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# Comparative Risk of Infections in Rheumatoid Arthritis Patients Treated with Tofacitinib vs. Adalimumab: A Retrospective Study from a Tertiary Center in Saudi Arabia

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**Abstract** **Background:** Rheumatoid arthritis (RA) is a chronic autoimmune disease that increases patients' vulnerability to both severe and non-severe infections due to immune dysregulation and the use of immunosuppressive therapies. Tofacitinib, a Janus kinase (JAK) inhibitor and adalimumab, an anti-TNF biologic DMARD, are commonly used in RA management but their comparative infection risks remain unclear, especially in local populations. **Materials and Methods:** A retrospective observational study was conducted at King Abdulaziz University Hospital in Jeddah, Saudi Arabia. Medical records of RA patients treated with either tofacitinib or adalimumab between January 2018 and February 2023 were reviewed. Patient demographics, treatment characteristics and outcomes including infection-related hospital admissions, ER visits and adverse events were analyzed using descriptive and inferential statistics via Jamovi software. **Results:** A total of 86 RA patients were included (88.4% female; median age 52.5 years). Tofacitinib was prescribed to 54.7% and adalimumab to 45.3% of patients. The two groups were similar in age, sex, BMI and disease duration. Tofacitinib-treated patients had higher rates of seropositivity and were more likely to receive monotherapy, whereas adalimumab-treated patients more frequently received combination therapy with methotrexate. Infection-related hospitalizations (8.5% vs. 10.3%) and major adverse cardiovascular events were comparable between groups. However, ER visits due to pain were significantly more common in the adalimumab group (28.2% vs. 6.4%, p = 0.023), suggesting better symptom control in the tofacitinib group. **Conclusion:** While infection and cardiovascular event rates did not significantly differ between treatment groups, tofacitinib may provide better pain control, as evidenced by fewer ER visits. Baseline differences such as seropositivity and combination therapy use should be considered in future studies. These findings provide real-world insight into RA treatment safety profiles in a Saudi population.

**Key Words** Rheumatoid arthritis, Tofacitinib, Adalimumab, Infection risk, Biologic therapy, JAK inhibitors, Saudi Arabia

## INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic autoimmune disease characterized by systemic inflammation that primarily affects the joints but also poses significant risks to overall health [1,2]. RA patients are particularly prone to infections, both severe and non-severe, due to a combination of factors including the immunological nature of the disease, comorbid conditions and the immunosuppressive effects of various RA therapies [3,4].

Over the past few decades, the management of RA has evolved significantly with the advent of disease-modifying anti-rheumatic drugs (DMARDs), which include conventional synthetic DMARDs, biologic DMARDs such as tumor necrosis factor inhibitors (anti-TNF agents) and more recently, targeted synthetic DMARDs like Janus kinase (JAK) inhibitors [5-7]. While these agents have improved disease control and patient outcomes, they are also associated with notable adverse effects, most importantly an increased risk of infections [2,8].

JAK inhibitors, such as tofacitinib, target intracellular signaling pathways involved in the immune response and have emerged as effective alternatives to biologic therapies [9]. However, concerns have been raised regarding their safety profile, particularly in relation to infections, malignancy and cardiovascular events. Regulatory authorities such as the U.S. Food and Drug Administration

(FDA) have issued warnings and mandated comparative safety trials of JAK inhibitors versus TNF inhibitors due to these risks [2,10-12].

Adalimumab, a widely used anti-TNF biologic, is a fully human monoclonal antibody that inhibits TNF-α, a pro-inflammatory cytokine central to RA pathogenesis [13,14]. Its clinical efficacy in reducing disease activity and improving functional outcomes is well documented [15,16]. Nevertheless, like other biologic DMARDs, adalimumab is associated with increased susceptibility to serious infections, including bacterial, viral and opportunistic pathogens [17].

Although international studies have evaluated infection risks across different RA therapies, findings remain inconclusive. Some data suggest that anti-TNF agents may pose a relatively lower risk compared to JAK inhibitors, while others report comparable infection rates [9,18-20]. Moreover, treatment response and safety profiles may vary across populations due to factors such as ethnicity, genetic background and comorbidity burden [21].

In Saudi Arabia (KSA), limited data exist regarding the comparative safety of RA therapies and no national registry currently captures long-term treatment outcomes. Cultural, genetic and healthcare system differences highlight the need for localized research to guide therapeutic decision-making [22].

This study aims to assess and compare the incidence of infections and related complications in RA patients treated with tofacitinib versus those receiving adalimumab at a tertiary center in Saudi Arabia. By addressing this gap, the findings will contribute valuable real-world evidence to inform safer and more effective RA treatment strategies within the region.

## MATERIALS AND METHODS

### Study Design and Setting

This retrospective observational study was conducted at King Abdulaziz University Hospital (KAUH), a tertiary care academic institution located in Jeddah, Saudi Arabia. The study aimed to compare infection rates and related complications among patients with Rheumatoid Arthritis (RA) who were treated with either tofacitinib or adalimumab. Data were obtained through a comprehensive review of patient medical records from January 2018 to February 2023.

### Study Population

The study included adult patients (aged 18 years or older) who had been diagnosed with RA based on the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [1]. Eligible patients had received either tofacitinib or adalimumab and were followed at the rheumatology clinic at KAUH during the specified timeframe. From a broader cohort of approximately 250 RA patients treated at the institution, a final sample of 86 patients was identified who met the study's inclusion criteria and were being managed with one of the two targeted therapies.

### Ethical Considerations

This study was approved by the Ethical Committee of King Abdulaziz University (approval number: 189-23). Given the retrospective design, informed consent was waived. Patient data were anonymized to maintain confidentiality and access to the records was restricted to authorized study personnel, in accordance with institutional data protection policies.

### Data Collection

Data extracted from medical records included patient demographics (age, sex, body mass index), RA characteristics (disease duration, rheumatoid factor and anti-cyclic citrullinated peptide antibody status), treatment details (monotherapy or combination therapy with methotrexate or corticosteroids) and clinical outcomes. Outcome variables included infection-related hospital admissions, Emergency Room (ER) visits, adverse events, drug discontinuation and Major Adverse Cardiovascular Events (MACE). Specific infection diagnoses such as COVID-19, urinary tract infections, herpes zoster and pneumonia were also documented. Additional data on comorbidities and pain-related ER visits were collected to support comparative analysis.

### Statistical Analysis

The collected data were entered and organized using Microsoft Excel and subsequently analyzed using the Jamovi statistical software package (version X.X) [2]. Continuous variables were assessed for normality. Normally distributed data were expressed as mean and Standard Deviation (SD), while non-normally distributed data were presented as median and interquartile range (IQR). Categorical variables were summarized using frequencies and percentages. For comparison between the tofacitinib and adalimumab groups, independent t-tests were applied to normally distributed continuous variables, while one-way ANOVA was used where appropriate. The chi-square test or Fisher's exact test was used to compare categorical variables. A p-value less than 0.05 was considered statistically significant.

## RESULTS

A total of 86 patients diagnosed with rheumatoid arthritis (RA) were included in the study. The majority of participants were female (88.4%), with a median age of 52.5 years (interquartile range: 42.3-61.0). Of these, 47 patients (54.7%) received tofacitinib, while 39 patients (45.3%) were treated with adalimumab.

Body Mass Index (BMI) data were available for 85 patients. Most were classified as either overweight (29.1%) or obese (39.5%). There were no statistically significant differences between the two treatment groups in terms of age, sex or BMI (Table 1).

Table 1: Baseline Characteristics of Rheumatoid Arthritis Patients Treated with Tofacitinib and Adalimumab

| Variable | | Adalimumab (N = 39) | Tofacitinib (N = 47) | Total (N = 86) | p-value |
|---|---|---|---|---|---|
| Age | Median | 48 | 54 | 52.5 | 0.2461 |
| | IQR | [39.0-62.5] | [45.5-60.0] | [42.3- 61.0] | |
| Gender | Female | 34.0 (87.2%) | 42.0 (89.4%) | 76.0 (88.4%) | 0.7532 |
| | Male | 5.0 (12.8%) | 5.0 (10.6%) | 10.0 (11.6%) | |
| Weight/Hight (BMI) | Normal | 11.0 (28.2%) | 12.0 (25.5%) | 23.0 (26.7%) | 0.6242 |
| | Not documented | 0.0 (0.0%) | 1.0 (2.1%) | 1.0 (1.2%) | |
| | Obese | 17.0 (43.6%) | 17.0 (36.2%) | 34.0 (39.5%) | |
| | Overweight | 9.0 (23.1%) | 16.0 (34.0%) | 25.0 (29.1%) | |
| | Underweight | 2.0 (5.1%) | 1.0 (2.1%) | 3.0 (3.5%) | |
| RA diagnosis | 3-5 years | 6.0 (15.4%) | 5.0 (10.6%) | 11.0 (12.8%) | 0.1192 |
| | 5-10 years | 19.0 (48.7%) | 22.0 (46.8%) | 41.0 (47.7%) | |
| | More than 10 years | 9.0 (23.1%) | 19.0 (40.4%) | 28.0 (32.6%) | |
| | Recent (less than 3 years) | 5.0 (12.8%) | 1.0 (2.1%) | 6.0 (7.0%) | |
| RA type | Seronegative | 29.0 (74.4%) | 6.0 (12.8%) | 35.0 (40.7%) | <0.0012 |
| | Seropositive | 10.0 (25.6%) | 41.0 (87.2%) | 51.0 (59.3%) | |
| RF level at diagnosis | NEGATIVE <20 U/ml | 27.0 (69.2%) | 6.0 (12.8%) | 33.0 (38.4%) | <0.0012 |
| | POSITIVE 20-50 U/ml | 1.0 (2.6%) | 9.0 (19.1%) | 10.0 (11.6%) | |
| | POSTIVE >51 U/ml | 8.0 (20.5%) | 25.0 (53.2%) | 33.0 (38.4%) | |
| | Done outside, seropositive in the note | 0.0 (0.0%) | 1.0 (2.1%) | 1.0 (1.2%) | |
| | Test not available | 3.0 (7.7%) | 6.0 (12.8%) | 9.0 (10.5%) | |
| Anti-CCP level at diagnosis | Done outside, seropositive in the note | 0.0 (0.0%) | 1.0 (2.1%) | 1.0 (1.2%) | <0.0012 |
| | Negative | 15.0 (38.5%) | 4.0 (8.5%) | 19.0 (22.1%) | |
| | Not available | 15.0 (38.5%) | 14.0 (29.8%) | 29.0 (33.7%) | |
| | Positive | 9.0 (23.1%) | 28.0 (59.6%) | 37.0 (43.0%) | |
| Single VS double VS Triple | Double | 17.0 (43.6%) | 15.0 (31.9%) | 32.0 (37.2%) | 0.0022 |
| | Single | 11.0 (28.2%) | 29.0 (61.7%) | 40.0 (46.5%) | |
| | Triple | 11.0 (28.2%) | 3.0 (6.4%) | 14.0 (16.3%) | |
| Single VS combined | Combined | 28.0 (71.8%) | 18.0 (38.3%) | 46.0 (53.5%) | 0.0022 |
| | Single | 11.0 (28.2%) | 29.0 (61.7%) | 40.0 (46.5%) | |
| Prednisolone | No | 32.0 (82.1%) | 37.0 (78.7%) | 69.0 (80.2%) | 0.7002 |
| | Yes | 7.0 (17.9%) | 10.0 (21.3%) | 17.0 (19.8%) | |
| Methotrexate | No | 17.0 (43.6%) | 38.0 (80.9%) | 55.0 (64.0%) | <0.0012 |
| | Yes | 22.0 (56.4%) | 9.0 (19.1%) | 31.0 (36.0%) | |
| Hydroxychloroquine | No | 32.0 (82.1%) | 45.0 (95.7%) | 77.0 (89.5%) | 0.0392 |
| | Yes | 7.0 (17.9%) | 2.0 (4.3%) | 9.0 (10.5%) | |

1. Linear Model ANOVA, 2. Pearson's Chi-squared test

Significant intergroup differences were observed in RA serology. Seropositivity was more common in the tofacitinib group (87.2%), while seronegativity predominated in the adalimumab group (74.4%) (p<0.001). Rheumatoid factor (RF) levels were significantly higher among tofacitinib patients, with 53.2% showing RF ≥51 U/ml compared to only 20.5% in the adalimumab group. Conversely, 76.9% of adalimumab patients were RF-negative (<20 U/ml) (p<0.001). A similar pattern was noted for anti-cyclic citrullinated peptide (anti-CCP) antibodies, which were positive in 61.7% of tofacitinib patients versus 23.1% of adalimumab patients (p<0.001) (Table 1).

Disease duration did not significantly differ between groups. Most patients (47.7%) had been diagnosed with RA for 5-10 years and 32.6% had a disease duration exceeding 10 years (Table 1).

Regarding treatment regimens, the use of combination therapy was more frequent among adalimumab patients (71.8%) compared to those on tofacitinib (38.3%) (p = 0.002). Methotrexate was used in 56.4% of the adalimumab group, significantly higher than in the tofacitinib group (19.1%) (p<0.001). Prednisolone was used in 19.8% of the entire cohort, with no significant difference between the two groups (p = 0.700) (Table 1).

Outcomes and adverse events are summarized in Table 2. Side effects were reported by 10.6% of tofacitinib-treated patients and 5.1% of adalimumab-treated patients (p = 0.448). Drug discontinuation due to side effects occurred only in the adalimumab group (5.1%) but was not statistically significant (p = 0.203).

Emergency Room (ER) visits were significantly more frequent among patients treated with adalimumab. A total of 51.3% of adalimumab patients had at least one ER visit compared to 25.5% in the tofacitinib group (p = 0.014). ER visits specifically due to pain were also more common in the adalimumab group (28.2%) than in the tofacitinib group (6.4%) (p = 0.023), indicating potentially better symptom control with tofacitinib (Table 2).

Infection-related hospital admissions were reported in 8.5% of tofacitinib patients and 10.3% of adalimumab patients, with no significant difference between groups (p = 0.534). The types of infections observed included COVID-19, herpes zoster, urinary tract infections and pneumonia (Table 2). Major adverse cardiovascular events

Table 2: Comparison of Outcomes in Rheumatoid Arthritis Patients Treated with Tofacitinib and Adalimumab

| Parameters | Tofacitinib N = 47 N (%) | Adalimumab N = 39 N (%) | p-value |
|---|---|---|---|
| Side effects<br>No (n = 79) Yes (n = 7) | 42 (89.4)<br>5 (10.6) | 37 (94.9)<br>2 (5.1) | 0.448˚ |
| History of drug discontinuation due to side effects<br>No (n = 84) Yes (n = 2) | 47 (100)<br>0 (0.0) | 37 (94.8)<br>2 (5.1) | 0.203˚ |
| Emergency room (ER) visit<br>No (n = 54) Yes (n = 32)<br>Pain (n = 14)<br>Rheumatoid arthritis flare (n = 10)<br>Others not related to RA (n = 8) | 35 (74.5)<br>12 (25.5)<br>3 (6.4)<br>6 (12.7)<br>3 (6.4) | 19 (48.7)<br>20 (51.3)<br>11 (28.2)<br>4 (10.3)<br>5 (12.8) | 0.014*<br>0.023* |
| Infection-related hospital admission<br>No (n = 78) Yes (n = 8)<br>Covid-19 (n = 2)<br>Herpes zoster(n = 2)<br>Urinary tract infection (n = 2)<br>Pneumonia/lung abscess (n = 2) | 43 (91.5)<br>4 (8.5)<br>2 (4.3)<br>1 (2.1)<br>1 (2.1)<br>0 (0.0) | 35 (89.7)<br>4 (10.3)<br>0 (0.0)<br>1 (2.6)<br>1 (2.6)<br>2 (5.1) | 0.534˚<br>0.391* |
| Major adverse cardiovascular events<br>No (n = 81) Yes (n = 5) | 46 (97.9)<br>1 (2.1) | 35 (89.7)<br>4 (10.3) | 0.172˚ |
| Other chronic diseases<br>No (n = 40) Yes (n = 46) | 25 (53.2)<br>22 (46.8) | 15 (38.5)<br>24 (61.5) | 0.173* |

˚Fischer Exact test, *Chi-square test, RA: Rheumatoid arthritis

(MACE) were recorded in 2.1% of patients in the tofacitinib group and 10.3% in the adalimumab group; this difference did not reach statistical significance (p = 0.172). The prevalence of other chronic diseases was slightly higher in the adalimumab group (61.5%) compared to the tofacitinib group (46.8%) but the difference was not statistically significant (p = 0.173) (Table 2).

## DISCUSSION

This retrospective study compared infection rates and adverse outcomes in Rheumatoid Arthritis (RA) patients treated with tofacitinib versus those treated with the anti-TNF agent adalimumab at King Abdulaziz University Hospital. Our analysis revealed that while there were no significant differences in infection-related hospital admissions or Major Adverse Cardiovascular Events (MACE) between the two groups, patients treated with adalimumab were more likely to visit the Emergency Room (ER), particularly for pain-related issues, compared to those treated with tofacitinib. No significant differences were observed in side effects or drug discontinuation due to adverse reactions. Additionally, notable differences were found in baseline characteristics, including the use of combination therapies and the presence of Rheumatoid Factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies, which may have influenced the outcomes.

JAK inhibitors like tofacitinib and anti-TNF agents such as adalimumab are both extensively used for RA treatment but their safety profiles have been subject to ongoing debate. Regulatory agencies have issued warnings about potential risks associated with JAK inhibitors, especially in specific high-risk patient populations [8]. One concern is the increased risk of infection, including opportunistic infections such as urinary tract infections, herpes zoster and pneumonia, due to the immune-modulatory effects of JAK inhibitors [7,10]. However, our study found no significant difference in infection-related hospital admissions between patients treated with tofacitinib (8.5%) and adalimumab (10.3%), which aligns with prior studies indicating comparable infection risks between these drug classes [9,23].

Kremer *et al.* [23], a five-year post-authorization safety study, revealed no significant differences in the risk of serious infection events with tofacitinib compared to both TNF inhibitors and non-TNF biologic agents. Another study from the United States also reported no significant differences in the risk of hospital admissions due to serious infections between tofacitinib and a range of biologic DMARDs, except etanercept [9].

However, a recent study by Balanescu *et al.* [1] reported higher rates of serious and non-serious infections among tofacitinib-treated patients compared to those treated with adalimumab, particularly in older individuals aged 65 years and above. Similarly, Choi *et al.* [24] found that the risk of herpes zoster was nearly double in patients receiving JAK inhibitors compared to those treated with anti-TNF agents. Nonetheless, their study did not find a significant difference in the rate of serious bacterial infections, supporting the view that overall infection risk may be comparable across these drug classes. Our findings are consistent with these results, suggesting that while general infection risk appears similar between tofacitinib and adalimumab, specific risks such as herpes zoster may vary.

In our study, patients treated with adalimumab were significantly more likely to be admitted to the ER for pain (28.2% vs. 6.4% in the tofacitinib group; p = 0.023). This may suggest that tofacitinib provides superior pain control, potentially due to its direct inhibition of the JAK-STAT pathway [7,25], which plays a central role in RA pathogenesis. Previous studies have shown that RA patients

commonly seek ER care for acute pain, stroke-like symptoms, infections or disease flares [26]. Therefore, the higher rate of ER visits in the adalimumab group may reflect less effective disease control or more severe baseline disease. These interpretations are further supported by the observed differences in baseline characteristics-patients receiving adalimumab were more likely to be on combination therapies, including methotrexate and corticosteroids, indicating possibly more severe or treatment-resistant disease. In contrast, the more frequent use of monotherapy among tofacitinib users may suggest better standalone efficacy in managing RA symptoms.

## CONCLUSIONS

In conclusion, this study found no significant differences in infection-related hospitalizations or major cardiovascular events between RA patients treated with tofacitinib and those treated with adalimumab. However, patients in the adalimumab group were significantly more likely to visit the ER for pain-related complaints, suggesting that tofacitinib may offer improved symptom control. Differences in baseline characteristics, particularly in seropositivity and use of combination therapies, underscore the importance of adjusting for confounding factors in future studies. Despite its limitations, this study contributes valuable real-world evidence regarding the comparative safety and effectiveness of tofacitinib and adalimumab in a Saudi clinical context.

### Strength and Limitations

This study has several strengths, including its real-world dataset, clearly defined inclusion criteria and robust statistical comparisons. However, several limitations should be noted. The retrospective design restricts control over confounding variables and causality cannot be established. Additionally, the single-center nature of the study limits its generalizability. Differences in baseline treatment regimens and seropositivity rates between groups may have influenced the outcomes and should be carefully considered when interpreting the findings.

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### Conflicts of Interest

The authors declare no conflicts of interest related to this study.

### Ethical Approval

This study was approved by the Ethics Committee of King Abdulaziz University, Jeddah, Saudi Arabia (Approval Number: 189-23). All procedures were conducted in accordance with institutional guidelines and the principles outlined in the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent was waived by the ethics committee.

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