Risk of cervical intraepithelial neoplasia during Janus kinase inhibitor treatment in patients with rheumatoid arthritis: a retrospective cohort study

Sirs,

Rheumatoid arthritis (RA) is an autoimmune disease characterised by synovitis, and the patients are predominantly female (1). Janus kinase inhibitors (JAKi) have emerged as a significant therapeutic option for managing RA, particularly in patients who have inadequate responses to traditional disease-modifying anti-rheumatic drugs (DMARDs) (2-4). Although JAKi effectively manage RA symptoms, their potential association with increased malignancy risks has raised concerns (5). Although several studies have examined the overall cancer risk in patients treated with JAKi (6), data specifically addressing the incidence and recurrence of cervical intraepithelial neoplasia (CIN), a precursor to cervical cancer (7), remain limited. This gap in knowledge has led to clinical hesitation when considering JAKi for patients with a history of CIN, even following successful treatment such as curettage resection. Therefore, this study aimed to investigate CIN recurrence in patients with RA treated with JAKi compared to tumour necrosis factor inhibitors (TNFi).

A retrospective cohort study was conducted at Asan Medical Center, a tertiary hospital, between January 1999 and April 2024. Among RA patients, 1,137 were treated with TNFi and 466 with JAKi. We investigated potential risk factors for the development and recurrence of CIN in patients with RA (8), including human papillomavirus (HPV) infection status, HPV vaccination history, and smoking habits. The occurrence of CIN was identified using diagnostic codes, and recurrence was assessed after taking medications (TNFi and JAKi) over 3 months. Additionally, we used Kaplan-Meier survival analysis to compare CIN recurrence between the two groups.

During follow-up, CIN occurred in 12 patients (median age at diagnosis 48 years), and all of them achieved complete remission by curettage. Among 12 patients, 6 were treated with JAKi and 6 with TNFi. In the JAKi group, 3 cases of CIN recurrence were observed (21.67/100 person-year), whereas 5 cases of CIN recurrence occurred in the TNFi group (20.09/100 person-year). However, there was no significant difference in recurrence rates between the two groups (χ^2=1.270, p=0.260). The baseline characteristics of the study population are presented in Table I.

Furthermore, JAKi did not significantly increase the risk of CIN recurrence compared to TNFi in RA patients previously cured of CIN. These findings indicate that the immunomodulatory effects of JAKi, while substantial in controlling RA symptoms, may not directly contribute to the development or recurrence of malignancies (9). Cordtz *et al*. (10) found no increase in HPV-related cancers after biological DMARD (bDMARD) treatment in women with a history of precancerous lesions of the uterine cervix. However, a comparison of CIN recurrence rates between patients treated with JAKi and bDMARDs is lacking.

There are several limitations in this study, such as the retrospective design and reliance on electronic medical records, which may have introduced selection bias. Additionally, the relatively small number of CIN events limits the generalisability of our findings. Nevertheless, our study is a large historical cohort with an extended follow-up, which enabled us to identify any possible CIN outcomes between the JAKi and TNFi groups. This supports the safety for RA patients with cured CIN, comparable to TNFi. However, prospective studies with larger cohorts are necessary to confirm these findings.

Table I. Characteristics of patients with previously cured CIN treated with JAK and TNF inhibitors.

	Patients	Age at enrolment (years)	Age at diagnosis of CIN* (years)	HPV* status	HPV vaccination history	Smoking status	Follow up duration of RA (years)	Serology*	Previous b/ts-DMARD	Current b/ts-DMARD	Exposure period# (months)	Number of recurrences	Time to recurrence after current medication (months)
JAK inhibitor	#1	55	47	+	-	-	12	RF(+)/ACPA(+)	Adalimumab Enbrel Tofacitinib,	Baricitinib	56	1	12
	#2	46	35	+	+	-	20	RF(+)	Etanercept Abatacept Tocilizumab Tofacitinib	Baricitinib	17	0	-
	#3	60	49	+	-	-	22	RF(-)/ACPA(-)	Golimumab	Baricitinib	39	0	-
	#4	45	42	+	-	-	7	RF(+)/ACPA(-)	Tocilizumab Etanercept Adalimumab	Upadacitinib	12	1	13
	#5	79	60	+	-	-	15	RF(+)/ACPA(+)	Adalimumab Tocilizumab	Tofacitinib	69	0	-
	#6	65	64	+	-	-	6	RF(+)/ACPA(+)		Tofacitinib	55	1	12
TNF inhibitor	#7	56	46	+	-	-	4	RF(+)/ACPA(-)		Adalimumab	29	2	12.18
	#8	75	59	+	-	-	24	RF(-)/ACPA(-)	Etanercept	Adalimumab	49	0	-
	#9	28	22	+	+	-	6	RF(-)/ACPA(-)		Adalimumab	24	1	16
	#10	44	29	-	-	-	18	RF(+)/ACPA(-)		Etanercept	96	1	12
	#11	69	56	+	-	-	4	RF(+)/ACPA(-)	Adalimumab	Infliximab	7	1	15
	#12	84	68	-	-	-	15	RF(+)/ACPA(-)		Infliximab	36	0	-

*RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; JAK: Janus kinase; TNF: tumour necrosis factor; CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus; bDMARD: biological disease-modifying anti-rheumatic drug; tsDMARD: targeted synthetic disease-modifying anti-rheumatic drug.
#Current b/ts-DMARD exposure period (month).

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