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Research Article

Safety Profile of Tofacitinib in Autoimmune Rheumatic Disease Patients

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Abstract

Aim and Objective: The study aims to assess the safety profile of Tofacitinib among Autoimmune Rheumatic Disease (ARD) patients in real life, attending the Rheumatology outpatient department of a tertiary care hospital. This short-term prospective observational study was done for 6 months involving 50 ARD patients. Patient's socio-demographic and clinical data were recorded in a predesigned proforma and were analysed for the given 50 patients based on the objectives.

Result: Among fifty randomly collected ARD patients, 58% were female and 42% were male. The mean disease duration was 7.8 years and the mean treatment duration was 8.8 months. No other significant Adverse Events (AEs) were found in the study, with slight lipid profile alterations and infections. Laboratory variables like lymphocyte count, LDL, HDL, SGPT and ALP were not normally distributed in the population and were expressed using median with quartiles. Normally distributed variables were expressed with mean with SD. MACE and DVT were observed in 2% of the study population, with 95% CI [0.4,10] each. Incidence of herpes zoster infection and upper respiratory tract infections were found in 4% and 6% of the study population with 95% CI: [1,10] and 95% CI: [2,20] respectively.

Conclusion: Tofacitinib demonstrated consistent safety over 6 months in patients with ARD in a real-life setting, where tofacitinib-induced alterations in lipid profile and incidence of infections are an exception.

Keywords: Tofacitinib; ARD; DMARDs; AEs

Abbreviations

ARD: Autoimmune Rheumatic Disease; RA: Rheumatoid Arthritis; PsA: Psoriatic Arthritis; AS: Ankylosing Spondylitis; SLE: Systemic Lupus Erythematosus; JAKI: Janus Kinase Inhibitors; TYKs: Tyrosine Kinase; DMARDs: Disease-Modifying Antirheumatic Disease; STAT: Signal Transducer Activation of Transcription; MACE: Major Adverse Cardiovascular Events; AEs: Adverse Events; LTE: Long-Term Extension; EULAR: European Alliance of Associations for Rheumatology; CASPAR: Classification Criteria for Psoriatic Arthritis; ASAS: Assessment of Spondylo-Arthritis International Society; DVT: Deep Vein Thrombosis; HZ: Herpes Zoster; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; VLDL: Very Low-Density Lipoprotein; TG: Triglycerides; ALP: Alkaline Phosphatase; SGOT: Serum Glutamic-Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase

Introduction

Auto-Immune Rheumatic Diseases (ARD) are a heterogeneous group of chronic inflammatory diseases characterised by self-directed inflammation, exhibiting comparable clinical, laboratory, and immunological symptoms. They may result in declining health, excruciating, incapacitating pain and a higher mortality rate. Stressful events in life, environmental factors including chemicals, physical agents, hormonal fluctuations, and genetic predispositions all contribute to their cause. ARDs are divided into three categories based on the presence of a pro-inflammatory response, auto-inflammatory which includes PsA and AS, overlapping Autoimmune which is RA and SLE and Sjogren's syndrome were categorised under Autoimmune [1-8].

DMARDs are the mainstay of treatment for ARD besides NSAIDs and corticosteroids, they include conventional synthetic DMARDs (Hydroxychloroquine, Methotrexate), biological DMARDs (Tumor Necrosis Factor (TNF) inhibitors and non-TNF biologics) and Targeted synthetic DMARDs/Janus Kinase Inhibitors (JAKi) like Tofacitinib [9-11].

Tofacitinib is an oral, potent, selective inhibitor of the JAK family (consisting of JAK1, JAK2, JAK3 and Tyk2) [12-14]. It is the first DMARD the FDA authorised in November 2012 for treating moderate to severe RA, PA, ulcerative colitis and juvenile idiopathic arthritis [15-17]. Tofacitinib acts at the intracellular level by suppressing the phosphorylation and activation of the JAK-STAT signalling pathway, primarily blocking heterodimer signalling comprising JAK3 and JAK1, with functional selectivity over receptors that signal through pairs of JAK2. When tofacitinib inhibits JAK1 and JAK3, signalling through the common gamma-chain carrying receptors for many cytokines-including interleukin 2 (IL-2), -4, -7, -9, -15, and 21 is blocked. Since the activation, proliferation, and function of lymphocytes depend on these cytokines, blocking their signalling may modify various elements of the immune response [1,14,18].

Tablets containing 5 mg and 10 mg of tofacitinib as well as an

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extended-release (XR) dosage of 11 mg are available for adult oral use. For children two years of age and up, it is also offered as a 1 mg/mL oral solution. Patients who are intolerant or contraindicated to one or more DMARDs use Tofacitinib [19-21].

Although some patients experience few adverse events (mostly headaches, nasopharyngitis, and nausea) tofacitinib is generally well tolerated. The most often reported Adverse Events (AEs) include infections (mainly URTI and HZ). Moreover, the reported adverse events include cardiovascular events, thrombosis, and laboratory abnormalities (neutropenia, lymphopenia, increased liver enzymes, or lipid level changes) [22-30,31]. In a study involving patients ≥ 50 years of age with at least one extra cardiovascular risk factor, the risks of Major Adverse Cardiovascular Events (MACE) associated with tofacitinib were assessed and contrasted with those of TNF inhibitors (ORAL Surveillance study) [18,25,32]. It was found that the tofacitinib group had a greater risk of MACE. In this short-term observational study, we sought to analyse the safety profile of Tofacitinib in patients with ARD based on haematological parameters, lipid profile, liver enzyme alterations along with the incidence of infections and thrombotic events and to report our own real-world experience from a single centre.

Methodology

Fifty Randomly selected ARD patients who were on Tofacitinib 5 mg BID, attended the Rheumatology department of a tertiary care hospital in Trivandrum, Kerala during the study period November 2023 to May 2023, were enrolled on this short-term prospective observational study. Based on EULAR (2010), CASPAR (2006) and ASAS (2009) classification criteria, patients diagnosed with RA, PA and AS were enrolled. Patient demographic details, laboratory investigation parameters, incidence of infections and thrombotic events were collected and evaluated. Inclusion criteria have both genders and patients who are on a stable dose of tofacitinib 5 mg BID for at least 3 months for ARD. Exclusion criteria include patients with malignancies, patients with a history of MACE, CKD and CLD patients, and patients under 18 years of age. The patient's medical records were examined, a thorough analysis and severity assessment of adverse events were conducted based on the physical examination results, laboratory testing, and symptoms.

Ethical clearance from the institute and written consent forms from the patients were collected beforehand.

Statistical Analysis

Descriptive statistics were used to summarise demographic and clinical data. All the continuous variables like Hb, TG, TC etc., were summarised with mean with SD or median with quartiles (Q1, Q3). All the categorical variables like gender, diagnosis, infections etc., were summarised using frequency and percentages. Ninety-five percent confidence intervals were calculated using the Wilson score interval for proportions, near 0 or 1. Visual methods and analytical methods (Kolmogorov-Smirnov) were used to decide whether a variable had a normal distribution. All the statistical analysis was done using SPSS version 19.

Result

There were 50 ARD patients (29 female, 21 male) receiving tofacitinib 5 mg BID. The mean age at diagnosis was 50.1 (27-81) years. The mean duration of tofacitinib treatment was 8.8 (1-30) months. The demographics and clinical features are summarized in Table 1.

Table 1: Baseline patient demographics.

	ARD (n = 50)
Sex (%)	
Female	29 (58%)
male	21 (42%)
Mean age (years)	50 (27-81)
Diagnosis	
RA	32 (64%)
PsA	12 (24%)
AS	6 (12%)
Mean duration of disease (years)	7.8 (1-30)
Indication for starting Tofacitinib	
Inadequate response	23 (46%)
Active disease	22 (44%)
others	5 (10%)
Mean duration of treatment (months)	8.8 (3-24)

The haematological, lipid profile and liver function test changes in patients who are on tofacitinib therapy were assessed using Kolmogorov-Smirnov normality assessment in (Table 2-4).

Among the continuous variable's lymphocytes, HDL, LDL, SGPT and ALP were not found to be normally distributed and were expressed using median with quartiles (Table 5) whereas all other variables which followed normality were expressed using mean with SD (Table 4). Normality was assessed using Kolmogorov-Smirnov test.

Table 2: Assessment of normality using Kolmogorov-Smirnov test.

	Kolmogorov-Smirnov		
	Statistic	**df**	**Significance (p).**
Age	0.08	50	0.2
Haemoglobin	0.068	50	0.2
Total count	0.065	50	0.2
Polymorphs	0.116	50	0.088
Lymphocytes	0.166	50	**0.001**
Platelet	0.118	50	0.081
ESR	0.118	50	0.079
Total. Cholesterol	0.099	50	.200*
HDL	0.156	50	**0.004**
LDL	0.133	50	**0.027**
VLDL	0.125	50	0.05
TG	0.114	50	0.119
SGOT	0.096	50	0.2
SGPT	0.17	50	**0.001**
ALP	0.129	50	**0.037**

Table 3: Laboratory parameters with normal distribution.

	Mean	Standard Deviation	N
Hb	12.4	1.3	50
TC	7713	1376	50
Polymorphs	53	11	50
Platelet	2.91	0.77	50
ESR	49	26	50
Total Cholesterol	227	30	50
VLDL	28	8	50
TG	150	19	50
SGOT	32.4	14.47	50

Table 4: Laboratory parameters without normal distribution.

	Median	Q1	Q3	N
Lymphocytes	38	34	42	50
HDL	43	36	54	50
LDL	144	132	160	50
SGPT	31.5	24	36	50
ALP	77	56	101	50

Median (min-max) or mean (± SD); Significant differences between parameters in the same letters, SD: Standard Deviation; Quartiles Q1-Q3.

MACE and other thrombotic events like DVT were observed in 2% each in the study population (Figure 1) with 95% CI: [0.4,10] each in patients >52 years of age having dyslipidaemia (Table 6) from both genders. No other significant cardiovascular events were observed during the study.

Infections were the most common drug-related AEs, of which upper respiratory tract infection and HZ were observed in 6% and 4% of the study population (Figure 2) with 95% CI: [1,10] and 95% CI: [2,20] respectively. URTI was mostly observed in males than in females whereas HZ was observed in females only.

Table 5: Incidence of MACE, DVT and other thrombotic events.

		n =50	Percentage (95% CI)
DVT	No infection	49	98 (90,100)
	with Infection	1	**2 (0.4,10)**
PE	No infection	50	100
MACE	No infection	49	98(90,100)
	With Infection	1	**2 (0.4,10)**

Table 6: The type and incidence of infections in patients.

		n= 50	Percentage (95% CI)
URTI	No infection	47	94(80,100)
	with infection	3	**6(2,20)**
HZ	No infection	48	96(90,100)
	with infection	2	**4(1,10)**
TB	No infection	50	100

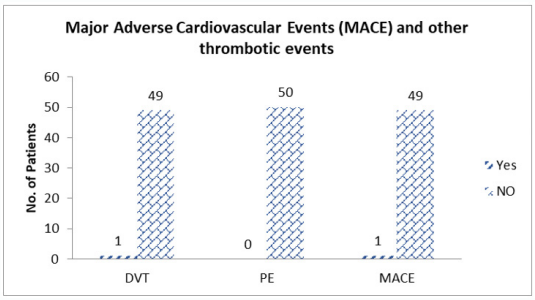

Figure 1: Major Adverse Cardiovascular Events (MACE) and other thrombotic events in patients on tofacitinib therapy.

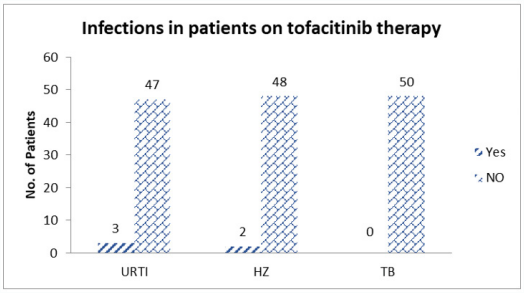

Figure 2: The types and incidence of infections in patients on tofacitinib therapy.

Discussion

This study prospectively analysed real-life data from fifty ARD patients treated with Tofacitinib to assess the safety profile of Tofacitinib in a clinical setting. Studies on phase II-IV and long-term extension evaluated the safety assessment of tofacitinib in RA, PsA and AS [17-22]. Tofacitinib which is a JAK-STAT inhibitor has been associated with a broad range of side effects notably increased risk of infections, liver enzyme elevations, venous thromboembolism, MACE, anaemia, neutropenia, leukopenia etc., and these findings were established through a study conducted.

For assessing the incidence of infections, the study population was categorized into 3 groups based on the type of infection being assessed, URTI, HZ and TB. In our study, 10% had developed any of these infections (6% - URTI, 4% - HZ and 0% - TB). A study conducted by Haraoui, et al. [28] reported results with similar findings with a significant rise in infections in the study population. In line with our findings, no statistically significant AEs were observed except for the incidence of infections mostly URTI and HZ along with slight alteration in laboratory parameters like lymphocytes, HDL, LDL, SGPT and ALP. MACE and DVT were also observed in 2% of each of the patient population [28].

Overall laboratory parameters change in this analysis was as expected with Tofacitinib treatment. Tofacitinib has been associated with an increased likelihood of liver enzyme elevation as reported by Nash, et al. [29] and for the present study population, SGPT and ALP were found to have altered from their normal range in the patients. Our study showed alters in HDL and LDL levels which remarks the ability of Tofacitinib to decrease the cholesterol ester catabolism and this tofacitinib-induced increase in lipid profile cannot be considered as a marker for the development of cardiovascular disease events. Akca, et al. [30] in a study reported that patients receiving tofacitinib 5 mg twice daily and other DMARDs had a similar risk of serious infection events when RA patients ≥ 65 years and younger had their incidence of infections and serious infections compared between the two treatments (tofacitinib versus biologic DMARDs) [30,31]. To assess whether an anomaly in LDL level causes MACE, LTE follow-up data is necessary [33].

Our study was based on real-life data on the safety profile of Tofacitinib, for three main diagnoses of ARD i.e; RA, PsA and AS unlike other studies based on single diagnosis, which provided a brief insight into the type of AEs, incidence of infections or any thrombotic events caused by the drug over a short period. The highly immunosuppressive drug, which is a recently approved drug has several side effects, therefore their use in a tertiary hospital setting should be made cautiously and continuous monitoring should be done by focusing on various parameters. Thereby helping practitioners in clinical settings to take precautions while treating patients with this drug and for efficient disease control.

Study Limitations

The main limitation is that it is a short-term study with a limited patient population that deals with real-life data. In contrast to clinical studies, follow-ups in real-life practice are less consistent and frequent. Besides, we did not correlate disease activity with the presence of AEs. Nevertheless, the real-life population analysis captures the variability of patient populations in clinical practice better than data on specific patients in controlled studies. We hope that the literature on the safety profile of tofacitinib will benefit from our real-life data.

Physician knowledge and awareness are crucial for the close monitoring of patients and detecting AEs.

Conclusion

The safety of tofacitinib has been established in clinical trials. This prospective observational analysis of real-life data shows that tofacitinib is also safe in a real-life setting. To assess whether an

anomaly in LDL level causes MACE, LTE follow-up data is necessary.

Further multi-centre studies involving a greater number of patients and real-life experience may shed more light on tofacitinib's safety profile. The safety profile of tofacitinib was mostly complied with earlier studies. In conclusion, for a better clinical outcome, our findings are consistent with the use of tofacitinib in the treatment of ARD.

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