https://doi.org/10.48047/AFJBS.6.16.2024.2217-2231

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

A Comparative Study of Topical 2% Tofacitinib Lotion Versus 1% Pimecrolimus Cream for The Treatment of Patients with Mild to Moderate Atopic Dermatitis.

Dr. Malini Panati[1], Mounika Nangineedi[2], M.S., Dr. N Sudheer[3], Pavithra Vakudavath[4] *

1. Dr. Malini Panati, MBBS, M.D Dermatology, Associate Professor, Osmania Medical College, Hyderabad, 500095, India.
2. Mounika Nangineedi, M.S, Senior Development Scientist, Haleon,Richmond, Virginia, 23220, USA.
3. Dr. N Sudheer, MBBS, MD Dermatology,Associate Professor,Osmania Medical College, Hyderabad, 500095, India.
4. Pavithra Vakudavath* MBBS, PG II Yr, Osmania Medical College, Hyderabad, 500095, India.

* Corresponding Author: Email: dermadoc.pavithra@gmail.com, Phone Number: 9492662411

Keywords: pimecrolimus, tofacitinib, atopic dermatitis

Volume 6, Issue 16, Dec 2024

Received: 15 Oct 2024

Accepted: 25 Nov 2024

Published: 09 Dec 2024

doi:10.48047/AFJBS.6.16.2024.2217-2231

Abstract:

Background: Atopic dermatitis (AD) is a chronic inflammatory skin condition with limited treatment options. Secondary to good skin care, calcineurin inhibitors such as pimecrolimus are prescribed. It may take several weeks for pimecrolimus to show its effects. Tofacitinib, a Janus kinase (JAK) inhibitor, is being explored as a potential treatment for atopic dermatitis.

Objective: This study was undertaken to estimate the efficacy and safety of tofacitinib as a treatment option for atopic dermatitis.

Materials and Methods: This was a single center, randomized, open label, two arm, comparative clinical study to evaluate the efficacy, safety and tolerability of tofacitinib lotion 2% w/v versus pimecrolimus cream 1% w/w for the treatment of patients with mild to moderate atopic dermatitis.

Results: A total of 30 patients (21 males and 9 females) afflicted with atopic dermatitis were included in the study. The mean and standard deviation of their ages were 44.07 and 12.15 years. The study population was randomly divided into two groups consisting of 15 patients each. 2-way ANOVA showed that there was a significant reduction in the VIGA and EASI scores of patients receiving tofacitinib compared to those receiving pimecrolimus treatment. No significant adverse effect was noted after treatment in either group; minor adverse effects did not require medical intervention.

Conclusion: The results of this single center study show that tofacitinib is an effective and well-tolerated treatment strategy for people afflicted with atopic dermatitis.

Introduction: Atopic dermatitis (AD) is a recurrent chronic inflammatory skin condition that causes pruritis, erythematous, and scaly skin frequently located on flexural surfaces. The classification of AD flares into mild, moderate, or severe is determined by the intensity and extent of common symptoms (Hanifin et al 2001). It is most common in children, but it can affect people of all ages. Children with AD are prone to contract food and environmental allergies, asthma, allergic rhinitis, ear infections, streptococcal pharyngitis, and urinary tract infections (Silverberg et al 2013; Serrano et al 2019). The exact cause of atopic dermatitis is thought to be a complex interplay of genetics (mutations in the FLG gene) and environmental factors coupled with skin barrier dysfunction, immune system dysregulation (Irvine et al 2011). People with a family history of eczema, asthma, or hay fever are more likely to develop atopic dermatitis. To manage AD, treatment plans include regular use of moisturizers; corticosteroid creams to reduce inflammation and itching; calcineurin inhibitor ointments to suppress the immune system and reduce inflammation; antihistamines to reduce itching; light therapy to reduce inflammation; and dupixent, a biologic medication that is injected to reduce inflammation. (Shaker 2014; Weidinger 2015)

Patients with AD are prescribed topical corticosteroids and calcineurin inhibitors when skin care with moisturizers fails to provide relief. Pimecrolimus is a topical medication used to treat mild to moderate atopic dermatitis (eczema) in some cases. Pimecrolimus belongs to a class of medications called topical calcineurin inhibitors (TCIs). TCIs work by suppressing the immune system's activity in the skin, specifically targeting a process involved in inflammation. By calming the overactive immune response, pimecrolimus helps to reduce itching, redness, and inflammation associated with eczema (Butala and Paller 2022). It may take several weeks of consistent use for pimecrolimus to show its full effects. Janus kinase (JAK) inhibitors are being explored as a potential treatment for atopic dermatitis, since they are actively involved in controlling inflammation commonly noticed in AD (Datta et al 2024).

Since the treatment options are limited, may not provide immediate relief and carry potential side effects, this study was undertaken to study the effect of tofacitinib as a reliable treatment for atopic dermatitis.

Materials and Methods:

1. Study Design:

This was a single center, randomized, open label, two arm, comparative clinical study to evaluate the efficacy, safety and tolerability of tofacitinib lotion 2% w/v versus pimecrolimus cream 1% w/w for the treatment of patients with mild to moderate atopic dermatitis. This study was approved by the Institute's ethics committee. Informed consent was obtained from all the study participants. Patients were recruited at Osmania General Hospital, Hyderabad, from May 2023 to April 2024 Following a screening period, the treatment was given for 5 weeks and followed up for 5 weeks.

2. Study Participants

Patients aged between 18 and 60 irrespective of sex were recruited for the study. Eligible patients had a confirmed clinical diagnosis of atopic dermatitis. Only those with a score of 2 (mild) or 3 (moderate) according to Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) were considered. Patients had to have a treatable body surface area of ≥5% to 20% at first visit to be enrolled in the study.

3. Exclusion Criteria

Patients with unstable AD requiring strong topical or oral corticosteroids for management were excluded. Patients with clinically significant medical disorder, condition, uncontrolled systemic diseases, immunocompromised patients, patients with a history of skin conditions like lupus erythematosus, psoriasis, mycosis fungoides, skin infections, genetic or environmental skin conditions were excluded from the study. Patients with any significant finding that may hinder the study or interfere with patient safety were excluded. People with atopic dermatitis that is severely inflamed and infected, in addition to those with other serious infections were excluded. Patients who have had eczema herpeticum within the last 12 months, or at least two separate occurrences of eczema herpeticum previously were also excluded. This study excludes patients who have used any of the following medications or therapies for atopic dermatitis within the past month: phototherapy, systemic immunosuppressants, cytostatic drugs, systemic corticosteroid, oral Janus kinase (JAK) inhibitor, monoclonal antibody, leukotriene antagonist, systemic antibiotics, investigative drugs, or herbal medications with unknown properties or known beneficial effects for atopic dermatitis. This study excludes patients who have used any topical medications on their skin within the past 14 days, including corticosteroids, tars, antihistamines, antibiotic creams, phosphodiesterase 4 [PDE4] inhibitors, retinoids or benzoyl peroxide products [BPO],

antibacterial medications or antibacterial products included in soaps, bleach baths, or topical sodium hypochlorite-based products. This study excludes patients who have used any other medications being studied for atopic dermatitis within the past 2 months. Patients with known hypersensitivity or allergic to Tofacitinib or Pimecrolimus. This study excludes patients who have a known current infection with hepatitis B, hepatitis C, or HIV.

4. Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD):

The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) is a standardized scoring system used to assess the severity of atopic dermatitis (eczema) in clinical trials and research studies (Simpson et al 2022). The vIGA-AD™ score is a single score assigned by a dermatologist based on the overall appearance of the eczema lesions on the patient's skin. The score is based on the extent and severity of AD. There are five categories in the vIGA-AD™ scale, with increasing severity:

- 0: No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
- 1: Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
- 2: Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
- 3: Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
- 4: Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

5. Eczema area and severity index (EASI):

The Eczema Area and Severity Index (EASI) is a validated scoring system specifically designed to measure the **extent and severity** of atopic dermatitis (eczema). The scoring system is detailed below:

- Divided into four body regions: head/neck, upper limbs, trunk, and lower limbs.

- Each region gets a score for both the percentage of area involved (0-6) and the severity (0-3 for redness, induration/swelling, and excoriation/scratching).
- Individual scores are then multiplied by a factor reflecting the body area size and summed for a final EASI score (ranging from 0, indicating no eczema, to 72, indicating maximal disease).

Results and Discussion:

The current study was carried out to explore the effect of tofacitinib in atopic dermatitis patients compared to pimecrolimus.

Patient Demographics: A total of 30 patients were included on the basis of inclusion and exclusion criteria mentioned. The mean and standard deviation of the study population's age were 44.07 and 12.15 years. Patients were randomly divided into 2 groups of 15 each; those in the group receiving pimecrolimus had ages with mean (SD) of 48.67 (7.18) and those in tofacitinib receiving groups had ages with mean (SD) 39.47 (14.15). In the study group, 9 were females and the rest were males. The mean of Atopic dermatitis affected area assessment & Calculation of treatable % Body surface area (BSA) for the pimecrolimus and tofacitinib groups is 6%. Patient characteristics are detailed in Table 1.

After screening and including patients in their respective study groups, the patients were assessed for the area affected by AD and the treatable body surface area. The BSA was calculated to be between 5-7% in both groups. Following screening, the treatment was started and the affected area was calculated every week until the 5th consecutive week. Figure 1 details the change in means of the affected area. Patients receiving tofacitinib had a significant reduction in percentage of affected area (Figure 2 and 3).

2 way ANOVA was carried out, with the rows detailing subsequent visits and the columns bearing **vIGA-AD** values for patients grouped into pimecrolimus and tofacitinib treatments. The analysis carried out to detect the effect of both drugs on AD patients showed that both drugs significantly reduced the extent of AD (Table 2). Figure 4 shows that the mean reduction of VIGA score is greater in patients receiving tofacitinib treatment.

Anova analysis also revealed that both groups reduced AD in the patients as weeks progressed (Table 3). The plotted graph also shows that the mean of EASI decreased

significantly more in patients receiving tofacitinib (Figure 5). The same trend was noted in the pruritis scale of patients receiving tofacitinib vs patients receiving pimecrolimus (Figure 6).

Tofacitinib was well tolerated overall with no serious or life threatening events occurring throughout the study. The following adverse effects were reported by patients: burning, stinging, itching in the pimecrolimus group, and itching and redness in the tofacitinib group. The symptoms subsided naturally without any medical intervention and without interruptions in the study protocol.

For atopic dermatitis patients unresponsive to good skin care, the next step may involve prescription medications like topical corticosteroids or calcineurin inhibitors. These medications can help reduce inflammation and improve symptoms. Topical calcineurin inhibitors (TCIs) are proven and effective treatment options for atopic dermatitis (eczema), particularly for mild to moderate cases. TCIs target calcineurin within the skin cells; calcineurin plays a key role in activating the immune system's T cells, which contribute to the inflammation and itching associated with eczema. By blocking calcineurin, TCIs suppress the activity of these T cells, leading to reduced inflammation and relief of eczema symptoms. Since TCIs are steroid free, they can be used long-term. While generally well-tolerated, TCIs can cause mild burning, stinging, or itching at the application site. Also, they are not recommended for children under 2 years of age. TCIs may also take several weeks of consistent use to show their full effect. Pimecrolimus is the commonly used TCI; it is a valuable treatment option for some people with mild to moderate atopic dermatitis, particularly those who cannot use topical corticosteroids or need treatment for sensitive areas.

Janus kinase (JAK) inhibitors are a new and promising class of medication for treating moderate to severe atopic dermatitis that hasn't responded well to other therapies. Both oral and topical pharmaceutical formulations of Janus kinase inhibitors have been recently introduced to treat atopic dermatitis. The activation of the JAK-STAT pathway is linked with the pathophysiology of atopic dermatitis. The cascade is crucial for the immune dysregulation that occurs, which promotes a response from Th2 cell and eosinophils, upregulates epidermal chemokines, pro-inflammatory cytokines, and pro-angiogenic factors and downregulates the function of the skin barrier (Bao et al 2023). JAK inhibitors are effective in the treatment of atopic dermatitis, since they inhibit the JAK-STAT pathway, resulting in an immunosuppressive activity (Nakagawa et al 2020, Papp et al 2021, Bissonnette et al 2016).

JAK inhibitors have shown significant effectiveness in clinical trials for patients with moderate to severe atopic dermatitis who haven't achieved adequate control with other treatments like steroids or calcineurin inhibitors. These offer fast-acting relief of symptoms, including itching and inflammation, compared to some traditional treatments. Although uncommon, patients with atopic dermatitis receiving topical JAK inhibitors may experience serious adverse effects (Wood et al 2022). JAK inhibitors can have side effects, including upper respiratory tract infections, headache, and increased cholesterol levels. Tofacitinib is a JAK inhibitor being explored as a potential treatment for atopic dermatitis. Clinical studies have shown tofacitinib ointment applied twice daily to be effective in reducing symptoms of atopic dermatitis. It significantly improved Eczema Area and Severity Index (EASI) scores compared to a placebo (Sadeghi and Mohandesi 2023). There was also an earlier onset of relief compared to traditional treatments.

The results of this study are in correlation with larger clinical trials involving tofacitinib. This study provides us with meaningful insights on the effects of tofacitinib in the Indian cohort. A larger study cohort may help us in better understanding any effects of tofacitinib and may help us in generalizing the efficacy against AD. Additionally, the patient cohort may be broadened so as to understand the inclusivity offered by the drug.

Conflicts of Interest: The authors do not have any conflict of interest

Funding source: This study did not receive any funding.

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Tables

Table 1: Demographic details of AD patients included in the study

Demographic	AD patients receiving pimecrolimus	AD patients receiving tofacitinib
	Mean (SD) / N	Mean (SD) / N
Age (years)	48.67 (7.18)	39.47 (14.15)
Gender		
Male	8	13
Female	7	2
Treatable %BSA	6%	6%

Table 2: 2 way ANOVA for vIGA-AD between groups receiving pimecrolimus and tofacitinib treatments

ANOVA table	SS	DF	MS	F (DFn DFd)	P value
Row Factor x Column Factor	5.271	4	1.318	F (4 112) = 2.919	**P=0.0244**
Row Factor	36.16	4	9.039	F (4 112) = 20.02	**P<0.0001**
Column Factor	6.161	1	6.161	F (1 28) = 4.799	**P=0.0370**
Subject	35.95	28	1.284	F (28 112) = 2.844	**P<0.0001**
Residual	50.56	112	0.4514		

Table 3: 2 way ANOVA for EASI between groups receiving pimecrolimus and tofacitinib treatments

ANOVA table	SS	DF	MS	F (DFn DFd)	P value
Row Factor x Column Factor	4.537	4	1.134	F (4 112) = 0.9114	P=0.4600
Row Factor	109.4	4	27.34	F (4 112) = 21.97	**P<0.0001**
Column Factor	41.82	1	41.82	F (1 28) = 5.149	**P=0.0312**
Subject	227.4	28	8.122	F (28 112) = 6.526	**P<0.0001**
Residual	139.4	112	1.245		

Figures

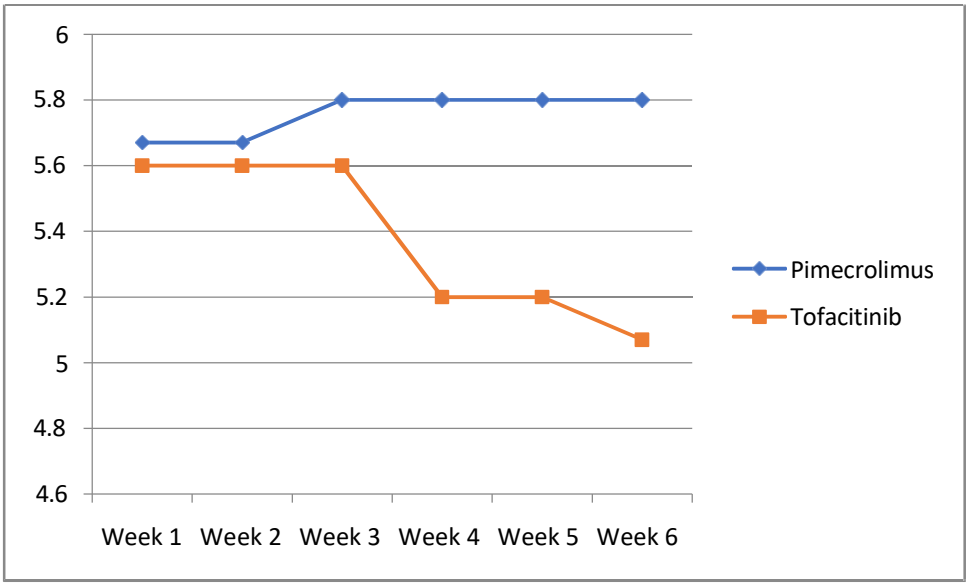

Figure 1: Change in mean of treatable % Body surface area (BSA) in groups receiving pimecrolimus and tofacitinib treatments

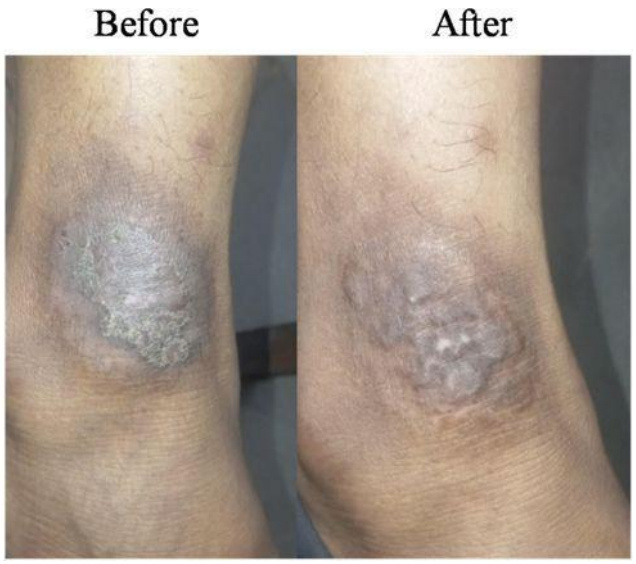

Figure 2: Clinical images of a patient with AD before and after treatment with pimecrolimus

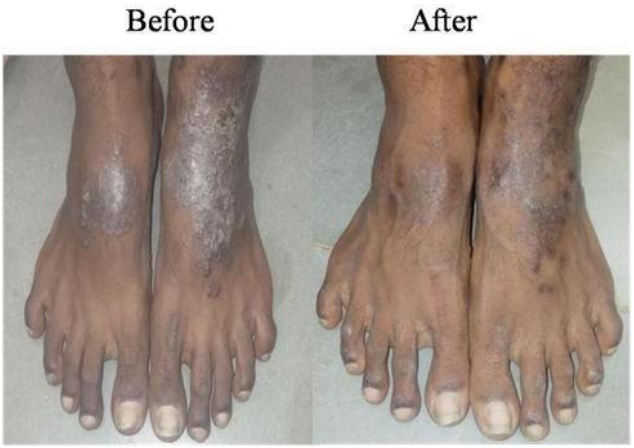

Figure 3: Clinical images of a patient with AD before and after treatment with tofacitinib

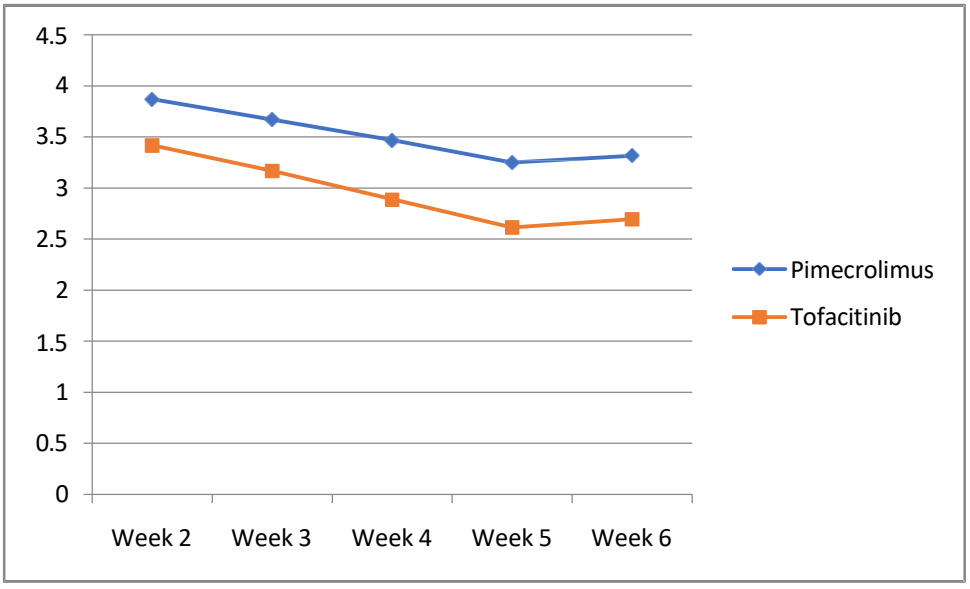

Figure 4: Change in mean of Validated Investigator Global Assessment for Atopic Dermatitis in groups receiving pimecrolimus and tofacitinib treatments

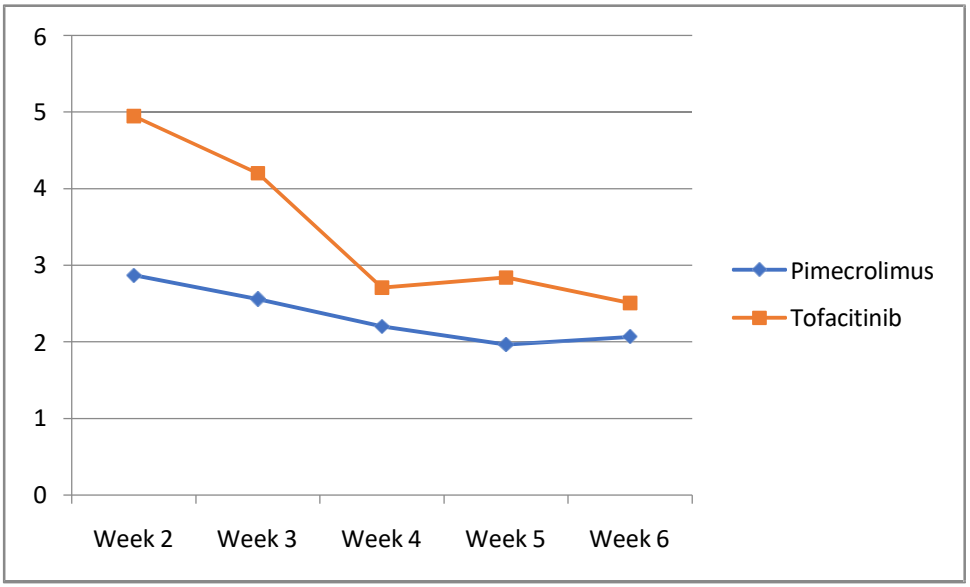

Figure 5: Change in means of Eczema area and severity index (EASI) in groups receiving pimecrolimus and tofacitinib treatments

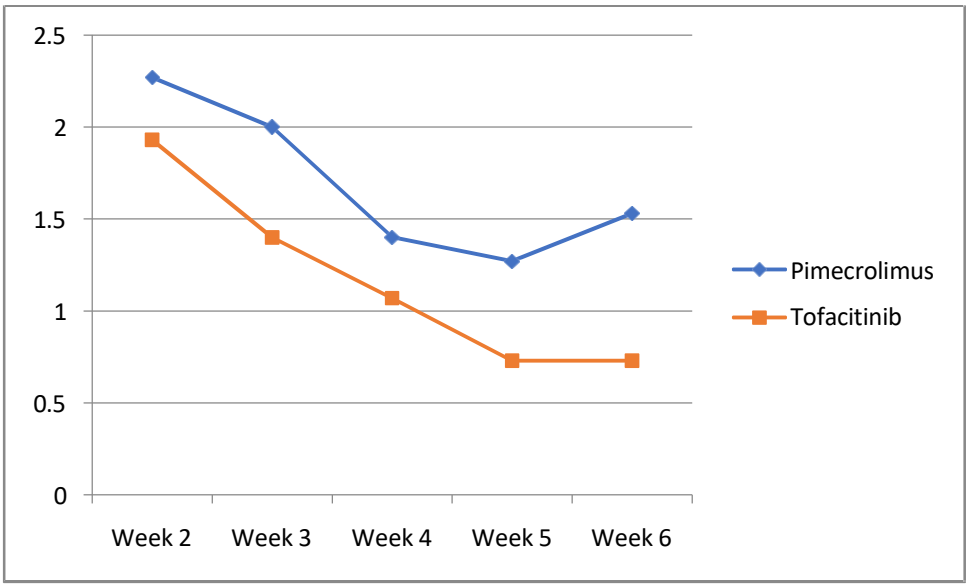

Figure 6: Change in means of Pruritis assessment scale in groups receiving pimecrolimus and tofacitinib treatments