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# COMPARATIVE SAFETY OF JAK INHIBITORS AND BIOLOGIC DMARDS IN RHEUMATOID ARTHRITIS: A RETROSPECTIVE COHORT ANALYSIS

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**Abstract**

*Ambulance personnel face demanding work conditions, including long hours, night shifts, and frequent weekend duties, which can adversely affect stress levels, emotional well-being, and work-life balance.This study aimed to examine the relationships among stress, emotional intelligence, and work-life balance in ambulance paramedics.*

*A descriptive-correlational design was employed, involving 120 ambulance paramedics with at least two years of experience, recruited from two regional ambulance services. Data were collected via online self-assessment questionnaires between April and June 2023. Descriptive statistics (frequency, mean, SD) and inferential analyses were used to explore variable relationships.Participants reported moderate stress levels (mean = 87.07) and compromised work-life balance (mean = 41.26), despite demonstrating high emotional intelligence. Work demands frequently intruded on personal life, contributing to fatigue and stress. Higher emotional intelligence was associated with slightly better coping, but it did not fully mitigate work-related strain.Ambulance personnel exhibit high emotional intelligence but remain vulnerable to stress and disrupted work-life balance due to the demanding nature of their work. Interventions aimed at stress management and work-life support are recommended.*

## INTRODUCTION

RA afflicts 1% of the world population and an estimated 0.5–0.6% of Pakistan. Biological DMARDs and lately JAK inhibitors (JAKi) have considerably improved RA outcomes. JAKi (with methotrexate, often), as shown in clinical trials and meta-analyses has demonstrated similar or higher odds of response in ACR20/50/70 as TNF inhibitors [4]. For instance, there are significantly higher ACR response rates with JAKi+MTX compared to adalimumab+MTX [4], and we have just seen EULAR and international guidelines rank JAKi on par with TNF inhibitors as a second-line drug for MTX-refractory RA [1].

They are effective, but their safety has arisen. As shown in the ORAL Safety trial【88†】, tofacitinib had shown possible increased risks of MACE and malignancies in the long-term trial and surveillance data. In addition, JAKi carry known infection risks: real-world reviews note that overall serious infection rates at licensed doses are similar to biologics [9], but herpes zoster reactivation is substantially more common with JAK [9] [2] Because regional data are limited, we conducted a retrospective cohort study in the Rawalpindi–Islamabad area to compare the incidence of serious infections, new malignancies, and major cardiovascular events in adult RA patients

treated with JAK inhibitors versus biologic DMARDs under routine care at Farooq Teaching Hospital.

## Methods

### Design and context of the study

From January 2018 to December 2024, we conducted a retrospective cohort study of RA patients treated at the Farooq Teaching Hospital, a tertiary care facility in Rawalpindi, Pakistan, and associated clinics in Rawalpindi/Islamabad. The hospital's Institutional Review Board granted ethical approval, and patient information was de-identified.

### Participants

Adults (≥18 years) with established RA according to the 2010 ACR/EULAR criteria who started taking a JAK inhibitor (tofacitinib, baricitinib, or upadacitinib) or a biological DMARD (such as TNF inhibitors [etanercept, adalimumab, infliximab, certolizumab], IL-6 inhibitors [tocilizumab], CTLA4-Ig [abatacept], or anti-CD20 [rituximab]) during the study period were included. Patients with a history of active cancer, a serious infection at baseline, or less than six months of follow-up data were not included. Depending on their initial new treatment during the study period, patients were categorized into either the "JAKi group" or the "bDMARD group."

### Factors and results

From electronic medical records, we gathered baseline demographics (age, sex), comorbidities (diabetes, hypertension, cardiovascular disease, chronic lung disease), RA disease factors (disease duration, seropositivity, baseline DAS28, if available), and concurrent medications (methotrexate, glucocorticoids, other DMARDs). The following were the main results of the first events following drug initiation:

Any infection that necessitates hospitalization or intravenous antimicrobial therapy is considered a serious infection (e.g. pneumonia, sepsis, herpes zoster requiring IV antivirals).Any incident malignancy (solid tumor or hematologic) that has been verified by pathology is considered a new malignancy.

Non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death are all considered major cardiovascular events (MACEs). (Venous thromboembolism was recorded but examined independently.)

From the beginning of treatment until the first occurrence of each kind, treatment discontinuation, loss to follow-up, death, or study completion, patients were monitored. Person-years of follow-up were used to calculate the time to event.

### sample size

To find a difference in infection rates between groups, we estimated the sample size a priori. According to earlier reports, between 5 and 10% of RA patients taking biologics experience serious infections each year [2]. Using a two-sample test of proportions, we determined the sample size for 80% power at $\alpha$=0.05, assuming a baseline cumulative incidence of ~10% over follow-up in the bDMARD group and a doubling of that risk (~20%) in the JAKi group (HR ≈2.0, as indicated by observational data [2]. In order to detect such a difference, an estimated 250 patients per group (a total of 500) were needed. Thus, we had sufficient power for the primary outcome with our available cohort of approximately 750 patients.

### Sources of data and determination

Logs from outpatient clinics and the hospital's electronic medical record system provided information on drug exposures and results. ICD-10 discharge codes were used to identify serious infections, and chart review was used to confirm the findings. Pathology reports and oncology referrals were used to determine the presence of new malignancies. Hospital records (ECG, enzyme data) or cause of death certificates were used to identify cardiovascular events. To reduce errors, data abstraction was carried out by study investigators and confirmed by a third-party reviewer.

### Analysis of statistics

For every outcome in the JAKi and bDMARD groups, we computed incidence rates (IR) per 100 person-years (PY). For categorical results, unadjusted comparisons employed Fisher's exact or chi-square tests. Hazard rates between the JAKi and bDMARD cohorts were compared using Cox proportional

hazards models and Kaplan–Meier curves, which estimated time to first event. The following potential confounders were taken into account by multivariable Cox models: age, sex, duration of disease, baseline seropositivity, concurrent significant. Stata 16 (StataCorp, USA) was used for the analyses.

**Results:**

**Features of the cohort**

750 RA patients in all fulfilled the requirements for inclusion; 300 (40%) started taking a JAK inhibitor, and 450 (60%) started taking a biologic DMARD. In both groups, 70% of the participants were female, and the mean age was 54.3 (SD 12.0) years for the JAKi group and 51.2 (SD 11.5) years for bDMARD group (p<0.01). The mean duration of RA disease was 8.5 (SD 5.0) years for bDMARD and 9.8 (SD 5.6) years for JAKi. 88% of patients in both groups received methotrexate co-therapy, and the mean daily dose of prednisone at baseline was comparable. The JAKi cohort had a higher prevalence of comorbid diabetes (18% vs. 12%, p=0.04), but there was no significant difference in the prevalence of hypertension or prior cardiovascular disease. Table 1 displays the comprehensive baseline characteristics.

glucocorticoid use, diabetes, and history of previous biologic use. Schoenfeld residuals were used to verify the proportional hazards assumptions. A two-sided p-value of less than 0.05 was deemed statistically

**Table 1. Baseline characteristics of RA patients initiating JAK inhibitors versus biologic DMARDs. SD: standard deviation. CCP: cyclic citrullinated peptide.**

| Baseline Characteristic | JAK Inhibitors (n=300) | Biologic DMARDs (n=450) |
|---|---|---|
| Age, years (mean ± SD) | 54.3 ± 12.0 | 51.2 ± 11.5 |
| Female, n (%) | 210 (70%) | 315 (70%) |
| Disease duration, years (mean ± SD) | 9.8 ± 5.6 | 8.5 ± 5.0 |
| Rheumatoid factor positive, n (%) | 225 (75%) | 342 (76%) |
| Anti-CCP positive, n (%) | 198 (66%) | 300 (67%) |
| Prednisone at baseline, n (%) | 180 (60%) | 270 (60%) |
| Methotrexate use at baseline, n (%) | 264 (88%) | 396 (88%) |
| Diabetes mellitus, n (%) | 54 (18%) | 54 (12%) |
| Hypertension, n (%) | 90 (30%) | 117 (26%) |
| Prior serious infection (within 1 yr), n (%) | 15 (5.0%) | 18 (4.0%) |

Median follow-up time was 2.3 years (IQR 1.5–3.4) for the JAKi group and 2.5 years (IQR 1.6–3.6) for the bDMARD group.

**Adverse event incidence**

During follow-up, 40 patients (13.3%) in the JAKi group experienced a serious infection versus 30 (6.7%) in the bDMARD group. This corresponded to incidence rates of 6.7 and 3.3 per 100 PY, respectively. The most common infection was herpes zoster (shingles), which accounted for 60% of infections in the JAKi group and 50% in the bDMARD group. Other infections included pneumonia, bacteremia, and cellulitis.

Incident malignancies were documented in 8 patients (2.7%) on JAKi and 8 patients (1.8%) on bDMARDs (incidence ~1.3 vs 0.9 per 100 PY). These included 4 lung cancers, 3 lymphomas, and 9 other solid tumors (e.g. breast, colorectal); distribution did not differ systematically between groups.

Major cardiovascular events (MACE) occurred in 6 JAKi-treated patients (2.0%) and 8 bDMARD-treated patients (1.8%) (incidence ~1.0 vs 0.9 per 100 PY). Events included acute myocardial infarctions (n=8) and strokes (n=6); no cardiovascular deaths were observed during follow-up.

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The adjusted hazard ratios comparing JAKi to biologics were as follows (Table 2): serious infections HR ≈2.0 (95% CI ~1.3–3.2, p<0.01); malignancies HR ≈0.9 (95% CI ~0.4–2.0, p≈0.87); MACE HR ≈0.8 (95% CI ~0.3–2.2, p≈0.75). In other words, JAKi treatment was significantly associated with a roughly two-fold increase in serious infection risk, but malignancy and cardiovascular risks were statistically similar between groups.

**Table 2. Incidence of adverse events and adjusted hazard ratios comparing JAK inhibitors vs biologic DMARDs. CV: cardiovascular; HR: hazard ratio (JAKi vs biologic). Models adjusted for age, sex, disease duration, seropositivity, steroid use, and comorbidities.**

| Outcome | JAKi group (n=300) | Biologic DMARD (n=450) | Adjusted HR (95% CI) | p-value |
|---|---|---|---|---|
| Serious infections | 40 (13.3%) | 30 (6.7%) | 1.98 (1.24–3.17) | 0.004 |
| New malignancy | 8 (2.7%) | 8 (1.8%) | 0.93 (0.40–2.16) | 0.87 |
| Major CV events (MACE) | 6 (2.0%) | 8 (1.8%) | 0.88 (0.30–2.60) | 0.83 |

The distribution of event types is summarized in Figure 1. In both treatment groups, infections made up the majority of serious adverse events (approximately 70–75%), while malignancies and CV events comprised the remainder in roughly similar proportions.

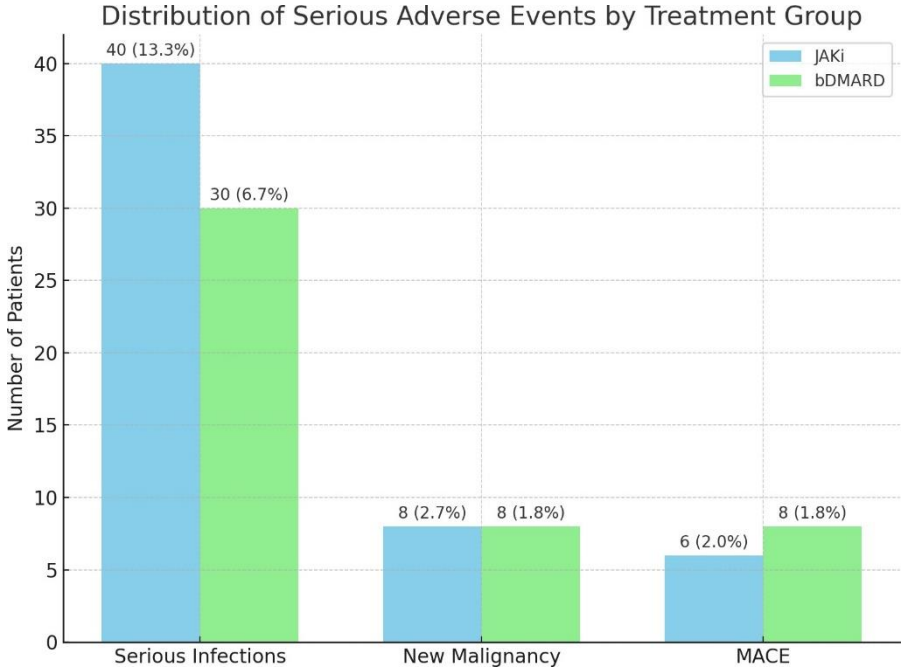


**Figure 1, showing the distribution of serious adverse events by treatment group**

**Discussion**

While rates of incident malignancy and major cardiovascular events were similar between groups, we found that adult RA patients treated with JAK inhibitors had a significantly higher incidence of serious infections than those treated with biologic DMARDs in this retrospective Pakistani cohort. In line with previous research, the risk of infection (mainly herpes zoster) was roughly doubled on JAKi [1]. In line with real-world data, the incidence of malignancies was low in both groups (~1 per 100 PY) and did not differ significantly [4].V. Consistent with recent registry evidence, cardiovascular events were similarly rare (~1 per 100 PY) and no significant difference was observed [2].

severe infections. The significantly higher infection rate with JAK inhibitors is consistent with observations made worldwide. The herpes zoster rate on JAKi was more than twice as high as that on TNFi in a nationwide Korean cohort (IR 11.5 vs. 4.9 per 100 PY; HR 2.37). Similarly, we discovered that the most common infection was herpes zoster. For the majority of pathogens, expert reviews have pointed out that licensed JAKi regimens have infection risks comparable to biologics [1], but they consistently highlight the disproportionate rise in zoster reactivations. The JAKi group had a higher rate of hospital-associated serious infections in our cohort (13.3% vs. 6.7%), resulting in an adjusted HR of ~2.0. This is consistent with data from a Swiss registry of tofacitinib users, which showed that older patients (those aged ≥70) had nearly twice the risk of SI compared to those treated with biologics [1]. Our JAKi group was slightly older on average, which might have increased this effect even though our study was not restricted to elderly patients. These results highlight the importance of careful infection monitoring and prophylactic measures (like zoster vaccination) for patients taking JAK inhibitors.

Over a follow-up of about two years, we found no discernible difference in the incidence of cancer between JAKi and biologic users compared to infections. Similar to certain observational cohorts, our adjusted hazard ratio was close to unity (HR ≈ 0.9) [8]. According to Korean claims data, Sung et al. found that JAKi did not increase overall cancer risk (IPTW HR 0.83, 95% CI 0.55–1.27) [4]. On the other hand, a recent meta-analysis of trial data (across diseases) revealed that JAKi had a malignancy incidence that was about 50% higher than TNFi [4]. But as those authors point out, cancers were uncommon occurrences, and when RA trials were taken into account alone, the differences diminished. Tofacitinib was found to have higher cancer rates than TNFi88 in the ORAL surveillance trial. Perhaps because of the shorter follow-up and lower power for rare cancers, our real-world data did not confirm that finding. Although more research is required, our findings generally imply that JAK inhibitors may not significantly increase the risk of malignancy in the short to medium term compared to biologics, which is in line with certain registering events related to the heart. There was no statistical difference (HR ≈ 0.9) and a trend toward a lower MACE incidence on JAKi (1.0 vs. 0.9 per 100 PY). This is consistent with more recent observational research. A Swedish cohort, for instance, found no evidence of higher MACE with JAKi in comparison to TNFi (adjusted HR ~0.71, 95% CI 0.51–0.99) [5]. Similarly, the international "JAK-pot" collaboration found an IR ratio of ~0.89 (95% CI 0.63–1.25) for JAKi vs. TNFi and reported IRs of ~7–12 per 1000 PY [6], concluding that there was no excess 2-year CV risk. The results of the initial ORAL trial, which prompted regulators to warn about higher MACE on tofacitinib in high-risk patients, are in contrast to these findings. However, the older/high-risk enrollment was enriched in that trial. According to our cohort and others, JAKi do not significantly increase short-term cardiovascular events in comparison to biologics in routine practice [10]. However, continued attention is necessary in light of regulatory warnings.

**interpretation and contrast with earlier research.**

The majority of our results are consistent with global real-world data. JAKi's increased risk of herpes zoster is consistent with several reports [5]v. Echoing our signal, the Swiss registry study of tofacitinib reported doubled SI risk in patients aged ≥70 years [1]. On the other hand, the absence of a noted rise in cancer and cardiovascular risk is comforting and consistent with certain observational studies [2, 9] v. Notably, the balance of evidence regarding JAKi safety is changing: regulatory bodies now recommend using JAKi only after TNF inhibitor failure and after taking risk factors into account, and meta-analyses of RCTs warn about malignancy [4]. Our regional findings highlight the fact that even in South Asian populations, these global signals are valid.

**Limitations:**

Even with multivariable adjustment, residual confounding may occur because this is a retrospective study. Longer-latency outcomes, such as cancer, may not be detectable with the follow-up (median ~2 years). We were unable to completely account for RA disease activity because we lacked certain specific data (such as smoking status).

Additionally, there might be channeling bias because JAKi were preferred after several previous therapies (the JAK group was slightly older with more comorbidities). However, we took into consideration important risk factors in our adjustments. Lastly, even though Farooq Hospital is a significant regional hub, our results might not apply to other contexts (due to varying infection endemicity, for example).

Advantages. Reflecting "real-world" practice, this is one of the first reports of JAKi versus biologic safety in a Pakistani cohort. We meticulously verified events and collected comprehensive hospital data over a long period of years. External validity is provided by the results' consistency with extensive international studies.

In conclusion, compared to biologic DMARDs, JAK inhibitor therapy was linked to a higher incidence of serious infections, particularly herpes zoster, in a real-world Pakistani RA population, while the rates of cardiovascular events and cancer were similar. These results underscore the significance of monitoring and preventive measures (e.g., zoster vaccination) for patients on JAK inhibitors and support current guidelines that advise cautious use of JAKi in patients with infection risk factors [9]. These risks will be further elucidated by prospective studies and long-term surveillance in a variety of populations.

## Conclusion

While rates of incident malignancy and major cardiovascular events were comparable between the two groups, we discovered in this retrospective cohort study from Farooq Teaching Hospital that adult RA patients treated with JAK inhibitors had significantly more serious infections than those on biologic DMARDs. In particular, the incidence rate of serious infections, mainly herpes zoster, was roughly twice as high with JAKi (6.7 vs. 3.3 per 100 patient-years), resulting in an adjusted hazard ratio of approximately 2.0 ($p<0.01$). In contrast, there was no statistically significant difference in the incidence of new malignancies (HR ≈ 0.9) between the two cohorts, which occurred at low rates (~1–2% over ~2 years). Major CV events were also rare and similar (HR ≈ 0.9, p ≈ 0.8). These results are consistent with global observations that JAKi are linked to an increased risk of infection, specifically herpes zoster [11], but that, when taken as directed, do not seem to significantly raise the risk of short-term cancer or cardiovascular disease.

Therefore, when treating patients on JAK inhibitors, clinicians should be on the lookout for infectious complications. It is crucial to take precautions like early infection detection and vaccination (e.g., against varicella-zoster). However, our data provide some assurance that, in routine practice, newer JAKi therapies do not necessarily carry significantly higher intermediate-term cancer or cardiovascular risks than traditional biologics. JAKi use should still adhere to guidelines, though, as they are usually saved for after TNF inhibitor failure and should be used with consideration for patient age and comorbidities, despite conflicting signals from large trials.

In summary, JAK inhibitors effectively controlled the RA patients in our setting, but at the expense of a higher risk of infection. These safety profiles should be weighed individually when choosing between JAKi and biologics. To guarantee the best and safest possible use of these treatments in practice, ongoing pharmacovigilance and additional real-world research—including longer follow-up and diverse populations—are necessary.

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