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ORIGINAL RESEARCH

Herpes Zoster Risk in Rheumatoid Arthritis Patients on Janus Kinase Inhibitors: A 17-Year Experience from Rheumatoid Arthritis Saudi Database (RASD)

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Background/Purpose: The advent of targeted therapies, such as biologic disease-modifying anti-rheumatic drugs (bDMARDs) and Janus kinase inhibitors (JAKi), has revolutionized the treatment of rheumatoid arthritis (RA) patients who do not respond adequately to conventional disease-modifying anti-rheumatic drugs (csDMARDs). Concerns have been raised about the increased risk of infections, especially herpes zoster (HZ). The association between JAKi treatment and HZ remains complex. The objective of this study was to assess the risk of HZ among RA patients in our Rheumatoid Arthritis Saudi Database (RASD) receiving JAKi and other DMARDs.

Patients and Methods: A 17-year retrospective multicenter chart review study was conducted in Saudi Arabia using RASD. We included patients diagnosed with RA according to the American College of Rheumatology criteria who were 18 years of age and above, on different modalities of treatment: csDMARDs, bDMARDs, targeted synthetic DMARDs (tsDMARDs) with or without concomitant GC. The following information was collected: demographics, comorbidities, medications, HZ occurrence, and vaccination history.

Results: A total of 614 patients diagnosed with RA were enrolled in the study of whom 87.6% (n=538) were female and 98.2% (n = 603) were of Arab ethnicity with a mean age was 48.79 ± 13.35 years. Herpes zoster (HZ) occurred in only 1.1% (n = 7) of patients. JAKi therapy was not associated with an increased risk of HZ (p = 0.454). However, Asian ethnicity (p = 0.010) and cumulative GC exposure ≥60 mg (p = 0.035) were significantly associated with higher HZ risk.

Conclusion: We did not detect any association between JAKi and HZ infection in our RASD. On the other hand, cumulative GC of 60 mg or more and Asian ethnicity were identified as significant risk factors. These findings provide a basis for future nationwide studies aimed to deliver personalized preventive strategies against HZ.

Keywords: infection, varicella zoster infection, glucocorticoids, tofacitinib, DMARDs

Introduction

The introduction of targeted therapies, including biological disease-modifying anti-rheumatic drugs (bDMARD) and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs), has transformed the management of rheumatoid arthritis (RA),[1] especially for patients who do not respond adequately to conventional disease-modifying anti-rheumatic drugs (csDMARDs).[1] Janus kinase inhibitors (JAKi) have demonstrated significant efficacy in treating various autoimmune diseases by selectively inhibiting the JAK-STAT pathway, a critical mediator of immune signaling.[1] However, this targeted immunomodulation has raised concerns regarding increased risk of infections,[2,3] particularly the reactivation of varicella-zoster virus

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(VZV) resulting in herpes zoster (HZ) infection.[2,3] Furthermore, RA patients are inherently more susceptible to HZ infection,[2] likely due to the underlying pathophysiology of their disease that dampens cell-mediated immunity.[2]

The relationship between JAKi therapy and HZ is complex, influenced by multiple confounding factors such as concomitant glucocorticoid (GC), use, background csDMARD treatment, and advanced age.[4] Remarkably, real-world data have shown a higher incidence of HZ reactivation among patients of Asian ethnicity treated with JAKi.[5] This observation underscores the importance of genetic and ethnic factors in impacting drug response and adverse effects.[6] Hence, the necessity to investigate the risk of HZ in patients who are on Jaki within different ethnic groups, as a genome-wide association study (GWAS) has highlighted that Arab populations possess novel Arab-specific loci that play a role in RA development.[7] Given these considerations, this study was designed to assess the risk of HZ reactivation and the usage of JAKi in real-world settings in the Saudi Arabian population.

Material and Methods

Study Design and Setting

A retrospective multicenter chart review was conducted across tertiary hospitals in Saudi Arabia included in our Rheumatoid Arthritis Saudi Database (RASD) between January 2007 and December 2024, to assess the risk of HZ among adults with RA receiving JAKi and other DMARDs, including csDMARDs and bDMARDs.

Participants

Patients aged ≥18 years with a confirmed diagnosis of RA based on the 2010 ACR classification criteria were included.[8] A non-probability sampling technique was adopted, and consecutive sampling was used as a subcategory. Eligible participants received at least one csDMARD, bDMARD, or tsDMARD, with or without concomitant GC.

Variables and Data Collection

Collected variables included demographics age, gender, nationality, ethnicity, region of residence, employment status, comorbidities, detailed medication history (agent, dose, start date, continuation status, end date if applicable), HZ occurrence and clinical features, and HZ vaccination status. Data were abstracted via structured chart review. HZ diagnosis was based on clinical documentation by the treating physician.

Ethics and Confidentiality

Institutional review board approval was obtained from King Abdulaziz University Hospital with the following reference number (83–22). Consequently, RASD has approved this research, and all centers affiliated with the RASD have agreed to participate on this study based on the approval obtained from King Abdulaziz University Hospital. Informed consent was taken from all the patients that participated. This study was conducted in accordance with the declaration of Helsinki. Data was anonymized. Where key information was missing, patients were contacted by telephone.

Statistical Analysis

Data was entered, edited and cleaned using Microsoft Excel software. The excel file was imported in SPSS software ver. 22 and further analysis was performed in SPSS program. Continuous variables were summarized as mean ± standard deviation (SD). Categorical variables were presented as counts and percentages. Ninety-five percent confidence intervals (CI) and odd ratio were calculated for key associations. Chi-square tests were used for categorical comparisons. Two-sided $p < 0.05$ defined statistical significance. Logistic regression analysis was done to identify independent association of HZ infection with the risk factors.

Sample Size

The sample size was calculated using Epi Info v3.01 (95% confidence, $\alpha = 0.05$, prevalence 50% and applying a design effect of 1.5 for the multicenter setting, the calculated sample size was 576. Sample size was increased by 10% to

accommodate the patient's data with missing information. The finally collected sample size was 614 RA patients receiving JAKi or other DMARD therapy, still sufficient to apply robust test of significance.

Results

Cohort Demographics, Comorbidities and Medication Exposures

Six hundred fourteen patients with RA were enrolled in the study. The cohort was predominantly female (87.6%) with a mean age of 48.79 ± 13.35 years; the sample was mostly of Arab ethnicity (98.2%) and mainly Saudi Arabian in nationality (89.7%) additional demographic information is presented in (Table 1). The most prevalent comorbidities were hypertension (20.7%) and dyslipidemia (17.6%) (Table 1). In regard to their medications, the majority 66.9% were on methotrexate, followed by JAKi 38.4% and 30.1% were on chronic maintenance GC. Additionally, 18.7% of the total cohort had a recorded to be exposure to ≥60 mg of GC at some point in their course of treatment (Table 1). Vaccination rates against HZ were low, with only 8.3% of patients having documented vaccination (Appendix Table A).

HZ Infection and Associations

Seven patients (1.1%) developed clinically diagnosed HZ infection. Presentations were single-dermatomal in 85.7%, 100% were diagnosed clinically, 42.9% of HZ cases were on 15 mg or more of GC at the time or shortly prior to reactivation (Appendix Table A). While determining association, we could not find any significant relationship between

Table 1 Demographic & Clinical Characteristics of the Study Cohort (n = 614)

Characteristics	Category	Number N	Percent %
Age Mean ± SD.	48.79±13.35		
Age group	≤20	3	0.5
	21–40	179	29.2
	41–60	313	51.0
	≥61	119	19.4
Gender	Female	538	87.6
	Male	76	12.4
Ethnicity	African	1	0.2
	Asian	9	1.5
	Arab	603	98.2
	Western	1	0.2
Nationality	Non-Saudi	63	10.3
	Saudi	551	89.7
Residential area	Central region	7	1.1
	Eastern region	2	0.3
	Northern region	1	0.2
	Southern region	218	35.5
	Western region	386	62.9

(*Continued*)

Table 1 (Continued).

Characteristics	Category	Number N	Percent %
Comorbidity	Hypertension	127	20.7
	Dyslipidemia	108	17.6
	Diabetes mellitus type 1	24	3.9
	Diabetes mellitus type 2	59	9.6
	Cardiac diseases	13	2.1
	Liver diseases	8	1.3
	Malignancy	7	1.1
	Renal diseases	2	0.3
	HIV	0	0
Medication	Hydroxychloroquine	133	21.7
	Methotrexate	411	66.9
	Adalimumab	161	26.2
	Etanercept	93	15.1
	Rituximab	24	3.9
	JAKi	236	38.4
	GC ≥ 60 mg	115	18.7
	Chronic GC usage	185	30.1
	Less than 5 mg daily	35	18.9
	5 mg −10 mg	141	76.2
	More than 10 mg	9	4.9

Abbreviations: HIV, Human immunodeficiency virus; JAKi, Janus kinase inhibitor; GC, Glucocorticoids.

the age group, gender, nationality, residential area and occupation. However, Asian ethnicity was significantly associated with p value <0.044 (Table 2). Moreover, we did not find any significant relationship with all comorbidity variables including coexisting SLE and diabetes (Appendix Table B).

There was no significant association with JAKi, adalimumab, methotrexate, etanercept, rituximab, hydroxychloroquine. However, chronic steroid use and a history of prior high-dose exposure (≥60 mg) of GCs were associated with increased HZ risk in the initial analysis with a p value of (0.029 and 0.026), respectively (Table 3). Yet, in logistic regression, in the final model chronic GC use became insignificant.

The overall fit of the logistic regression model was evaluated using the Omnibus Tests of Model Coefficients, which assess whether the predictors significantly improve the model compared to a model with only the intercept. The test yielded a significant chi-square value of 137.810 (df = 2, p < 0.001), indicating that the model fits the data better than the null model. The classification accuracy of the model was 98.9%. The model explained 19.0% (Nagelkerke R 2) of the variance in HZ The analysis examined factors influencing HZ infection, with HZ infection serving as the dependent variable (coded as 1 for success ie infection "Yes" and 0 failure). Ethnicity was found to be a significant predictor (p = 0.010), with Asian race associated with an increased likelihood of HZ infection (Wald test = 4.926; odds ratio=12.479; 95% CI = [1.343,115.935]). In addition, GC more than 60 mg was also a significant predictor (p = 0.035) of HZ infection

Table 2 Association Between Herpes Zoster Occurrence and Demographic Characteristics (n = 614)

Demographic Data	Herpes Zoster Development				X^2	P
	No		Yes			
	607		7			
	No.	%	No.	%		
Age						
20 and less	3	100.00%	0	0.00%	0.183	0.98
21–40	177	98.90%	2	1.10%		
41–60	309	98.70%	4	1.30%		
61 and above	118	99.20%	1	0.80%		
Gender						
Males	76	100.00%	0	0.00%	1	0.395
Females	531	98.70%	7	1.30%		
Ethnicity						
African	1	100.00%	0	0.00%	8.075	0.044*
Asian	8	88.90%	1	11.10%		
Arab	597	99.00%	6	1.00%		
Westerns	1	100.00%	0	0.00%		
Nationality						
Non-Saudi	62	98.40%	1	1.60%	0.125	0.533
Saudi	545	98.90%	6	1.10%		
Residential area in Saudi Arabia						
Central	7	100.00%	0	0.00%	1.601	0.809
Eastern	2	100.00%	0	0.00%		
Northern	1	100.00%	0	0.00%		
Southern	217	99.50%	1	0		
Western	380	98.40%	6	1.60%		

Notes: *Indicates a significant P value ≤ 0.05.
Abbreviations: X^2, Chi-square value; P, P value.

(Wald test = 4.442; odds Ratio = 5.958; 95% CI = [1.315,26.998]). However, steroid dose less than 5 mg (p = 0.05) did not significantly predict to the model (Wald test = 3.833; odd ratio = 6.958; 95% CI = [1.301,37.217]). The results illustrate that patients of Asian ethnicity were 12.479 times likely to develop Hz infection as compared to other ethnicities. Similarly, patients, who were exposed to a dose equal to or more than 60 mg of GC were 5.958 times more likely to develop HZ infection (Table 4 and Appendix Table C).

Discussion

This retrospective multicenter study examined the potential risk factors and epidemiology of HZ among RA patients receiving JAKi in Saudi Arabia over a 17-year period. The analysis included a total of 614 patients, collected from

Table 3 Association Between Herpes Zoster Occurrence and Medication Exposures (n = 614)

Medication Type	Herpes Zoster Development				X^2	p
	No		Yes			
	607		7			
	No.	%	No.	%		
Jaki						
No	373	98.70%	5	1.30%	0.291	0.454
Yes	234	99.20%	2	0.80%		
Type & dose of Jaki						
Baricitinib 2 mg OD	6	100.00%	0	0.00%	1.021	0.907
Baricitinib 4 mg OD	61	100	0	0		
Tofacitinib 5 mg BID	12	100.00%	0	0.00%		
Tofacitinib 11 mg OD	81	98.80%	1	1.20%		
Upadacitinib 15 mg OD	74	98.70%	1	1.30%		
Hydroxychloroquine						
No	475	98.50%	7	1.5	1.939	0.356
Yes	132	100.00%	0	0.00%		
Methotrexate						
No	203	100.00%	0	0.00%	3.497	0.059
Yes	404	98.30%	7	1.70%		
Adalimumab						
No	446	98.50%	7	1.50%	2.517	0.118
Yes	161	100.00%	0	0.00%		
Etanercept						
No	517	99.20%	4	0.80%	4.23	0.074
Yes	90	96.80%	3	3.20%		
Rituximab						
No	583	98.80%	7	1.20%	0.288	0.591
Yes	24	100.00%	0	0.00%		
Chronic GC Use						
No	427	99.50%	2	0.50%	5.737	0.029*
Yes	180	97.30%	5	2.70%		
Less than 5 mg	33	94.3	2	5.70%	9.55	0.023*
5–10 mg	138	97.90%	3	2.10%		
More than 10 mg	9	100.00%	0	0.00%		

(*Continued*)

Table 3 (Continued).

Medication Type	Herpes Zoster Development				X^2	p
	No		Yes			
	607		7			
	No.	%	No.	%		
GC ≥ 60 mg						
No	496	99.20%	3	0.80%	6.864	0.026*
Yes	111	96.60%	4	3.40%		

Notes: *Indicates a significant P value ≤ 0.05.
Abbreviations: JAKi, Janus kinase inhibitor; GC, Glucocorticoids; X^2, Chi-square value; P, P value.

Table 4 Binary Logistic Regression Analysis to Find Out Predictors of Herpes Zoster Infection

		B	S.E	Wald	df	Sig.(p Value)	Exp (B)	95% C.I for EXP (B)	
								Lower	Upper
Step 3[c]	Ethnicity Asian (1)	−3.138	1.226	6.551	1	0.010*	0.043¶	0.004	0.479
	Dose steroid (1)	−1.782	0.910	3.833	1	0.050*	0.168	0.028	1.002
	More than 60 (1)	−1.720	0.816	4.442	1	0.035*	0.1794**	0.036	0.886
	Constant	1.100	1.483	0.550	1	0.458	3.005		

Notes: *Indicates a significant P value ≤ 0.05. ¶ Odds Ratio = (12.479; 95% CI= [1.343–115.935]). **Odds Ratio = (5.958; 95% CI= [1.315–26.998]).
Abbreviations: B, unstandardized regression coefficient; S. E, standard error; df, degree of freedom; Sig, significance value; Exp(B), Odds Ratio; CI, confidence interval; C, Variable (s) entered in step 3.

various healthcare centers across the region. Our aim was to address a significant gap in regional data by investigating whether the use of JAKi contributed to an increased risk of HZ in the Saudi population, often underrepresented in existing research. In our study sample, we found very low risk of HZ, and we demonstrated no significant association between JAKi use and the risk of HZ reactivation. On the other hand, GC exposure cumulatively (60 mg dose or above along the course of treatment) increased the risk of HZ infection. Additionally, Asian ethnicity was significantly associated with a heightened risk.

The use of JAKi in RASD was not associated with an increased risk of HZ infection. This observation aligns with several recent studies. A nested case-control study in 2022 based on real-world data indicated that although high disease activity in RA patients using JAKi was a risk factor for HZ, the JAKi themselves did not independently increase this risk.[9] Additionally, a more recent prospective study also found no association between JAKi usage and a higher risk of HZ infection.[10] Moreover, while it is important to recognize that RA and immune-mediated inflammatory skin conditions have different pathophysiological mechanisms, examining data from studies on skin conditions can still provide valuable insights into the safety profile of JAKi as a meta-analysis of thirty-two randomized clinical trials involving 11,917 patients with immune-mediated inflammatory skin diseases (IMISD) found that serious infections occurred in only 0.62% of those receiving JAKi, compared to 0.51% of controls, reinforcing the safety profile of JAKi in this context.[11]

In contrast to our finding, studies conducted outside of Saudi Arabia have reported an increased risk of HZ infections linked to JAKi therapy.[3,5,12,13] We attribute the lack of association between JAKi and risk of HZ in our sample possibly to the genetic background of Arabs as a multinational Arab GWAS has identified novel Arab-specific loci linked to RA susceptibility and pathogenesis.[7] This may indicate the presence of protective genes that mitigate infection risk in the Arab population, potentially accounting for the discrepancy observed between different populations. Further research is needed to better understand these region-specific genetic and environmental factors, as this knowledge could have

important implications for public health strategies, including vaccination programs. If certain genetic profiles confer protection against HZ in the Arab population, it may influence the prioritization and timing of vaccination campaigns, ensuring that resources are directed towards individuals at higher risk and ultimately reduce the burden of HZ among RA patients in Saudi Arabia.

Genetic predisposition and ethnicity are intrinsically interconnected, making it difficult to discuss one without mentioning the other. The susceptibility to HZ is plausibly influenced by underlying genetic factors and environmental influences that are specific to ethnic groups. We found in our study that Asian ethnicity is associated with a higher risk for HZ compared to other ethnicities. This finding aligns with multiple studies[14–16] that reported increased rates of HZ among Asian populations. This might stem from the identified specific loci associated with increased susceptibility to HZ in the Asian populations.[6] As a GWAS revealed that a variant near the IL17RB gene, prevalent in East Asians, was linked to a higher risk for HZ in patients treated with tofacitinib.[6]

In addition to genetic predispositions, epigenetics may also play a role in influencing susceptibility to HZ. Epigenetic modifications such as DNA methylation, histone modifications, and non-coding RNA regulation can alter gene expression without changing the underlying DNA sequence.[17] Environmental factors, including stress, infections, diet, and exposure to certain pollutants can induce these epigenetic changes,[18] potentially impacting immune function.[17] These epigenetic factors may contribute to differences in immune responses across ethnic groups depending on each geographical exposures, further modulating the risk of HZ in diverse populations.

Medication-related factors such as GC use also play a significant role in modulating the risk of HZ, as we showed in our analysis GC were strongly associated with a heightened risk of HZ. A history of prior high-dose exposure (≥60 mg) was documented in 18.7% of our patients and was significantly associated with HZ ($p = 0.035$). Many international studies persistently demonstrated that GC use is associated with an increased risk of HZ in RA patients.[19–22] In a large cohort, prednisolone use in RA patients was associated with a higher risk of incident HZ (adjusted odds ratio [aOR] 1.48, 95% CI 1.08–2.03), and the prolonged use further increased the risk (aOR 2.16, 95% CI 1.46–3.19).[19] A population-based cohort demonstrated that systemic GC use was associated with a 59% increased risk of HZ compared to nonusers with a heightened risk with cumulative exposures.[20] In a systematic review and a meta-analysis assessing the safety of long-term low-dose GC in RA patients, it was found that they do not significantly increase the overall risk of adverse events, serious adverse events, or mortality compared to placebo, but there is a clear increased risk of infections.[21] Of note, the only trial within the preceding meta-analysis that found a higher risk for infection with GCs low dose is the GLORIA trial[22] which is the only trial conducted in an elderly RA population. Hence, it could explain why we could not find an association between HZ risk and the maintenance low dose of GC as the mean age of our study sample was 48.79 ± 13.35 years.

A critical consideration in evaluating the relationship between GC use and HZ risk involves assessing RA associated comorbidities and disease activity as all play an interconnected multifactorial role in influencing HZ susceptibility. Furthermore, the presence of comorbidities within our sample did not demonstrate a significant association with HZ risk in logistic regression analysis, probably due to the low prevalence of comorbidities within our study sample. This finding is concurrent with a previous RASD registry study, which reported a low incidence of comorbidities among Saudi RA patients,[23] with osteoporosis identified as the most prevalent comorbidity.[23]

Disease activity was not incorporated into the analysis for logistical reasons. Nonetheless, prior studies utilizing the RASD registry have indicated that RA patients in Saudi Arabia are unlikely to experience a severe or difficult to control disease course.[24,25]

An important area for further investigation is the potential role of anti-TNF therapy in HZ risk, given the observed variability in risk among different agents within this class. In our cohort, no significant association was identified between the use of anti-TNF agents in general and the occurrence of HZ. There are variabilities in the reported risk with HZ, the British society for rheumatology biologics register reported an adjusted hazard ratio (HR) for HZ of 1.8 (95% CI 1.2–2.8) in RA patients treated with anti-TNF agents compared to those on nonbiologic DMARDs and agent-specific differences were observed: infliximab conferred the highest risk (HR 2.2), followed by etanercept (HR 1.7), while adalimumab had a lower but still elevated risk.[26] Moreover, a large prospective cohort from the German RABBIT registry further supported this, indicating that anti-TNF agents collectively were associated with a higher incidence of HZ compared to traditional DMARDs, with rates particularly high for monoclonal anti-TNF antibodies such as infliximab

and adalimumab, the registry found no statistically significant increased risk with etanercept, a soluble TNF receptor fusion protein (HR 1.28, 95% CI: 0.90–1.81).[3] Overall, while existing findings suggest that anti-TNF therapy in RA may be associated with an increased risk of HZ, the evidence remains inconclusive due to differences in study designs, patient populations, and treatment durations. Consequently, further large scale, region specific and prospective studies are necessary to definitively determine the true relationship between anti-TNF therapy and HZ risk.

Concerning vaccination rates in our cohort, they were low (8.3%), consistent with national reports showing 7–11% uptake among adults in Saudi Arabia.[27–29] While based on limited numbers, our findings are in line with the strong efficacy of recombinant zoster vaccine (RZV) demonstrated in clinical trials, where efficacy exceeded 90% in older adults.[30] Saudi studies also show that awareness of the HZ vaccine exceeds 50% but uptake remains limited.[27–29] Increasing awareness among patients and clinicians, together with structured vaccination programs, may help improve coverage in RA care in Saudi Arabia.

There were several limitations to this study. Our data represented a specific RA population in Saudi Arabia. The results may not be applicable to other regions. We did not include disease activity in our analysis for logistical reasons. Moreover, there were some precise information missing that may add more value to our findings like precise antiviral courses, and vaccine product. It's important to note that the low HZ incidence in our sample resulted in wide confidence interval, which in turn impacts the precision and generalizability of the odds ratios. Additionally, under reporting by patients is not uncommon in registries which could have impacted our results.

Conclusion

In conclusion, this study found no significant link between JAKi use and HZ risk in RA patients included in RASD, potentially due to genetic factors related to the Arab ethnicity. There was a higher HZ incidence among Asians. Our results found that GC use remains one of the strongest modifiable risk factors for HZ in RA patients. Clinicians should remain vigilant for infection risk and other potential adverse effects, particularly in older adults and those with comorbidities when prescribing GC. To further establish and validate these findings, prospective nationwide studies in the Arab and Saudi populations are necessary to implement tailored approaches to effectively reduce the burden of HZ and improve overall patient outcomes in diverse populations.

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Disclosure

The authors report no conflicts of interest in this work.

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