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ORIGINAL ARTICLE

Effectiveness of generic tofacitinib in idiopathic inflammatory myositis (IIM)—a retrospective analysis from Indian Myositis Registry (MyoIN)

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Abstract

Objectives Determine domain-based-outcomes and steroid-sparing efficacy of generic tofacitinib in IIM.

Methods This is a multicenter retrospective study wherein clinical phenotype, autoantibody profile, prior immunosuppressives, and outcomes at 3, 6, and 12 months were retrieved for IIM patients prescribed tofacitinib. Overall clinical response was assessed as complete or partial remission as per physician judgment. Changes in cutaneous and calcinosis domain were recorded as per physician global assessment (PGA), lung domain as per medical research council (MRC) dyspnea scale, and muscle strength by Manual Muscle Testing-8 (MMT-8).

Results Forty-two patients of IIM with mean age 38.7 ± 16 years; (76.2% ($N=32$) women), median duration of illness 48 (19;88) months were included. Commonest indication for initiating tofacitinib was either for refractory or as steroid sparing for cutaneous domain ($N=25/42$, 59.5%) followed by calcinosis ($N=16/42$, 38%). Overall complete and/or partial remission was achieved in 23/37 (64.8%), 30/35 (85.7%), and 29/30 (96.6%) patients at 3, 6, and 12 months, respectively. At 12-month follow-up, there was a reduction in prednisolone dose, with absolute decrease from a daily dose of 17.5 mg (IQR 5;50) to 2.5 mg (IQR 0;5) ($p<0.001$). Individual domain assessments revealed improvement in cutaneous domain [16/25 (64%)] and calcinosis [6/15 (40%)]. Adverse effects included herpes zoster ($N=2/42$, 4.8%) and dyslipidemia ($N=4/42$, 9.5%).

Conclusions Treatment with generic tofacitinib significantly reduces the daily dose of corticosteroids and is effective in cutaneous domain including calcinosis in IIM.

Key points

- *This multicenter retrospective study is the first real-world data from India, elucidating steroid sparing efficacy of generic tofacitinib in patients with inflammatory myositis.*
- *Domain-based outcome assessment suggests good clinical improvement especially in cutaneous domain, even those with refractory disease.*
- *Modest benefits were evident in calcinosis, but its effect on the muscle and pulmonary domain appears limited.*

Keywords Refractory myositis · Dermatomyositis · Janus kinase inhibitor · Tofacitinib · Calcinosis · Anti-MDA-5 antibody · Interstitial lung disease

Introduction

Idiopathic inflammatory myopathies (IIM) are a group of rare autoimmune diseases characterized by inflammation primarily of the skeletal muscle, often accompanied by involvement of other major organs as well, such as skin, lungs, heart, and joints [1]. The current standard of care includes treatment with glucocorticoids and additional immunosuppressive agents [2]. There is no large data or randomized clinical trial to support choice of steroid sparing immunosuppressive drugs and is largely as per physician discretion [3]. Despite adequate immunosuppressive therapy, many patients exhibit incomplete response, and some are even refractory to conventional treatment [4–6].

Currently, novel therapeutic options are being developed by exploring and targeting the underlying immune-pathogenic pathways implicated in IIM pathogenesis [7–9]. In the past few decades, type-I IFN dysregulation has been

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demonstrated to be one of the key pathogenic mechanisms particularly in dermatomyositis (DM) [10, 11]. The intracellular IFN signaling occurs via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. Blocking this downstream signaling pathway with Janus kinase inhibitors (JAKi) is gaining momentum in the therapeutic armamentarium of refractory IIM.

The data for use of JAKi in IIM is sparse, and there are no randomized control trials on JAKi efficacy and safety in IIM so far, though few trials are in the pipeline. Currently, the evidence of JAKi efficacy and safety is available from few retrospective studies and case series involving many different Jakinibs, such as tofacitinib [12–14], ruxolitinib [15], baricitinib [16, 17], and upadacitinib [18]. Tofacitinib, a pan JAK inhibitor, seems to be the forerunner amongst these JAKi due to its comprehensive inhibition of cytokines. Several preliminary studies and a systematic literature review have shown promising results, particularly in the management of refractory cutaneous and muscle domains, including a reduction in interferon gene expression [19, 20].

Steroids, while effective in symptom amelioration, are associated with significant side effects and risk of comorbidities. The steroid sparing effect, safety, and tolerability of tofacitinib were demonstrated in a prospective open-label trial in patients with cutaneous predominant refractory DM. Furthermore, those who could discontinue steroids remained off steroids during the long-term extension study spanning 96 weeks [21, 22]. Hence, by reducing steroid dependency, tofacitinib offers a promising alternative therapy in the management of IIM patients.

These results suggest that tofacitinib could be considered a therapeutic option for patients with refractory IIM, offering domain specific efficacy, reduction of steroid dependence and a favorable safety profile over an extended treatment period. It is also cost-effective, safe, and readily available in the Indian market as a generic version. Here, we report a retrospective analysis of use of tofacitinib and domain based outcomes in IIM led by the members of Indian Myositis Registry (MyoIN), which is a pan-India collaborative network of centers interested in myositis research from all over India [23].

Materials and methods

This is a retrospective study from members of Myositis Special Interest Group in the Indian rheumatology association wherein rheumatologists who have ever prescribed tofacitinib for IIM were invited to participate. Both adult and juvenile IIM patients diagnosed as per EULAR/ACR classification criteria and those who had received tofacitinib at doses of 10 mg per day for at least 3 months were included. The data captured included demographics, total duration of illness, domains of IIM affected, prior immunosuppression, the glucocorticoid dose prescribed, the autoantibody profile, and the relevant laboratory parameters. Indication for initiation for tofacitinib either as a steroid sparing agent or refractory disease or both was documented. Refractory disease was defined as lack of response to at least two immunosuppressive agents, and steroid sparing effect is defined as ability to reduce the glucocorticoid dose while on coprescription with tofacitinib.

The duration of prescription and the follow-up data was recorded at 3, 6, and 12 months after initiation of tofacitinib. Skin and calcinosis improvement was assessed as per physicians' judgment (PGA).The lung domain assessment was as per medical research council (MRC) dyspnea scale, and muscle improvement was assessed using Manual Muscle Testing (MMT-8) scores. Physician (PhGA) and patient/parent (PtGA) global assessment were recorded by using 0–10 visual analogue scale (VAS), and the overall clinical response was recorded as either complete or partial improvement. Complete clinical response was defined as significant decrease or resolution of all symptoms while on stable immunosuppression as per Oddis et al. [24]. This requires absence of myositis disease activity, consistent muscle strength and function, and normal muscle enzyme levels. Maintaining muscle strength and function stability requires keeping alterations within a 15% range in semi quantitative scores for a minimum of 3 months. We defined partial improvement as a minimum of 25% reduction in symptoms while on stable immunosuppression. Equivalent prednisolone dose at each visit was documented. Adverse events attributable to tofacitinib and reasons for discontinuing therapy were noted. Patients who had at least one follow-up data were included in the final analysis of domain outcome.

Statistics

Continuous variables including MMT-8, prednisolone dose, CPK, LDH, and AST were reported using mean (standard deviation) or median (quartiles) as appropriate. Categorical data, such as disease phenotypes and comorbidities, were described using frequencies and percentages. To compare MMT-8, prednisolone, CPK, LDH, and AST at different time points, Friedman's test, a non-parametric alternative to repeated-measures ANOVA, was used. Post hoc comparisons were conducted using the Wilcoxon test.

Results

Nine rheumatologists provided data for 42 IIM patients who had been prescribed tofacitinib, the mean age being 38.7 ± 16 years (76.2% females). The median duration of illness was 48 (19.88) months. Their clinical characteristics,

Table 1 Overview of cohort at IIM diagnosis ($n=42$)

Variables	N (%)
Age in years (mean ± SD)	38.7 ± 16
Disease phenotypes	
Dermatomyositis	28 (66.7%)
Overlap myositis	6 (14.3%)
Juvenile dermatomyositis	6 (14.3%)
Polymyositis	2 (4.8%)
Median duration of illness (months)	48 (19.88)
Clinical parameters	
Muscle weakness	27/38 (66.7%)
MMT-8 (mean ± SD)	62 ± 10.6
Calcinosis	17 (40.5%)
HRCT evidence of ILD	11/24 (45.8%)
Arthritis	15 (45.5%)
Heliotrope rash	18 (42.9%)
Gottron's rash	9 (21.4%)
Gottron's papules	14 (33.3%)
Mechanics hand	4 (9.5%)
V sign	10 (23.8%)
Shawl sign	12 (28.5%)
Holsters sign	3 (7.1%)
Calcinosis	17 (40.5%)
Periungual hypertrophy	6 (14.3%)
Cutaneous ulcers	8 (19%)
Panniculitis	4 (9.5%)
Prior immunosuppression	
Methotrexate	29 (69%)
Azathioprine	9 (21.4%)
Mycophenolate mofetil	13 (31%)
Rituximab	7 (16.6%)
Tacrolimus	4 (9.5%)
Cyclophosphamide	5 (11.9%)
Hydroxychloroquine	13 (30.9%)
Baseline investigations	
Creatinine kinase (unit/l)	1243.2 (89.6,1332.7)
Lactate dehydrogenase (unit/l)	470 (250;894)
Aspartate aminotransferas e(unit/l)	69 (34.116)
MRI evidence of myositis ($N=13$)	9 (63.3%)
Myopathy pattern on EMG ($N=19$)	15 (78.9%)
Muscle Biopsy ($N=6$)	4 (66.6%)
Myositis-specific/myositis-associated autoantibodies ($N=29$)	
Mi-2	6 (20.7%)
MDA 5	12 (41.4%)
Ro 52	6 (20.7%)
Pm-Scl	6 (20.7%)
NXP2	3 (10.3%)
Ku	5 (17.2%)
SRP	3 (10.4%)
TIF 1y	1 (3.4%)
SAE	1 (3.4%)
Jo-1	1 (3.4%)

Results are presented as mean ± SD or median with inter quartile range (IQR) as appropriate

Table 2 Indications for initiation of tofacitinib

Indications for initiation on tofacitinib ($N=42$) %	
Refractory disease only	23 (54.7%)
Steroid-sparing agent only	11 (26.2%)
Both refractory + steroid sparing	8 (19%)
Indications based on each individual domains	
Steroid sparing	
Muscle	6 (14.3%)
Skin	11 (26.2%)
Lung	3 (7.1%)
Calcinosis	4 (9.5%)
Refractory disease	
Muscle	4 (9.5%)
Skin	14 (30.3%)
Lung	4 (9.5%)
Calcinosis	12 (28.6%)
Arthritis	4 (9.5%)
Upfront tofacitinib	3 (9%)

laboratory parameters including autoantibody profile at diagnosis of IIM, and the prior immunosuppressives are represented in Table 1. Table 2 depicts the indications for tofacitinib prescription. Dermatomyositis (66.7%; $N=28$)) was the most common clinical phenotype. Indication for tofacitinib was either refractory disease in 54.7% ($N=23$) or as a steroid-sparing agent in 26.2% ($N=11$), while 8 (19%) were prescribed for both. IIM domain-specific indications were largely active cutaneous disease ($N=25/42$, 59.5%), and calcinosis ($N=16/42$, 38%). Methotrexate ($N=15/42$, 35.7%) was the most commonly co-prescribed immunosuppressive agent.

We included 38 patients for outcome analysis, who had at least 3 months of follow-up, the median follow-up duration being 14 (IQR 12, 21.7) months. Overall, 23 patients were on steroids with a median dose of 17.5 mg [(IQR) 5;50] at the initiation of tofacitinib. In 16/23 (69.5%) patients, steroid tapering was successfully accomplished, and 6/23 (26%) patients were completely off steroids by the end of the 12-month period. Figure 1 depicts the median steroid dose at 3, 6, and 12 months (7.5 mg [IQR 5;10], 5 mg [IQR 2.8;6.8], and 2.5 mg [IQR 0;5]), respectively, as compared to the baseline ($p<0.001$).

The evaluation of overall clinical response revealed a consistent trend of improvement with 23/37 (64.8%), 30/35 (85.7%), and 29/30 (96.6%) showing either partial or complete remission at 3, 6, and 12 months, respectively, after starting tofacitinib. This is also reflected in significant decline in the median PhGA at 12 months as compared to the baseline [6.5 (4;7) vs. 2 (1;3) ($p=0.001$)] (supplementary Table 1).

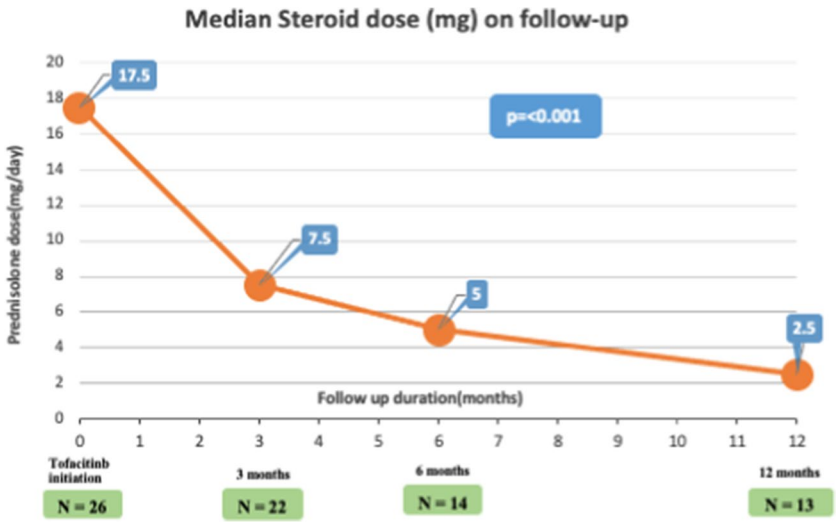

Fig. 1 Median glucocorticoid dose on follow-up visits after initiation of tofacitinib

Of 25 patients who had active skin disease, 16 (64%) achieved cutaneous inactivity as per physicians' assessment at 12 months. Further, 6 out of 15 (40%) patients with calcinosis showed improvement at 6 and 12 months of follow-up. Of 19 patients with muscle weakness [median MMT-8 = 66 (60;71)], neither significant improvement in the MMT-8 scores ($p = 0.96$) nor reduction in any of the muscle enzyme levels was noted, thereby indicating limited effect in muscle domain (supplementary Table 1). Assessment of patients with interstitial lung disease (ILD) was made based on dyspnea grades revealed that 3 of 5 patients experienced improvement, 1 remained static, and another initially improved at 3 months but later experienced a flare while on tofacitinib at 6 months. Among 16 patients with arthritis, 11 (68.7%) demonstrated improvement. The trends of improvement in each individual domain are depicted in Fig. 1.

Subgroup analysis of 12 patients with antiMDA-5 antibody positivity, 9/11(81.8%) attained complete or partial remission by 12 months. More specifically, 7/9 (77.7%) achieved inactivity in cutaneous disease, while 3/5 (60%) showed improvement in calcinosis over the same period. The trends of improvement in each individual domain are depicted in Fig. 2.

Majority of patients tolerated tofacitinib well, adverse effects included herpes zoster ($N = 2/42$, 4.8%) and dyslipidemia ($N = 4/42$, 9.5%). Tofacitinib was discontinued in eight patients (19%): in two patients due to herpes zoster infection, sepsis in one, and worsening disease in two patients (one with an interstitial lung ILD flare and one with worsening calcinosis). Additionally, in one patient, tofacitinib was discontinued after achieving remission, and another two patients had self-discontinued treatment. No

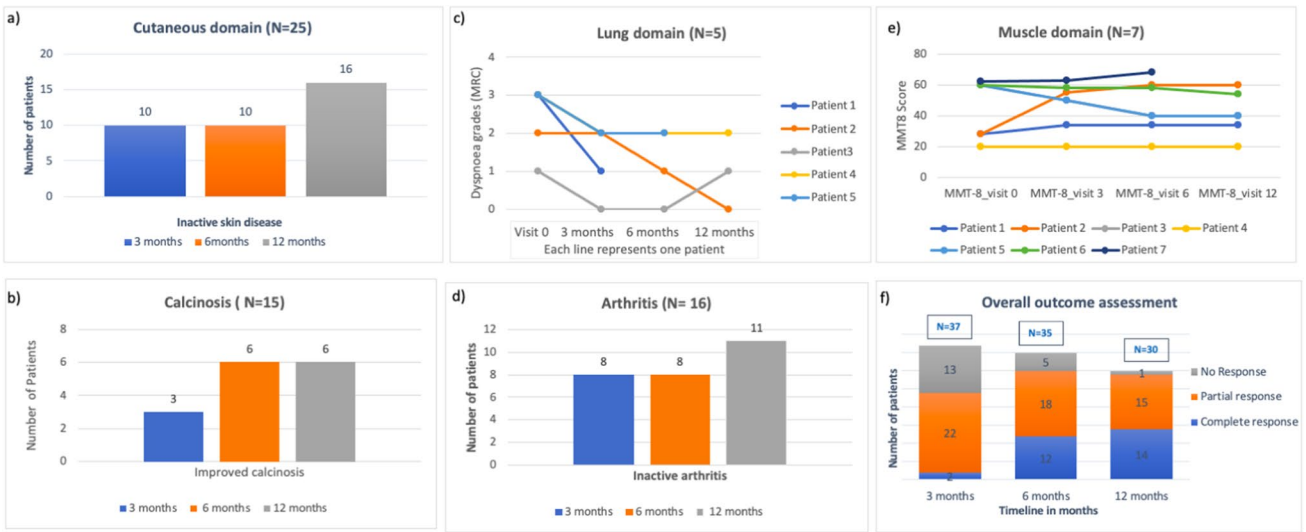

Fig. 2 Domain-based outcome assessment at follow-up visits after initiation of tofacitinib

cardiovascular, thromboembolic events, or deaths were reported.

Discussion

This multicenter retrospective study explores the steroid sparing efficacy of generic tofacitinib in refractory IIM from the Indian subcontinent, offering valuable insights into its real-world effectiveness in several domains of IIM and safety. The steroid-sparing effect of JAK inhibitors was first evidenced in two pilot studies conducted in refractory adult DM patients by Paik JJ et al. [21, 22] and Landon-cardinal et al. [25]. Similarly, in a retrospective analysis involving 101 patients with refractory JDM over 19 months of follow-up, approximately 40% of patients achieved glucocorticoid discontinuation after initiation of JAK inhibitors [26]. Our results also suggest that tofacitinib is an effective steroid sparing immunosuppressive option for IIM patients, with resultant reduction of dosage of steroid, as early as 3 months, thereby minimizing its adverse effects. A compilation of prior studies showcasing domain-specific effectiveness of tofacitinib in IIM is summarized (supplementary Table 2).

The efficacy of tofacitinib in the skin predominant and amyopathic DM has been well documented [27]. In the present study, around 64% of participants attained cutaneous inactivity within 12 months, including those with anti-MDA5 antibody. Paik JJ et al. had reported significant improvement in skin-related activity measures such as cutaneous dermatomyositis disease area and severity index (CDASI) in refractory dermatomyositis treated with tofacitinib over 2 years [21, 22]. An analysis from a recent systematic review and meta-analysis of 91 patients also reported that tofacitinib results in significant reduction of mean CDASI scores (−20.00 (95% CI: −34.9 ~ −5.1) [28].

In the present study, about 1/3rd of patients had muscle weakness at the time of initiation of tofacitinib. However, there was no notable improvement in muscle weakness, as measured by MMT-8 scores and the muscle enzymes. A recent retrospective analysis of 41 refractory IIM patients by Beckett et al. also demonstrated a lack of improvement in muscle domain ($p=0.16$), while significant improvement in cutaneous domain was noted ($p<0.001$) with tofacitinib [29]. Another recent single-center pilot study involving 16 patients with refractory skin and/or muscle disease were treated with either baricitinib or ruxolitinib. They also demonstrated a significant reduction in mean CDASI scores, but the mean MMT-8 remained unchanged over a follow-up period of 1.8 ± 0.7 years [25].

In the context of ILD dominant myositis, several promising findings have emerged. Chen et al. showed that addition of tofacitinib achieved a 6-month survival advantage of amyopathic dermatomyositis (DM) with early ILD (< 3-month duration, forced vital capacity (FVC) 50%), as compared to historical controls (100% vs. 78%, $p=0.04$) [30]. Moreover, in refractory cases of rapidly progressive ILD (RP-ILD), the addition of tofacitinib to triple therapy showed a survival benefit compared to historical controls [31]. In another retrospective study involving 88 refractory JDM patients from China, about 60% experienced both clinical and radiological recovery in ILD by 12 months after initiating tofacitinib [32]. However, there were no cases with RP-ILD in our cohort. Following tofacitinib addition, three of five patients experienced clinical improvement with reduced dyspnea grades.

Calcinosis poses treatment challenges and suggests persistently active disease along with damage. In current study, within 6 months of tofacitinib therapy, 40% ($N=6/15$) experienced either complete or partial reduction in lesion size, and only one patient worsened while on tofacitinib. Similarly, Zhang et al. reported reduction of calcinosis size in the majority 75% ($N=15/20$) of patients with five patients achieving complete resolution after initiating tofacitinib [32].

Similar to other studies, tofacitinib was well tolerated and deemed safe in our study as well. Of eight patients who discontinued tofacitinib, three did so due to infections; however, no serious adverse events or mortality were reported.

Limitations

Our study has few limitations. Firstly, it was retrospective in design, with its inherent drawbacks, a relatively small cohort size, and a potential for survival selection bias. We were also limited by inability to use objective validated measures for other than in the muscle domain. Further, we could not apply the 2016 ACR/EULAR criteria for assessing clinical response through total improvement scores (TIS), thereby limiting the estimation of true extent of clinical improvement in the study population. As we did not directly compare the generic tofacitinib with any other treatment options, we cannot comment on the relative efficacy and safety compared to alternative treatments.

Despite these limitations, we believe that generic tofacitinib is pocket-friendly, effective, steroid sparing, and safe in IIM. The result of this analysis opens up a new facet of treatment options for refractory IIM. Further studies including larger randomized controlled trials with longer follow-up periods are needed to confirm these findings and understand the role of tofacitinib in the management of IIM better.

Conclusion

This study presents the first real-world data from India on the use of generic tofacitinib in patients with IIM. The study indicates that tofacitinib can be effectively used as a

steroid sparing agent, simultaneously demonstrating clinical improvement, particularly in the cutaneous domain. Additionally, modest benefits were observed in other domains such as calcinosis, while its impact on muscle domain and pulmonary domain appears to be limited. No major adverse events were reported. Overall, tofacitinib emerges as a promising option for both steroid-sparing and refractory disease management in patients with IIM.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-024-07019-x.

Data availability Data will be provided on reasonable request to corresponding author.

Declarations

Ethics approval Ethics approval was obtained from respective ethics committees: Institutional Ethics Committee, St. John's Medical College & Hospital. IEC Ref No. IEC/1/1054/2023 dated 10/September/2023.

Conflict of interest The authors declare no competing interests.

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