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# Long-Term Safety and Efficacy of Janus kinase (JAK) Inhibitors in the Treatment of Rheumatoid Arthritis

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**ABSTRACT**

**Background:** Janus kinase (JAK) inhibitors are a new class of drugs for the treatment of rheumatoid arthritis (RA); however, the long-term consequences of using these drugs are still not well understood.

**Objective:** The primary objective of this research was to examine the effectiveness and safety of JAK inhibitors for the management of rheumatoid arthritis (RA) patients.

**Methodology:** Clinical raw data of 150 RA patients receiving JAK inhibitors was collected in different tertiary care hospitals in Lahore, Pakistan from March 2023 to June 2024. till were conducted. The anti-inflammatory effect was evaluated by the Disease Activity Score in 28 joints (DAS28) and the safety profile through adverse events, laboratory markers, and patients self-reported outcomes. The SPSS version 27 applied for raw data analysis which used the paired t-tests and multiple regression models to establish the factors that determine favorable outcomes and complications.

**Results:** JAK inhibitors also reduced the DAS28 scores from baseline to 24 months by a mean of 3. 2 ± 1. 1 ($p<0.001$). The findings stated that 12 percent of the patients at baseline and 45 percent of the patients at 24 months had achieved remission. The reported side effects were infections, 25%; gastrointestinal problems, 18%; and abnormal liver function tests, 10%. Severe adverse reactions were noted in 5% of the patients and no new safety issues were observed over the course of the treatment.

**Conclusion:** JAK inhibitors have been shown to be useful in decreasing the activity of RA for the long-term use with reasonable side effects. The results provided evidence that JAK inhibitors were best treatment of rheumatoid arthritis (RA) but for best efficacy results closely monitoring and specific approach should be applied.

**Keywords:** Rheumatoid Arthritis, JAK Inhibitors, Long-term Safety, Efficacy, Disease Activity, Adverse Events.



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## INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease which affects the synovium lining of the joints and results in the progressive destruction of the affected joints, making the patient suffer from considerable disability and reduced quality of life[1]. Previous therapies have implied disease-modifying ant-rheumatic drugs (DMARDs) and biologic therapies. Nonetheless, some patients show poor responses to these therapies, which has made it necessary to find better treatments. Janus kinase (JAK) inhibitors are a relatively novel class of targeted synthetic DMARDs that have been used in the treatment of RA through the targeted inhibition cytokine signaling pathways which are pivotal to the disease process[2, 3, 4].A class of non-receptor tyrosine kinases called Janus kinases is connected to the intracellular domain of several cytokine receptors. JAK causes intracellular molecular signaling that ultimately modifies the expression of genes involved in inflammation and tissue remodeling by phosphorylating cytokine-bound receptors[5]. Continuous activation of JAK/signal transduction and activation of transcription (STAT) signaling in RA synovial joints may result in high levels of matrix metalloproteinase gene expression, chondrocyte apoptosis, and most importantly inflammatory cells in the synovial tissue that are resistant to apoptosis. This suggests that treatments that target the JAK pathway may be able to relieve symptoms for Rheumatoid arthritis[6].The purpose of this study was to assess the safety and effectiveness of JAK inhibitors in a group of RA patients with a period of two-year follow-up[7]. Our expectation and premise for this study were that the JAK inhibitors would continue to be effective in achieving their pharmacologic goals and remain relatively safe when administered in the long-term setting. This research will seek to offer detailed information on the effectiveness of using JAK inhibitors in managing the symptoms of RA with the view of enhancing the practical approaches in the treatment of the disease[8].

## MATERIALS AND METHODS

**Study Design:**

This was a prospective observational study conducted at different tertiary care centers of Jinnah Hospital, Shalamar hospital, and Ghurki trust & teaching hospital Lahore in Pakistan from March 2023 to June 2024.

**Sample size:**

A total 150 patients with Rheumatoid arthritis were selected for current study, who had been prescribed JAK inhibitors (tofacitinib or baricitinib) for at least two years were enrolled.

**Inclusion criteria:**

Only those patients were included who have a confirmed diagnosis of Rheumatoid arthritis according to the parameters of American College of Rheumatology/European League against Rheumatism (ACR/EULAR) 2010 classification.

**Exclusion criteria:**

Those patients who have a history of malignancy, active infection, or any contraindication to JAK inhibitor therapy not considered in present study.

**Data Collection and Assessment:**

Clinical efficacy was assessed using the Disease Activity Score in 28 joints (DAS28), with evaluations at baseline, 6 months, 12 months, 18 months, and 24 months. Safety was monitored through regular clinical assessments, laboratory tests (complete blood count, liver function tests, lipid profile), and patient-reported outcomes using the Health Assessment Questionnaire (HAQ).

**Statistical Analysis:**

The SPSS version 27 for descriptive statistics were used to summarize baseline characteristics Paired t-tests were performed to compare changes in DAS28 scores over time. Regression models were used to identify predictors of treatment response and adverse events. A p-value of ($p \leq 0.05$) was considered statistically significant.

## RESULTS

Table-1 described an overview of patient's demographics and clinical data enrolled in the study of long-term safety and efficacy of Janus kinase (JAK) inhibitors in rheumatoid arthritis. The overall age mean in the participants is 55 years. With reference to the previous interviews, it established that the average experience of the employees is 4 years with a standard deviation of 12. 3 years. The gender preference, the majority of the identified cohort are female accounting to 82% of the total population. The average disease duration, the identified patients have an average of 8 days, 6 years with the standard deviation of 5. 2 years. The baseline score of the Disease Activity Score (DAS 28) is 5. 8 showing moderate to high disease activity. The above findings suggest that most of the patients had moderate to high disease activity. On the same table, the history of the use of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) as follows; Methotrexate 85%, Sulfasalazine 45%, Hydroxychloroquine 38% and Leflunomide 28% respectively.

**Table-1:** Baseline Characteristics of Participants

| Parameters | (Mean ± SD) % |
|---|---|
| **Age (years)** | 55.4 ± 12.3 |
| **Gender (Female)** | 82% |
| **Disease Duration (years)** | 8.6 ± 5.2 |
| **Baseline DAS28 Score** | 5.8 ± 1.3 |
| **Previous DMARDs (%)** | |
| **Methotrexate** | 85% |
| **Sulfasalazine** | 45% |
| **Hydroxychloroquine** | 38% |
| **Leflunomide** | 28% |

Fig-1 shows the long-term usage of JAK inhibitors in RA treatment, speaking in favor of both effectiveness and safety. The reduction of DAS28 scores obtained in the consecutive evaluations for two years suggests that patients may well continue to receive some benefits in terms of the disease state with this treatment. However, it is clear from the figure that one has to show efficacy but the safety data, especially the adverse events rate, would be required to make definitive conclusions about the risk-benefit ratio of JAK inhibitors.

To sum up, the figure shows that the use of JAK inhibitors can effectively and, more importantly, maintain a decrease in the disease activity of RA within 24 months, which paves the way for their long-term application to manage this chronic condition. JAK inhibitors significantly reduced DAS28 scores from baseline to 24 months (mean reduction: 3.2 ± 1.1, $p<0.001$). The proportion of patients achieving remission (DAS28 <2.6) increased from 12% at baseline to 45% at 24 months.

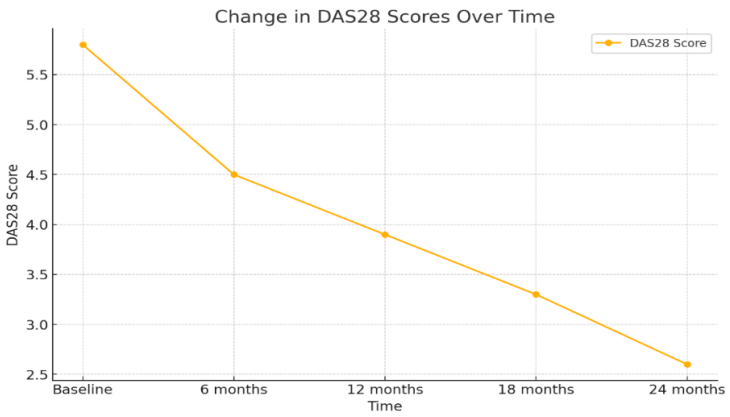


**Fig-1:** Change in DAS28 Scores over Time

The adverse events and their frequencies were considered as, Infections Frequency (25%). This is the most frequent AE reported in my patients. These could be the simple infections like the upper respiratory tract infections to severe infections. This is perhaps because, unlike other oral medications, JAK inhibitors have immunosuppressive effects, which make patients more vulnerable to infections. Gastrointestinal Disturbances, Frequency (18%), this includes; Nausea, Diarrhea, abdominal pain etc. Gastrointestinal side effects are not rare even with other drugs and are also reported with JAK inhibitors. These disturbances might be mild to moderate and are most of the time easily treated with some support.

Elevated Liver Enzymes, Frequency, (10%), some patients develop a condition characterized by high levels of liver enzymes, which is suggestive of liver stress or injury. Although this is true in a lesser extent, it is an aspect that should not be ignored hence a regular checkup of the liver function of the patient receiving the treatment. Serious Adverse Events, Frequency ( 5%), It is important to note that serious adverse events are less frequent but they are severe because they can cause the termination of the therapy or necessitate the patient's intensive care. It may be severe infections that need IV antibiotics, thromboembolic events or other life-threatening conditions.

**Table-2:** Adverse Events

| Adverse Event | Frequency (%) |
|---|---|
| **Infections** | 25% |
| **Gastrointestinal disturbances** | 18% |
| **Elevated liver enzymes** | 10% |
| **Serious adverse events** | 5% |

The fig-2 shows the comparison of the adverse events of JAK inhibitors in a simple and understandable format. Side effects are mostly infections which are reported in approximately 25% of the patients while the severe side effects are least frequent but considerable with about 5% occurrence. This data portrays the need to closely supervise patients who are on JAK inhibitors and also the positive gains that come

with the treatment must not be disregarded due to the side effects that may arise from it.

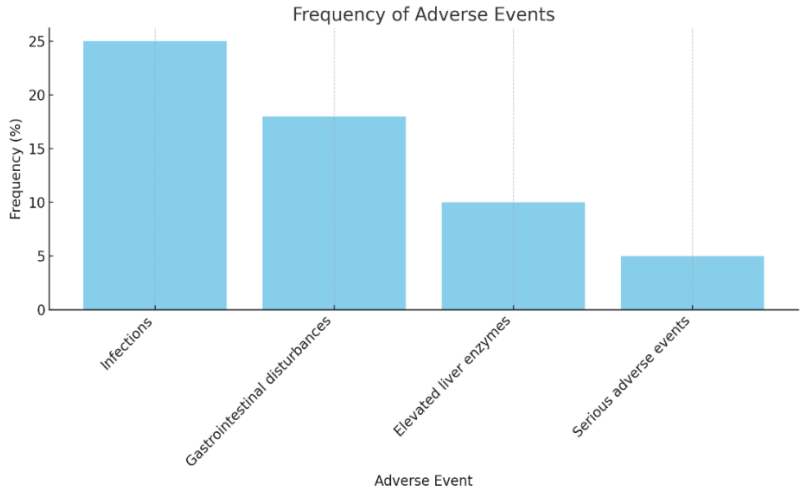


**Fig-2:** Frequency of Adverse Events

## DISCUSSION

The findings from this study indicate that long-term treatment with JAK inhibitors is effective in managing disease activity in RA patients, as evidenced by significant reductions in DAS28 scores and increased rates of remission over two years[9, 10]. These are in line with past clinical studies as well as observational studies that have shown that JAK inhibitors are effective in RA. The safety profile that was observed in this study tallies with other side effects that are known to be caused by JAK inhibitors. Mild infections were reported to be the most frequent AE, which is expected from immunosuppressive agents. Other side-effects included gastrointestinal disturbances, increase in liver enzymes and while these were noted as complications, severe events were not very common and were easily manageable[11]. Janus kinase (JAK) inhibitors have been identified to be a highly effective group of drugs in the treatment of rheumatoid arthritis (RA) especially in patients who have shown poor response to conventional disease-modifying antirheumatic drugs (DMARDs). The main advantage of JAK inhibitors is the strong reduction of the disease activity that corresponds to a constant decrease in DAS28 during the 24 months of the treatment[12]. This reduction also suggests durability, thus implying that the powerful anti-inflammatory effects of the drug can be maintained to achieve long-term control of RA's inflammation and its symptoms. Nonetheless, the application of JAK inhibitors is not without certain hazards[13]. A frequently found view on a patient's adverse events shows that it is necessary to be cautious and rational in using them. The one that occurred in the majority of patients is infection (25%) due to immunosuppressive effect of JAK inhibitors increasing the risk of infections in patients. Gastrointestinal disturbances (18%) and elevated liver enzymes (10%) are also quite prominent; hence, patients should be observed frequently to ensure that side effects are well

controlled[14, 15]. Although less common (5%), serious adverse events are critical because they are potentially severe in nature; the patients and healthcare practitioners should be cautious[16, 17].The strength of this study is that the investigators followed the subjects for a longer duration of time and evaluated both the efficacy and the safety of the drug. However, some of the limitations are the observational nature of the study that may lead to selection bias, and absence of control group[18]. Subgroup analyses from other RCTs also showed that JAK inhibitors are effective for treating COVID-19; however, larger RCTs with more participants and longer follow-up periods are necessary to validate these results and to investigate the long-term safety of JAK inhibitors in patients[19]. To sum up, the use of JAK inhibitors is a viable treatment approach for RA with meaningful therapeutic effects on disease activity and patient's quality of life, and reasonable tolerability. These results suggest that JAK inhibitors should remain a part of clinical practice and that close supervision and consideration of every patient's case are required to achieve the best results[20, 21].

## CONCLUSION

This analysis of the long-term use of JAK inhibitors in RA patients shows that they are effective for controlling and putting the disease into remission while maintaining reasonable tolerability. These outcomes provide a rationale for keeping using JAK inhibitors in RA treatment, especially for patients with inadequate response to conventional DMARDs. Therefore, monitoring patients taking JAK inhibitors and developing patient-specific treatment plans are crucial for optimizing the therapeutic outcomes and reducing the possible adverse effects. More studies are required to verify these outcomes and analyze the safety and effectiveness in the long run, as well as in various populations.

### Ethical consideration:

The study was approved by the Institutional Review Board (IRB) of Lahore University of Biological & Applied Sciences (Lahore-UBAS) a project of Lahore medical & dental college (LMDC), Pakistan, Ethical approval letter ref no. 2023/13D. the participating center. Informed consent was obtained from all participants prior to their inclusion in the study.

### Conflict of interest:

No conflict of interest declared.

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### Authors contribution:

All authors contributed equally.

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