm/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**

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± 3.43months. **Table 2**

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

	Patients (n = 45)
Months sincesarcoid 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**

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, PapularCutaneous sarcoidosis occurred in 20 (44.4%) patients and Photo-aggravatedCutaneous 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**

Table 4: Cutaneous sarcoidosisand 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 disorder characterized by the development of non-caseating epithelioid cell granulomas where any organ can be affected, and the lung is the most frequent site involved. Although it is a rare disease, it has a worldwide distribution, being more prevalent in northern European and African American individuals[19, 20].

There are currently no approved steroid-sparing therapies for sarcoidosis. The lung is the most commonly affected organ in sarcoidosis and treating patients with pulmonary disease is an important and unmet need[21]. The JAK-STAT (Janus kinase signal transducer and activator of transcription) signallingpathway plays a central role in innate and adaptive immunityas well as haematopoiesis[22]. JAK inhibitors haverecently emerged as a promising class of therapeuticsfor a growing list of inflammatory skin disorders suchas psoriasis, atopic dermatitis, alopecia areata, andvitiligo[23].

Additionally, a recent gene expressionstudy found that the JAK-STAT signalling pathway issignificantly differentially expressed betweensarcoidosis patients and healthy controls, and aseverity score developed using the gene signatureidentified in the study correlated with sarcoidosisdisease severity[24]. This evidence suggests that JAKSTAT signalling may be implicated in the pathogenesis of sarcoidosis. The Janus kinase (JAK)signal transducerand activator of transcription (STAT) pathway appears to play a role in pathogenesis[25].

To our knowledge, there is a limited prospective study of a JAKinhibitor as a steroid-sparing agent in pulmonary sarcoidosis.In a previous case series examined 5 patientstreated by Tofacitinib 5 mg twice daily and found that Pulmonary function was stable for all patients,

with all variances within the established 10%margin of inter-test variability. SGRQ scores improved in all categories over the course ofthe study by clinically significant margins. Chest x-rays improved for 2 patients and werestable for 2 patients[26].

In Damsky et al. [27]performed open-label trial of tofacitinib and evaluated the efficacy in 10 sarcoidosis patients with cutaneous sarcoidosis. In all 10 patients, disease control with a tofacitinib-based regimen was superior to the patients preceding immunotherapeutic regimen,particularly for skin involvement. Four of five patients entering the study taking prednisone were able to discontinue or significantly reduce the dose. The mechanistic evaluation suggested that IFN-γ is a key driver of sarcoidosis and is a critical cytokine targeted by tofacitinib with effective treatment.

Their observation is consistent with prior work showing that IFN-γ is elevated in circulation and in tissues of sarcoidosis patients and correlates with disease activity,andmakes teleological sense given the fundamental role of IFN-γ in classical macrophage activation, granuloma formation, and protection against Mycobacterium tuberculosis[28, 29].

Tofacitinib appears to provide an effective means of suppressing IFN-γ, which signals via JAK1/2, in sarcoidosis.The activity of other cytokines including GM-CSF (JAK2), IL-15 (JAK1/3), IL-6 (JAK1/2), IL-12 (JAK2/ TYK2) and TNF (JAK-independent) are also evident in sarcoidosis. GM-CSF has been shown to promote the differentiation of monocytes into inflammatory macrophages in autoimmunity, IL-15 can re-enforce CD4+ T cell effector responses, and IL-6 isan additional proinflammatory cytokine implicated as a potential treatment in sarcoidosis[30, 31].

IL-12 has previously been implicated in sarcoidosis, however, interestingly, a clinical trial using ustekinumab, an inhibitor of p40 (both IL-12 and IL-23) was not effective in pulmonary sarcoidosis.A potential advantage of JAKinhibition (compared to TNF inhibition) is the simultaneous,direct inhibition of multiple cytokines[32].

This is consistent with a prior case report, showing a better response of widespread sarcoidosis to tofacitinib 10 mg twice daily than to 5 mg twice daily. Moving forward,improved suppression of IFN-γ activity could be achieved by either an increased dose of tofacitinib insome patients, or potentially, by evaluation of more targeted JAK inhibitors, such as a JAK1-or JAK1/2-specific inhibitors[33].

The strengths of this study include its prospective design, close monitoring of spirometry, respiratory symptoms, andchest imaging, and its focus on pulmonary disease, which is the most common indication forthe treatment of sarcoidosis.

The limitations of this study include its small size, lack ofplacebo or control, Metrics of glucocorticoid toxicityand global quality of life were also not included due to the small size and short duration ofthis study. Moving forward, a randomized, placebo-controlled multi-centre study isnecessary to further investigate JAK-inhibitors for pulmonary sarcoidosis.

Conclusions: Tofacitinib is a PROMISING STRATEGY FOR treatment of pulmonary and cutaneous sarcoidosis

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