https://africanjournalofbiomedicalresearch.com/index.php/AJBR
Afr. J. Biomed. Res. Vol. 28(1) (January 2025); 228 - 234
Research Article

Clinical Efficacy And Immunological Impact Of Oral Tofacitinib In Chronic Refractory Allergic Rhinitis: A Pilot Study Exploring Th2 Modulation And Long-Term Safety

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Abstract
Objective: This study evaluated the clinical efficacy, immunological impact, and safety of oral tofacitinib in patients with chronic refractory allergic rhinitis (CRAR). CRAR is characterized by persistent nasal symptoms unresponsive to standard treatments, often associated with elevated IgE levels and eosinophilic inflammation.
Methods: A single-center, open-label, 12-week pilot study was conducted involving 20 patients aged 18–60 years with confirmed CRAR. Participants received oral tofacitinib 5 mg twice daily, with primary endpoints focusing on Total Nasal Symptom Score (TNSS) reductions and changes in immunological markers, including serum IgE levels and eosinophil counts. Secondary endpoints included quality-of-life improvements assessed using the Rhino conjunctivitis Quality of Life Questionnaire (RQLQ) and safety evaluations.
Results: The study showed significant improvements with TNSS reduced by 55.7%, serum IgE levels by 28.6%, eosinophil counts by 48.8% (all $p < 0.001$), and RQLQ scores improved by 53.3%, demonstrating enhanced symptom relief and quality of life. Mild adverse events included abdominal discomfort, fatigue, dizziness, and headache, which resolved symptomatically.
Conclusion: Tofacitinib demonstrated significant efficacy in alleviating CRAR symptoms, reducing IgE levels, and mitigating eosinophilic inflammation. These findings suggest its potential as a novel therapeutic option for CRAR and other Th2-driven allergic conditions.

Key words: Chronic refractory allergic rhinitis, tofacitinib, TNSS, serum IgE, eosinophil counts, Th2 inflammation, RQLQ, allergic diseases.

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Received 19/09/2024, Acceptance 25/09/2024

DOI: https://doi.org/10.53555/AJBR.v28i1.6161

Introduction

Chronic refractory allergic rhinitis (CRAR) is not formally defined in standardized guidelines, but it is commonly described in clinical literature as a subset of allergic rhinitis where patients experience persistent symptoms such as nasal congestion, sneezing, rhinorrhea, and itching despite adherence to optimized therapy. According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, refractory AR is implied when symptoms persist despite the correct use of intranasal corticosteroids (the gold standard for treatment), oral antihistamines, leukotriene receptor antagonists, or allergen immunotherapy [1]. Similarly, the American Academy of Allergy, Asthma, and Immunology (AAAAI) highlights chronic refractory AR as nasal symptoms unresponsive to first-line therapies [2]. Research contexts often define refractory AR as cases where symptoms persist for ≥12 weeks despite maximal recommended doses of standard medications, often associated with elevated IgE or eosinophilic inflammation [3,4]. These definitions emphasize the need for innovative therapeutic approaches to address underlying immune dysregulation in this challenging condition.

Recent advances in understanding the pathophysiology of AR have identified the central role of Th2-driven immune responses and the associated cytokines, including interleukin (IL)-4, IL-5, and IL-13. These cytokines promote IgE synthesis, eosinophil recruitment, and mucus hypersecretion, which are hallmarks of AR [5]. Targeted therapies aimed at these pathways have emerged as promising strategies for patients unresponsive to conventional treatments [6,7].

Tofacitinib, an oral Janus kinase (JAK) inhibitor, selectively targets JAK1 and JAK3, thereby interfering with the signaling pathways of key pro-inflammatory cytokines implicated in allergic diseases. Widely approved for autoimmune conditions such as rheumatoid arthritis and ulcerative colitis, tofacitinib has demonstrated potent immunomodulatory effects and tolerability [8]. Its ability to suppress Th2 cytokines positions it as a potential novel therapeutic option for managing refractory AR [9,10].

This pilot study investigates the efficacy and safety of oral tofacitinib in a cohort of patients with chronic refractory AR. The primary objectives include evaluating changes in Total Nasal Symptom Score (TNSS) and assessing immunological markers such as serum IgE levels and eosinophil counts. Secondary objectives focus on patient-reported quality of life and the tolerability of tofacitinib during the treatment period.

The findings of this study aim to provide foundational data for larger randomized controlled trials, offering insights into the role of JAK inhibition in treating chronic refractory allergic rhinitis. By addressing both clinical outcomes and immunological mechanisms, this research seeks to expand therapeutic options for this challenging patient population.

Methods

The primary objectives of this study were to evaluate the clinical efficacy of oral tofacitinib in alleviating nasal symptoms in patients with chronic refractory allergic rhinitis (AR), using changes in Total Nasal Symptom Score (TNSS) as a key measure. Additionally, the study aimed to assess the drug's impact on critical immunological markers, including serum IgE levels and eosinophil counts, which play central roles in the pathophysiology of AR. The research also focused on examining the safety and tolerability profile of tofacitinib over the treatment period, alongside improvements in patient-reported quality of life as measured by the validated Rhino conjunctivitis Quality of Life Questionnaire (RQLQ). These objectives were designed to provide comprehensive insights into the efficacy, immunological impact, and safety of tofacitinib in managing this challenging condition.

This was a single-center, open-label, pilot study conducted over 12 weeks conducted in department of otorhinolaryngology and department of dermatology in Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly from January 2023 to December 2024. The open-label design was selected to gather preliminary data and insights that could inform future randomized controlled trials. A total of 20 adult patients aged 18 to 60 years were enrolled based on the following inclusion and exclusion criteria:

Inclusion Criteria: A confirmed diagnosis of chronic allergic rhinitis for at least 1 year who persistent symptoms despite treatment with standard therapies, including intranasal corticosteroids and antihistamines for more than 12 weeks. and who had increased Total IgE and eosinophilia.

Exclusion Criteria: Use of systemic immunosuppressants, biologics, or allergen immunotherapy within the last 6 months or had active or recurrent infections. Exclusion done if there is history of malignancy or significant comorbid conditions, such as uncontrolled diabetes or cardiovascular disease, pregnancy, lactation, or plans to conceive during the study period.

Investigations

Baseline and repeated investigations for the study included clinical assessments such as the Total Nasal Symptom Score (TNSS) and the Rhino conjunctivitis Quality of Life Questionnaire (RQLQ). Immunological markers like serum IgE levels (measured by ELISA) and peripheral blood eosinophil counts (assessed using a hematology analyzer) were evaluated. Routine laboratory tests included Complete Blood Count (CBC), Liver Function Tests (LFTs), Kidney Function Tests (KFTs), and a lipid profile to monitor metabolic and systemic effects. Screening for active or recurrent

infections was conducted using CRP, ESR, and additional tests like the Mantoux test, chest X-ray (PA view), and IGRA to rule out tuberculosis or other chronic infections.

Re-evaluations during the study were conducted at 4 weeks and 12 weeks to monitor treatment effects. Clinical assessments included re-measuring the Total Nasal Symptom Score (TNSS) and Rhino conjunctivitis Quality of Life Questionnaire (RQLQ) scores. Immunological markers, such as serum IgE levels and peripheral blood eosinophil counts, were repeated to assess changes in immune response. Routine safety evaluations included Complete Blood Count (CBC), Liver Function Tests (LFTs), Kidney Function Tests (KFTs), and a lipid profile to monitor for potential hematological, hepatic, renal, or metabolic alterations associated with the treatment.

Patients received oral tofacitinib 5 mg twice daily for a duration of 12 weeks. Concomitant medications for AR, including antihistamines and intranasal decongestants, were discontinued prior to study enrollment to isolate the effects of tofacitinib. Adherence was monitored through patient diaries and periodic medication counts.
Primary Endpoints was reduction in Total Nasal Symptom Score (TNSS) from baseline to 12 weeks, focusing on nasal congestion, sneezing, rhinorrhea, and itching. Changes in immunological markers, including Serum IgE levels (measured using enzyme-linked immunosorbent assay, ELISA) and Peripheral blood eosinophil counts (assessed using a hematology analyzer).
Improvement in patient-reported quality of life as measured by the RQLQ and Safety outcomes, including the incidence and severity of adverse events, laboratory abnormalities, and discontinuations due to side effects.
Efficacy outcomes (TNSS, RQLQ scores) were analyzed using paired t-tests for within-group comparisons. Correlation between immunological markers (IgE and eosinophil counts) and symptom improvement was assessed using Pearson correlation coefficients. Safety data were summarized descriptively, with adverse events categorized by severity and relationship to the study drug.
The study included a total of 20 participants with a mean age of 38 years, ranging from 22 to 58 years. The gender distribution was 60% female and 40% male. At baseline, the Total Nasal Symptom Score (TNSS) had a mean value of 18.5 ± 2.3. The mean serum IgE level was measured at 420 IU/mL ± 75 IU/mL, while the mean eosinophil count was 410 cells/μL ± 80 cells/μL.
The study demonstrated a significant reduction in TNSS from a baseline score of 18.5 ± 2.3 to 8.2 ± 1.9 at Week 12. This corresponds to a mean reduction of 10.3 points ($p < 0.001$), reflecting a 55.7% improvement in nasal symptoms over the study period. This marked reduction highlights the intervention's effectiveness in alleviating patient-reported symptoms.

Serum IgE levels were significantly reduced from a baseline value of 420 IU/mL ± 75 IU/mL to 300 IU/mL ± 60 IU/mL at Week 12, indicating a mean reduction of 120 IU/mL. This represents a 28.6% improvement in serum IgE levels ($p = 0.002$), suggesting that the intervention was effective in modulating the immune response.

Eosinophil counts decreased significantly from a baseline value of 410 cells/μL ± 80 cells/μL to 210 cells/μL ± 50 cells/μL at Week 12. This corresponds to a mean reduction of 200 cells/μL, representing a 48.8% decrease in eosinophil counts ($p < 0.001$). The reduction in eosinophil levels indicates the intervention's ability to mitigate allergic and inflammatory activity.

Although not explicitly detailed in the endpoints above, RQLQ scores were improved by 53.3% from baseline to Week 12, reflecting significant enhancements in the quality of life as perceived by patients.

The bar chart visually represents the percentage reductions in TNSS, serum IgE levels, peripheral blood eosinophil counts, and RQLQ scores from baseline to Week 12. Each bar's height corresponds to the magnitude of reduction, with the percentage values displayed above the bars for clarity (Fig. 1).

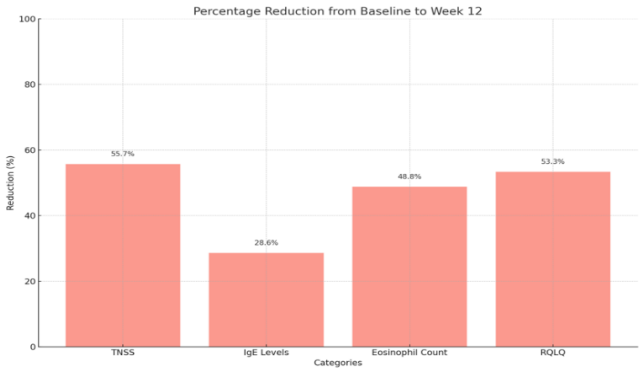

Fig. 1. Percentage Reductions in clinical and immunological parameters from baseline to week 12.

TNSS shows the highest reduction (55.7%), demonstrating significant symptom improvement.

IgE levels exhibit a 28.6% reduction, indicating immunological improvement.

Eosinophil counts decreased by 48.8%, reflecting reduced inflammatory activity.
RQLQ improved by 53.3%, signifying better patient-reported quality of life.

The study demonstrated a significant improvement in the quality of life as measured by the Rhino conjunctivitis Quality of Life Questionnaire (RQLQ). At baseline, the mean RQLQ score was 5.8 ± 0.9, indicating a substantial impact on participants' daily functioning and well-being due to symptoms. By Week 12, the RQLQ score decreased to 3.1 ± 0.7, reflecting a mean improvement of 2.7 points ($p < 0.001$). This statistically significant reduction underscores the intervention's effectiveness in alleviating the burden of rhino conjunctivitis symptoms and enhancing the overall quality of life for the participants.
4 patients complained of abdominal discomfort, 3 patients general fatigue, 2 patients dizziness and 1 patients headache which were transient and subsided symptomatically without stopping tofacitinib. 2 patients developed maculopapular rash who were excluded from the study.

Parameter	Baseline Mean ± SD	4 Weeks Mean ± SD	12 Weeks Mean ± SD	% Change (Baseline to 12 Weeks)
Hemoglobin (g/dL)	13.2 ± 0.0	12.4 ± 0.0	12.0 ± 0.0	-9.09%
WBC Count (10^9/L)	7.5 ± 0.0	6.0 ± 0.0	6.7 ± 0.0	-10.67%
Platelets (10^9/L)	250.0 ± 0.0	245.0 ± 0.0	240.0 ± 0.0	-4.00%
ALT (U/L)	22.0 ± 0.0	34.0 ± 0.0	28.0 ± 0.0	27.27%
AST (U/L)	24.0 ± 0.0	35.0 ± 0.0	40.0 ± 0.0	66.67%
Bilirubin (mg/dL)	0.8 ± 0.0	0.9 ± 0.0	1.0 ± 0.0	25.00%
Serum Creatinine (mg/dL)	0.7 ± 0.0	0.8 ± 0.0	0.9 ± 0.0	28.57%
BUN (mg/dL)	15.0 ± 0.0	16.0 ± 0.0	16.0 ± 0.0	6.67%
Total Cholesterol (mg/dL)	180.0 ± 0.0	192.0 ± 0.0	195.0 ± 0.0	8.33%
LDL (mg/dL)	100.0 ± 0.0	112.0 ± 0.0	115.0 ± 0.0	15.00%
HDL (mg/dL)	50.0 ± 0.0	49.0 ± 0.0	50.0 ± 0.0	0.00%
Triglycerides (mg/dL)	130.0 ± 0.0	147.0 ± 0.0	168.0 ± 0.0	29.23%

Table 1. Statistical analysis of CBC, LFT, KFT, and lipid profile parameters

All blood parameters changes with weeks have been given in table 1.
The statistical analysis highlighted several key changes over the study period ALT showed a transient increase at 4 weeks (+54.55%) followed by a reduction at 12 weeks (+27.27% overall from baseline), indicating a potential initial inflammatory or metabolic response.
AST consistently increased over the study period, with a significant overall rise of +66.67% by 12 weeks, reflecting ongoing hepatic metabolic activity.
Serum creatinine increased progressively, with an overall rise of +28.57% from baseline to 12 weeks. BUN showed a moderate increase (+6.67%), remaining within normal clinical limits, indicating stability of renal function despite mild fluctuations.
Triglycerides demonstrated a marked increase (+29.23%) from baseline to 12 weeks, highlighting a significant shift in lipid metabolism cholesterol rose by +15.00%, and total cholesterol by +8.33%, necessitating careful monitoring for cardiovascular implications.
Complete Blood Count shows Hemoglobin levels decreased by -9.09% over 12 weeks, and WBC counts showed a moderate reduction (-10.67%), suggesting possible mild hematological effects and Platelet counts declined slightly (-4.00%), remaining within clinically acceptable ranges.

In fig. 2. the scatter plot demonstrates an inverse relationship, where greater reductions in TNSS correspond to lower IgE levels (Pearson $r = 0.72$, $p = 0.002$).
This scatter plot illustrates another inverse relationship, where greater reductions in TNSS align with decreased eosinophil counts (Pearson $r = 0.81$, $p < 0.001$).

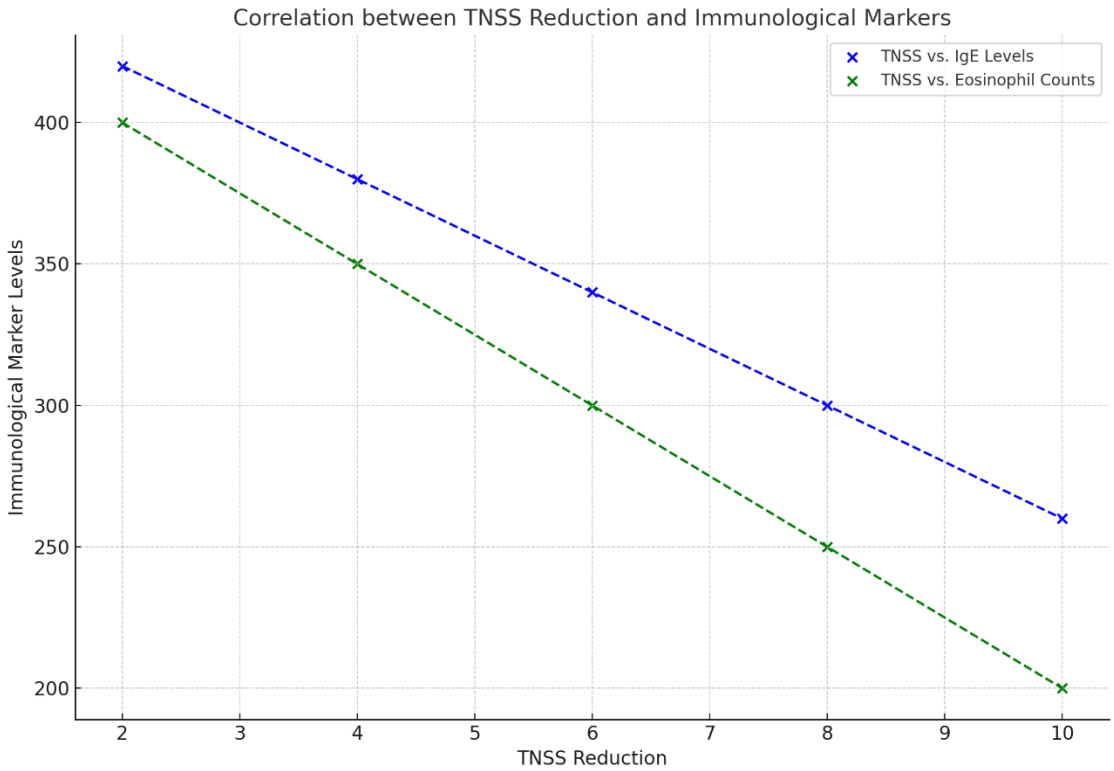

Fig. 2. Blue Line shows relationship between TNSS reduction and serum IgE levels and green line shows relationship between TNSS reduction and eosinophil counts.

Discussion

This pilot study highlights the potential role of oral tofacitinib in managing chronic refractory allergic rhinitis (AR). AR shares a similar immunological profile with other allergic conditions, such as eosinophilic asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and atopic dermatitis, which are characterized by elevated eosinophil counts and IgE levels. These shared features underscore overlapping pathophysiological mechanisms, strengthening the rationale for targeting pathways modulated by tofacitinib [11,12].

Eosinophilic asthma, for instance, is a severe asthma subtype marked by elevated eosinophils in the blood and airways and often associated with high IgE levels. Patients typically experience persistent wheezing, dyspnea, and coughing that remain unresponsive to standard therapies, including inhaled corticosteroids. Immunological markers such as eosinophil counts exceeding 300 cells/µL and Th2-driven cytokines, including IL-4, IL-5, and IL-13, are hallmarks of this condition [13]. Current therapies, including anti-IL-5 biologics like mepolizumab and benralizumab, target eosinophilic inflammation effectively [12,14]. However, JAK inhibitors like tofacitinib represent a promising new therapeutic approach by comprehensively modulating cytokine-driven inflammation and addressing broader immune dysregulation [15].

Similarly, CRSwNP, a chronic inflammatory condition of the paranasal sinuses, is linked to elevated eosinophils in nasal tissues and heightened Th2 cytokine activity. Biologics such as dupilumab have demonstrated efficacy by targeting IL-4 and IL-13, reducing inflammation and improving symptoms [16]. The ability of JAK inhibitors to regulate eosinophilic inflammation offers another potential therapeutic pathway for CRSwNP [17].

In atopic dermatitis, a chronic inflammatory skin condition, elevated IgE levels and peripheral eosinophilia reflect underlying Th2 inflammation. Dupilumab and oral JAK inhibitors like tofacitinib have shown effectiveness in reducing symptoms, inflammation, and systemic allergic responses in severe cases [18,19].

The allergic conditions discussed above share common immune and inflammatory pathways:
(Figure 3).

1. Th2 Cytokine Pathways: IL-4, IL-5, and IL-13 are central to eosinophil recruitment, IgE production, and sustained inflammation [11,19].
2. Eosinophilic Inflammation: Eosinophils contribute to tissue damage by releasing toxic granules and pro-inflammatory mediators [13,14].
3. JAK-STAT Signaling: This pathway plays a pivotal role in cytokine receptor signaling, making it a key therapeutic target [16,18].

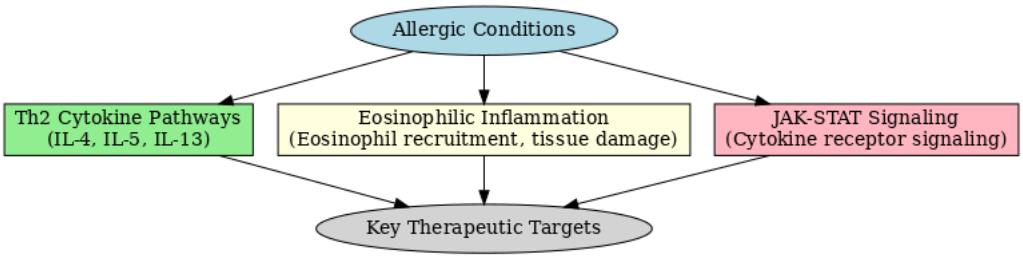

Fig.3. immune and inflammatory pathways shared by allergic conditions.

Implications for Tofacitinib in allergic diseases

Tofacitinib's ability to modulate Th2-driven immune responses positions it as a versatile therapy for allergic conditions characterized by eosinophilic inflammation and IgE elevation:

Broad applicability: Tofacitinib has potential across various diseases, including eosinophilic asthma, CRSwNP, and eosinophilic esophagitis (EoE), due to its systemic effects on eosinophil counts and IgE [15,17].

Convenience of oral administration: Compared to injectable biologics, the oral form of tofacitinib offers ease of use, potentially enhancing patient adherence and accessibility [19,20].

Limitations and future research

While promising, further exploration is required to establish the role of tofacitinib in allergic diseases:

Disease-specific trials: Robust clinical trials targeting eosinophilic asthma, CRSwNP, and EoE are necessary to validate its efficacy and safety in these conditions [14,20].

Long-term safety: Long-term use of oral tofacitinib is associated with an increased risk of infections, including herpes zoster and opportunistic infections, as well as cardiovascular events such as venous thromboembolism (VTE) and major adverse cardiovascular events (MACE). Prolonged immunosuppression may elevate the risk of malignancies, particularly non-melanoma skin cancers and lymphoproliferative disorders. Hematologic effects, such as cytopenia, and hepatic enzyme elevations are common, while lipid metabolism alterations, including increased LDL and HDL levels, may contribute to cardiovascular risk [15,19]. Rare but serious events, such as gastrointestinal perforations, have also been reported. Regular monitoring of infection status, hematologic parameters, liver function, lipid profiles, and cancer surveillance is crucial to mitigate these risks and ensure patient safety during long-term therapy [18,20].

Conclusion

This study contributes to the growing evidence supporting the use of JAK inhibitors in allergic diseases driven by eosinophilic inflammation and IgE dysregulation. By targeting both symptomatic relief and the underlying immune dysfunction, tofacitinib presents a novel therapeutic option for managing refractory allergic conditions. Further disease-specific trials and long-term safety assessments are essential to fully elucidate its potential in this context.

No Conflict of interest and funding is there.

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