Rapid paper

Efficacy and safety of switching Jak inhibitors in rheumatoid arthritis: an observational study

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ABSTRACT

Objective. *Different Jak inhibitors (jakinibs) have shown efficacy in rheumatoid arthritis (RA), but in a significant proportion of patients, an insufficient response leads to therapy withdrawal. We describe the efficacy and safety of a second jakinib in patients stopping the first due to insufficient response or side effects.*

Methods. *This is an observational retrospective multicentric study of 31 patients with RA sequentially treated with baricitinib or tofacitinib in any order in clinical practice in ten medical centres in Spain.*

Results. *We identified 31 patients, sequentially treated with both jakinibs. An equal proportion had received tofacitinib or baricitinib first. Most patients (87%) had previously received one or several bDMARD, median 4 (2–5). Median survival for the first jakinib was 5 (3–8) months, and the reasons for withdrawal were inefficacy in 61% and adverse effects in 39%. Most patients (23/31, 74%) maintained the response to the second jakinib after a mean follow-up of 19.5 (12–24) months. In all 8 patients who discontinued the second jakinib, the reason was inefficacy. The treatment suspension rate was similar among patients that had discontinued the first jakinib for inefficacy (26%) or for adverse effects (25%).*

Conclusion. *Therapy of RA with a second jakinib seems a safe and efficacious option after discontinuation of the first, either for inefficacy or for side effects.*

Introduction

In recent years, a new class of drugs with inhibitory activity on different members of the Janus kinases (Jak) family has shown remarkable efficacy in rheumatoid arthritis (RA) (1). Jak inhibitors or jakinibs interfere with the intracellular signalling of a large number of cytokines that depends on activation of different members of Jak and signal transduction and activator of transcription (STAT) families (2). Different jakinibs display variable biochemical selectivity for isolated Jak (Jak1, 2, 3 or Tyk2) kinase in *in-vitro* assays. However, and partially due to the cooperation of different Jak pairs in the signaling of a particular cytokine (*i.e.* Jak1/3, Jakl1/2, Jak1-2/Tyk2), the selectivity for the signaling of different cytokines is limited and therefore, its clinical implications on the efficacy or toxicity of the different jakinibs is unknown (3).

Baricitinib and tofacitinib received approval from the European Medicines Agency (EMA) for the treatment of RA in 2017, upadacitinib has been recently approved, and many others are in different phases of clinical development (4). They have shown efficacy in patients after csDMARD and after bDMARD (either anti-TNF or non-anti- TNF) failure (5, 6). Particularly, in the group after bDMARD, a greater proportion of patients are expected to discontinue jakinib therapy due to insufficient response or toxicity and have limited therapeutic options at this stage. One of them is using a different jakinib, which appears a rational option considering the mentioned differences on Jak selectivity (7, 8). Since clinical trials or other studies reporting switching from one jakinib to another are lacking, we report observational data of patients switching jakinibs in clinical practice.

Patients and methods

This is a multicentric, retrospective observational study of patients diagnosed of RA according to 2010 EULAR/ACR criteria (9), sequentially treated in clin-

Table I. Baseline characteristics of 31 patients with RA sequentially treated with two different jakinibs.

Clinical characteristics	n 31
Female	25 (80.6%)
Age*	62 (51-67)
Disease duration*	11 (6-18)
Rheumatoid Factor (+)	25 (80.6%)
Anti-CCP (+)	22 (71%)
Erosions	16 (51.6%)
Extra-articular manifestations	10 (32.3%)
Rheumatoid nodules	6 (19.4%)
Secondary Sjögren's syndrome	4 (12.9%)
Previous therapy	
bDMARD	27 (87%)
Previous bDMARD (n)*	4 (2-5)
Anti-TNF	24 (77.4%)
Non-anti-TNF	22 (70.9%)
Disease activity#	
TJC*	10 (7.24-14.3)
SJC*	6 (4-10)
DAS28*	5.3 (5-5.9)
High disease activity	71%
Moderate disease activity	24%
Low disease activity	5%

*Data represent median (IQR), or number (%); #At start of the second jakininb.

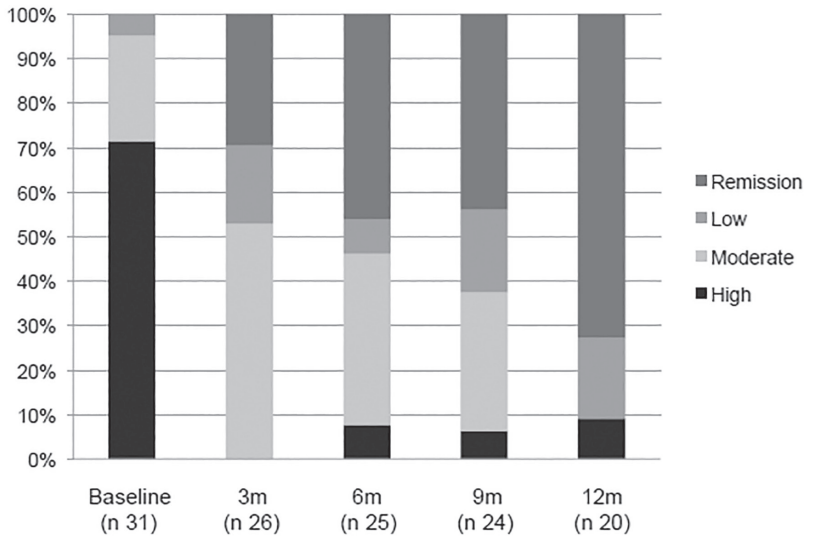

Fig. 1. Disease activity during the first year of follow-up after start of the second jakinib. Proportion of patients reaching the specified disease activity status after switching from first to second jakinib, according to DAS28 at the specified follow-up time points.

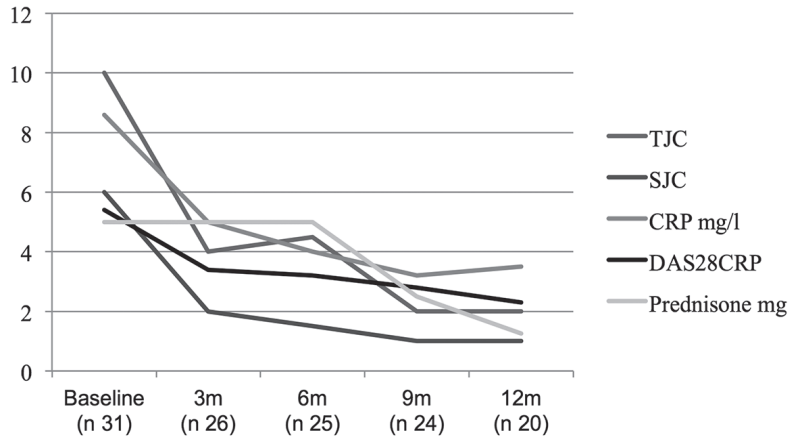

Fig. 2. Evolution of DAS28 and tapering of prednisone therapy after start of the second jakinib. The evolution of DAS28 and individual DAS28 domains along follow-up after switching from the first to the second jakinib is shown (median).
TJC: tender joints count; SJC: swollen joints count; CRP: C-reactive protein.

ical practice with either baricitinib or tofacitinib, after the withdrawal of the first jakinib due to lack of efficacy or adverse event. Patients were identified from pharmacy registers review in ten reference hospitals in Spain.

Patients had been evaluated according to regular clinical practice standards, and were included if a 100 mm VAS pain, swollen joint count (SJC), tender joint count (TJC) and C-reactive protein (CRP) were available permitting 28-joint Disease Activity Score (DAS28) calculation, and a minimal of 6 months of follow-up after starting the 2nd jakinib had been completed. We retrospectively obtained clinical data on previous and concomitant therapies, the reason for first jakinib withdrawal, and efficacy (DAS28-CRP change) and toxicity data of each jakinib. The study received approval by the Ethics Committee of Hospital 12 de Octubre (20/078). Numerical data are reported as median and interquartile range (IQR).

Results

We identified 31 patients with RA sequentially treated with baricitinib, either at 4 or 2 mg once a day, and tofacitinib (5 mg twice a day). Sixteen patients (51.6%) received tofacitinib, and fifteen patients received baricitinib (48.4%) as the first jakinib. The patients' characteristics are summarised in Table I. Median survival for the first jakinib was 5 (3–8) months; in case of tofacitinib was 5 (3–8) months and in case of baricitinib was 6 (3–11) months. The reason for withdrawal was inefficacy in 19 cases (61.3%) and adverse events in 12 (38.7%) (drug retention of 3 (2–7) months and 6 (5–10) months, respectively). The more frequent adverse effects were non-serious infections and digestive intolerance. Two patients stopped the first jakinib for herpes zoster infection. Most relevant effects of the first jakinib were DVT (1 case) and central artery thrombosis (1 case), both with bariticinib. In these cases, the second jakinib was started under anticoagulation in thrombotic cases, or after herpes zoster resolution.

Most patients were on high activity at the start of the second jakinib. Concomitant therapy with the second jakinib included glucocorticoids in 26 patients (84%), at a median dose of prednisone equivalent of 7.5 (5–10) mg, and a cs-DMARD in 22 patients (71%), methotrexate in 17 (54.9%) and leflunomide in 5 patients (16.1%). In 9 patients (29%) jakinibs were used as monotherapy.

Most patients responded to the second jakinib (n 23, 74.2%) and maintained the response after a mean follow-up of 19.5 (12–24) months. Disease activity data along follow-up are depicted in Figure 1. Median dose of prednisone at second jakinib start was 7.5 (5–10) mg, 5 (0–5) at 6 months, and 1.25 (0–5) after one year (Fig. 2). In 8 patients (25.8%) the second jakinib was discontinued, at a median time of 3 (3–11) months, and in all cases, the reason was inefficacy. The treatment suspension rate was similar among patients discontinuing the first jakinib for inefficacy (5/19, 26.3%) or for adverse effects (3/12, 25%). Most of them (7/8), received concomitant treatment with csDMARD.

Discussion

In patients with RA and inefficacy to an anti-TNF drug, the use of a second anti-TNF or an alternative target is recommended (7, 8). The rational for using a second anti-TNF could be explained by immunogenicity or certain pharmacokinetic and pharmacodynamic differences between different antagonists (10). Very few data have been reported regarding the switch between drugs with non-TNF targets, particularly between drugs sharing the same target. In the case of jakinibs, differences in Jak selectivity and pharmacokinetics of the different drugs may support individual differences in the response to one or another drug and therefore, switching between different drugs (2, 3).

Our observations show a significant improvement of disease activity as evaluated by DAS28, and a satisfactory survival of the second jakinib after failure or toxicity of the first. We observed a similar response after either failure or toxicity to the first jakinib. The observed efficacy data with the second jakinib, compare favourably with what observed in phase III trials on the efficacy of the initial use of baricitinib or tofacitinib after failure to one or more biologics (5, 6). In this series, most of the patients had received several anti-TNF and non-TNF biologics and are therefore comparable to the more refractory patients included in phase III trials of baricitinib or tofacitinib after biologic therapy failures.

Indirectly, these data suggest that pharmacological differences between these drugs could be relevant. Regarding selectivity, baricitinib displays predominant Jak1 and Jak2 selectivity, whereas tofacitinib has a higher relative activity on Jak3, which in cellular systems leads to a higher activity on gamma/receptor signaling in lymphocytes and a higher trend to lymphopenia in LTE studies (3, 11). New drugs upadacitinib and filgotinib also display higher Jak1 and Jak2 *versus* Jak3 selectivity, and therefore, studies on the potential use of these drugs after failure to the first jakinib will require further studies (12, 13).

In the absence of RCTs comparing the effects of switching between jakinibs versus alternative therapies with different targets, this observation provides support on the switching between baricitinib and tofacitinib as a valid strategy in patients with RA refractory to biologics. Since new jakinibs are being developed, the possibility of switching between different jakinibs will be an option increasingly considered for multi-refractory patients. Studies comparing this with alternative strategies are clearly needed.

Conclusions

Our data show that therapy with a second jakinib is an efficacious option after discontinuation of the first due to either inefficacy or side effects. The response rate to the second jakinib is similar in patients with inefficacy or side effects, which suggests that failure to the first does not reduce the chance of response to the second.

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