Comment on: Real-world single centre use of JAK inhibitors across the rheumatoid arthritis pathway

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Dear Editor, we read with interest the paper entitled “Real-world single centre use of JAK inhibitors across the rheumatoid arthritis pathway” by Fitton et al, describing the real-life experience with the first two approved Janus Kinase (JAK) inhibitors (JAKinibs) baricitinib and tofacitinib (1). Among the 115 patients, 8 have been treated with both drugs for lack of response (n=4) or side effects (n=4).

The secondary loss of response to biological Disease Modifying Anti-Rheumatic Drugs (bDMARds) has been explained by several factors, including the drug immunogenicity. This is not the case with JAKinibs that are synthetic drugs; however, in randomized clinical trials and in real-life setting, a small percentage of patients (around 3.5%) withdraw the treatment for lack or loss of efficacy (2-4).

In case of loss of response to a bDMARD, EULAR recommends switching to a second bDMARD or targeted synthetic (tsDMARD) (5). Based on the literature data, if one TNF inhibitor has failed, EULAR suggests either to switch to a different mode of action or start a second anti-TNF (5). Data on switch between two anti-IL-6 receptor are limited. The open label extension of the ASCERAIN study showed that patients treated with tocilizumab obtained a sustained clinical efficacy when switching to sarilumab (6). Switch among JAKinibs is one of the points of the EULAR 2019 research agenda.

The JAKinibs differ for their selectivity: tofacitinib and baricitinib are first generation JAKinibs inhibiting preferentially JA3/JAK1 and JAK1/JAK2, respectively; upadacitinib and filgotinib are second generation JAKinib targeting JAK1.

Patients included in the study by Fitton et al are long-standing RA who had previously failed a median of 3 bDMARDs (ranging from 0 to 9). All 4 JAKinibs are effective in RA patients regardless different disease duration and previous treatment failure, showing to be superior to placebo in patients with long-term disease and inadequate response to bDMARDs (7).

Overall, at Sapienza Arthritis Center, 145 patients started baricitinib (n=91), tofacitinib (n=45) or upadacitinib (n=3); in the whole cohort, 15 (10.3%) discontinued the tsDMARD due to lack of efficacy (LaE) and 4 (2.7%) for loss of efficacy (LoE). In the light of the potential biological difference within the JAKinib family, we switched 10 out of the 19 patients showing inadequate response (either for LaE or LoE) or adverse events with the first targeted synthetic DMARDs (tofacitinib n=4 and baricitinib n=6) to a different JAKinib (baricitinib n=2, tofacitinib n=6, upadacitinib n=2). Eighty percent of patients were treated in monotherapy with both tsDMARDs. Table 1 summarizes the disease trend during the first and second course of treatment with JAKinibs. Four out of 10 patients

discontinued the second JAKinib for lack of efficacy (n=3) or adverse events (n=1). Five out of 9 patients (55.5%) who had at least 4 weeks of follow-up (the tenth has only 9 days of exposure to upadacitinib after the failure of tofacitinib) showed a moderate-good EULAR response with the second JAKinib. Fifty percent of patients stopping the first JAKinib for LaE did not respond to the second one. One patient withdrew after 4 weeks of treatment due to grade III lymphopenia.

In the cohort described by Fitton and colleagues, the switch to a second JAKinib was effective in 5 out of 7 patients; all 5 patients switched to baricitinib after having discontinued tofacitinib and the mean (standard deviation) improvement of DAS28 was 1.42 (2.03) at 6 months (1). In line with their results, we detected a mean DAS28 reduction of 1.67 (1.35). Six patients are still treated with the second JAKinib, after a median of 24 (interquartile range 22) weeks; 5 patients have at least one follow-up visit and 80% have reached the treatment target: 3 patients achieved remission and 1 low disease activity.

According to the EULAR definition, all patients switching to a second tsDMARD in our cohort are difficult to treat RA patients (8). The three patients of our cohort failing both JAKinibs for LaE have a multi-drug resistant RA and had previously failed more than 3 csDMARDS and 5-8 bDMARDs; in these 3 cases the JAKinibs have been prescribed as a “last chance” therapy.

Serological status, monotherapy, number of previous bDMARDs ($\leq$ 2 vs > 2) and cause of discontinuation of the first JAKinib seem not to influence the response to the second one. This data should be interpreted with caution due to the small number of patients.

None of the patient switching for LoE or AE discontinued the second JAKinib, and 75% achieved a EULAR response (Table 1).

Showing a moderate-good response in more than a half of patients, our experience supports the use of a second JAKinib in patients failing a drug of the same family, confirming that switching among JAKinibs could be a valuable treatment, above all in those switching after LoE and AE, or in patients with limited therapeutic options.

KEY MESSAGE: switching among JAKinibs is a valuable option in patients failing a previous tsDMARD.

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	sex	age	Disease Duration (months)	ACPA/RF	FIRST JAKinib	N° of previous bDMARDs	baseline DAS28_CRP	last DAS28_CRP	treatment duration (weeks)	Cause of withdrawal	SECOND JAKinib	baseline DAS28_CRP	last DAS28_CRP	Eular response Good/Mod /None	treatment duration (weeks)	Withdrawal No/Yes (cause)
1	F	62	63	-/-	tofacitinib	2	4.94	5.53	12	LaE	baricitinib	5.51	5.81	None	4	Yes (AE)
2	M	68	139	+/+	baricitinib	5	6.64	5.53	24	LaE	tofacitinib	5.39	7.25	None	24	Yes (LaE)
3	F	51	201	+/+	baricitinib	2	4.04	5.60	24	LaE	tofacitinib	4.86	1.21	Good	24	No
4	F	59	184	+/+	baricitinib	4	4.37	3.89	48	LoE	tofacitinib	3.89	3.20	Mod.	48	No
5	F	58	144	+/+	baricitinib	8	6.16	5.40	12	LaE	tofacitinib	5.32	5.47	None	12	Yes (LaE)
6	F	38	112	+/+	tofacitinib	5	4.92	5.49	12	LaE	baricitinib	5.49	5.32	None	12	Yes (LaE)
7	F	48	178	-/-	baricitinib	4	4.15	1.99	12	AE	tofacitinib	3.53	1.13	Good	24	No
8	F	42	193	-/-	baricitinib	5	3.62	3.2	12	LaE	tofacitinib	3.13	1.77	Good	24	No
9	F	46	145	-/-	tofacitinib	2	4.73	4.18	40	LoE	upadacitinib	4.16	3.85	Mod.	4	No
10	F	33	59	-/+	tofacitinib	3	5.02	3.77	96	LoE	upadacitinib	3.77	n.a.	n.a.	2	No

Table 1. demographic and clinical data of patients switching JAK inhibitors.

ACPA = anti-citrullinated protein antibody; bDMARDs = Biologic Disease-modifying antirheumatic drugs; DAS28_CRP = disease activity score28_c reactive protein; F = female; JAK = Janus Kinases; LaE = Lack of efficacy; LoE = Loss of efficacy; M = male; mod. = moderate; RF = rheumatoid factor.