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

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Abstract

Objectives. To evaluate real world efficacy of approved JAK inhibitors (JAKi) tofacitinib and baricitinib in a large, single-centre cohort of RA patients across the treatment pathway, including those refractory to multiple biologic drugs.

Methods. All RA patients, treated with tofacitinib (from time of compassionate access scheme) or baricitinib since approval in 2017 had DAS28-CRP scores and components recorded at baseline, 3 and 6 months (with retrospective data for compassionate access scheme). Efficacy was evaluated in the total cohort, each treatment group, and subgroups of number of prior biologic classes failed.

Results. One hundred and fifteen patients were treated with a JAKi (tofacitinib 54, baricitinib 69, 8 both); 76.4% female; mean (SD) age 57.3 (14.3) years. On average patients had received 3 previous bDMARDs; 11 (9.6%) were bDMARD naïve. Combined group baseline DAS28-CRP (SD) 5.62(1.14) improved by 1.49(1.44) and 1.67(1.61) at 3 and 6 months respectively, comparable in individual JAKi groups; with 24% in at least low disease activity at 3 months. The biggest improvement was observed in the biologic-naïve group (mean DAS28-CRP improved from 5.16 to 2.14 after 6 months); whilst those with prior exposure to minimum 3 bDMARD classes had DAS28-CRP improvement of >1.2. 5/8 patients treated with both JAKi sequentially responded. Twelve patients previously unresponsive to IL-6 blockade responded to JAKi. No unexpected safety events were recorded. Two cases of venous thrombo-embolism were observed.

Conclusion. JAK inhibition is effective in a real world population of RA patients, including in a subset of patients refractory to multiple previous bDMARDs.

Key words: Rheumatoid arthritis, targeted therapy, Janus Kinase inhibitor, Tofacitinib, Baricitinib.

Key messages:

Benefit of JAKi observed across real world cohort comprising early and multiple bDMARD-refractory RA.

JAKi efficacy also recorded following failure of IL-6 inhibition and also with successive JAKi cycling

Expected adverse events were observed and included two thromboembolic events associated with additional risk factors.

Background

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that is associated with significant disability and multiple potential systemic complications (1). Over the last 20 years anti-cytokine and cell pathway biological disease modifying anti-rheumatic drugs (bDMARDs) have significantly improved the management of RA. Despite these advances, many patients fail to achieve the key treatment target of disease remission in the early stages of disease (2) and it is increasingly apparent that patients refractory to multiple targeted bDMARDs exist in our clinical practices (3-5). This highlights the need for new approaches to treat RA. Janus Kinase inhibitors (JAKi) are the first targeted synthetic DMARDs (tsDMARD) licensed for the treatment of RA with comparable efficacy to bDMARDs. Unlike the single cytokine targeting approach of bDMARDs, which are large molecules administered parenterally, JAKi are orally available small molecules specifically designed to inhibit intracellular signalling molecules common to the receptors of multiple inflammatory cytokines implicated in RA pathogenesis(6, 7).

JAKs are a family of protein tyrosine kinases that comprise JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAK pairs facilitate the signalling of cytokines in ligand-specific combinations (6). Tofacitinib and baricitinib have been approved for use in the treatment of RA, with others soon to be launched or in development (8). JAKi differ in their specificity. In vitro assays demonstrate tofacitinib predominantly inhibits JAK1 and JAK3, whereas baricitinib is a selective inhibitor of JAK1 and JAK 2 (with moderate activity against TYK2) (9). Both drugs have shown efficacy in the management of RA both as monotherapy (10, 11) and in combination with methotrexate (MTX) (11, 12), following MTX-inadequate response (13, 14) and following TNFi failure (15, 16). In addition, tofacitinib in combination with MTX has been shown to be non-inferior to the anti-TNF monoclonal antibody adalimumab in combination with MTX (17). Baricitinib in combination with MTX has demonstrated a modest, but statistically significant advantage over adalimumab (18). These data demonstrate the utility of targeting the downstream effects of multiple cytokines across the RA therapeutic pathway. Their safety profile has been comparable with other bDMARD in both clinical trials and real world data (19), other than a small increase in the risk of herpes zoster infection (20) and suggestion of increased venous thromboembolic events that needs further clarification (21, 22) .

We report our initial experience with the JAKi tofacitinib and baricitinib in patients across the treatment pathway with the objective of highlighting the real world efficacy of JAK inhibition both as first-line targeted therapy and in those who have tried and failed multiple targeted therapies due to a combination of inefficacy and adverse effects. We also report a small number of cases of patients who have switched directly between the two available JAKi.

Methods

Study design

Leeds Teaching Hospitals NHS Trust (LTHT) is a large, tertiary centre for Rheumatology with a dedicated bDMARD clinic managing over 1500 RA patients who have been treated with 1 or more targeted therapies. A prospective database was maintained for all patients with RA at LTHT treated with a JAKi, from time of licensing of both baricitinib and tofacitinib in 2017. In addition, retrospective data were collected from clinical notes and electronic health records where indicated for patients starting tofacitinib on a compassionate access scheme between November 2014 and November 2017. This scheme was available for patients' refractory to other classes of bDMARD. This study includes all patients who began a JAKi between November 2014 and November 2019.

Patients and methods

All patients had previously tried and failed two conventional synthetic (cs) DMARDs, including methotrexate as per NICE guidelines (23, 24). Most had previously been treated with one or more bDMARDs. Disease duration, serological status, current csDMARD use and history of previous bDMARD exposure were recorded on the database. Disease activity score 28 joint count-C-reactive protein (DAS28-CRP) scores, as well as DAS28-CRP components were recorded at baseline and after 3 and 6 months of therapy, along with reason for drug withdrawal when necessary. Where a patient visual analogue score (VAS) was not recorded a 3 point DAS score of tender joint count (TJC), swollen joint count (SJC) and CRP was calculated (25). Where patients discontinued therapy during the study period, discontinuation date and reason for drug withdrawal (lack of effectiveness, adverse event, loss to follow-up) were recorded. Adverse events and serious adverse events of special interest were recorded.

Statistical analysis

Patient demographics and clinical characteristics were summarized for each group using proportions of patients, median with interquartile range or mean with standard deviation as appropriate. Mean changes in DAS28-CRP score from baseline were calculated at 3 and 6 months and reported for the combined cohort and individual treatment groups. Sub analyses according to number of prior bDMARD failures were performed. All patients had baseline DAS 28 scores and components recorded. Ten patients had data missing at 3 months, but had results available at 6 months and were included for 6 month analysis. Twenty patients had data missing at 6 months, partly due to the interruption in follow-up with the onset of the COVID-19 pandemic.

Results

Baseline characteristics

Between November 2014 and November 2019 115 patients with RA were treated with a JAKi (76.4% female; mean (SD) age 57.3 (14.3) years). Eight patients were treated with both JAKi sequentially (7 switching from tofacitinib to baricitinib and 1 from baricitinib to tofacitinib). **Table 1** shows the baseline characteristics of the combined JAKi cohort and those treated with tofacitinib and baricitinib, including the number of classes of targeted therapy that patients had been exposed to prior to starting JAKi.

As expected, in line with the compassionate access scheme, those treated with tofacitinib had a longer disease duration and had been previously exposed to a greater number of targeted therapies, than those on baricitinib. Thirty-three patients in total were treated under this scheme. The majority of the patients had been exposed to between 2 and 4 previous targeted therapies and had failed them due to a combination of non-response and adverse effects (see supplementary table 1 for demographics of compassionate access patients).

Efficacy

Table 2 shows baseline DAS28-CRP score, DAS28-CRP components and the mean change in these measures at 3 and 6 months for the combined JAKi cohort and individual tofacitinib and baricitinib cohorts. Fourteen of 54 patients treated with tofacitinib stopped treatment due to lack of efficacy during the study period. Twenty six patients remain on tofacitinib with a median treatment duration of 23.5 months (Interquartile range, IQR 23) to date. Two patients have been lost to follow up. Fifteen of 69 patients have stopped baricitinib due to lack of efficacy. Forty-five patients remain on baricitinib with a median treatment duration of 13 months (IQR 6). In the combined JAK inhibitor group 84.6% of patients remained on their JAKi at 3 months and 73.2% of patients were still on drug at 6 months after the combined effects of lack of efficacy and toxicity (see below). A total of 40.7% of patients stopped their JAKi during the entire study period. Kaplan Meier survival analysis for the cohort over the whole study period, according to prior bDMARD exposure, suggests lower cumulative survival of JAK inhibitors in patients who have previously been exposed to 2 -4 previous classes of targeted therapy (see supplemental figure 1 for Kaplan Meyer survival curve for cohort over the whole study period).

Figure 1 shows the percentages of patients in each DAS28-CRP cut-off category >5.1, >3.2-≤5.1, ≥2.6-≤3.2 and <2.6 at baseline, 3 and 6 months for both tofacitinib and baricitinib. **Figure 2** shows the combined results for both JAK inhibitors based on the number of previous classes of targeted therapies the patient had been treated with prior to the introduction of a JAKi.

Response in patients previously treated with IL-6 inhibition

Seventy six patients had previously been treated with the anti-IL-6 receptor monoclonal antibody tocilizumab. Twenty eight patients in our cohort had a documented primary non-response to tocilizumab, 25 had secondary loss of response and 23 had stopped due to adverse effects. Thirty six of these patients responded to a JAKi with a mean DAS28-CRP improvement of 2.29 (SD1.19), Twenty six did not respond and 14 stopped due to adverse effects. Twelve of 28 of those with a primary non-response to tocilizumab responded to JAKi (4 tofacitinib, 8 baricitinib), with a mean improvement in DAS28-CRP score of 2.18 (SD 1.08) at 6 months (mean DAS28 score improving from 5.54 to 3.36).

JAKi cycling

Seven patients switched from tofacitinib to baricitinib due to either lack of response (n=3) or intolerance (n=4). Five patients responded to baricitinib after 6 months of treatment and mean (SD) DAS28-CRP improvement of 1.42 (SD 2.03). One patient switched from baricitinib to tofacitinib due to lack of response but did not have improvement in DAS28-CRP. The patient continued tofacitinib however due to an improvement in a co-existing skin condition.

Toxicity

Twelve patients treated with tofacitinib stopped treatment due to adverse effects (3 infection, 1 rash, 2 deranged liver function tests, 2 headache, 1 dizziness, 2 diarrhoea and 1 malignancy). Nine patients treated with baricitinib stopped treatment due to adverse events (2 headache, 2 deranged LFTs, 5 due to infections and 1 angioedema). However, a further 4 patients down-titrated from 4mg daily to 2 mg daily due to nausea and/or other gastrointestinal side effects and continued to respond at this lower dose. Two patients out of the 69 treated with baricitinib developed a deep vein thrombosis, although in both cases other provoking factors were present (long haul travel and lower limb trauma, and obesity). Due to lack of alternative treatment options (after multiple bDMARD failure in one case and severe needle phobia in the other) and after careful consultation with the patients involved and haematology colleagues, both patients elected to remain on baricitinib with anticoagulation.

Discussion

We report on the largest single centre UK real-life experience of RA patients treated with JAK inhibitors to date. Of over 120 RA patient exposures, a significant proportion of patients were refractory to a number of previous targeted therapies. Our results show efficacy of JAK inhibition in both bDMARD naïve and experienced patients including those with refractory disease.

Despite the established role of bDMARDs for people with RA, suboptimal responses are still observed in a sizeable proportion across the treatment pathway. JAK inhibition offers an alternative approach, through blockade of the signalling of multiple cytokines implicated in the pathogenesis of RA. Our report in a real-life population further consolidates these data with demonstration of meaningful clinical improvement. Our patient population represents a typical mixed population, three quarters seropositive, with wide-ranging disease duration (from 1 year to over 57 years) and a spread of previous exposure to both csDMARDs and bDMARDs. A quarter of patients had previous exposure to ≤1 bDMARDs. In contrast, a compassionate access scheme meant patients treated with tofacitinib in our cohort had on average longer disease duration, previous exposure to a greater number of bDMARDs and higher baseline disease activity. Nevertheless, clinical improvement in this subgroup was also observed.

Diminishing response of DMARDs including bDMARDs is generally recognised following successive treatment failure (26, 27). Clinical trial data suggest this may not be the case with JAKi, likely attributable to the broader targeting of JAK inhibition. Comparable response profiles have been reported in MTX-IR and the more refractory bDMARD-IR (16, 28, 29) trial cohorts, with impressive efficacy in head to head trials against TNFi, the most established bDMARD.
IL-6 is also an important therapeutic target in RA. JAK is involved in signal transduction of type I and II cytokine receptors including IL-6 receptor, suggesting that IL-6 blockade may be an important factor in the clinical efficacy of JAKi. Response following failure of IL-6 targeted therapy was also noted in our cohort, including in 12 patients who had failed to achieve a clinical response to tocilizumab therapy. This implies that the clinical efficacy of JAK inhibition is due to effects beyond the interruption of IL-6 signalling.

In our cohort, the association of lower survival of JAKi in patients with previous exposure to higher numbers of targeted therapies needs to be interpreted with caution. Longer follow-up of patients that started their JAKi drug through the early compassionate access scheme compared to patients with less refractory RA who have been censored at the end of the study period introduces a source of bias. The more refractory cohort with more limited (or no) further treatment options may also have influenced the decision to continue therapy for longer than would have been done in patients with still treatment options available.

Meaningful DAS28-CRP improvements were observed in the most refractory groups, with 41.2% patients achieving DAS28-CRP<3.2 (70.8% starting in DAS28-CRP >5.1). Specifically, DAS28-CRP treatment responses were recorded in 14 patients who received tofacitinib on the compassionate access scheme. One patient who had a primary non-response to seven previous targeted therapies (including compassionate access tofacitinib), responded sufficiently well to baricitinib in combination with leflunomide to meet DAS28-CRP <2.6 after 6 months of treatment (DAS 28 improvement from 6.40 to 2.02). Nevertheless, perhaps unexpectedly, the most notable improvement in DAS28-CRP scores was still observed in patients who received a JAKi as their first line targeted therapy (figure 3).

The role of switching between JAKi is also of interest, particularly in those with limited therapeutic options. TNFi (and IL-6 targeted) bDMARD cycling can be efficacious, even in the event of apparent primary non-response to the first drug (30). Differences in drug molecule, binding affinity, target and pharmacokinetics all likely play a role (31). The differing selectivity of JAKi and individual drug specific bioavailability and tissue penetrance may provide a rationale for why switching between JAKi may be successful in patients who failed to respond to their first JAKi. Our preliminary data shows that this approach can be successful with five of seven patients switching from tofacitinib to baricitinib responding to treatment.

Toxicity with the two JAK inhibitors was in line with expected adverse events. Two patients sustained a DVT but both had known risk factors. Nevertheless, the decision to continue them both on JAKi highlights the challenging decisions in clinical practice compared to clinical trials. Here, a multi-disciplinary discussion with haematology and a shared decision-making approach with fully informed patients were central components to the management plan.

This report has its obvious limitations. It is a modest-sized, observational cohort combining both prospective and retrospective data, with all the associated caveats including absence of a ‘control’ cohort, channelling bias, and descriptive outcomes. These factors make the study unsuitable for regression analysis to identify predictive factors of good response, which would have been valuable. Long-term outcomes for evidence of attrition on JAKi will also be clearly important to evaluate. Whilst the focus is of clinical responses of the entire cohort, we have also presented data for tofacitinib and baricitinib separately – but would caution that this unmatched, observational study does not permit direct comparison of outcomes.

In summary, we present the largest single-centre UK experience with JAKi reported to date. In a markedly heterogeneous cohort, we clearly observed clinical improvement in patients treated with JAK inhibition following MTX-inadequate response and in the most bDMARD-refractory of patients. These data underscore the potential for JAKi to avoid some of the effects of cytokine redundancy, which could give them a unique role in the broad management of RA as well as more complex, advanced disease.

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Declaration of interests

JF has received speaker fees from Pfizer.

PE has received consultant fees from AbbVie, BMS, Eli Lilly, MSD, Novartis, Pfizer, Roche, Samsung, Sandoz and UCB and received research grants paid to his employer from AbbVie, BMS, Pfizer, MSD and Roche.

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Table 1: Baseline characteristics of the combined JAKi cohort and those treated with tofacitinib and baricitinib

Characteristic	Combined JAK inhibitor group (n=123)	Tofacitinib (n=54)	Baricitinib (n=69)
Demographics			
Age (mean) (SD)	57.2 (14.3)	59.1 (14.0)	55.8 (14.3)
Female, n (%)	94 (76.4)	40 (74.1)	54 (78.2)
RA profile			
Disease duration, years; median (IQR)	16 (7)	17 (5)	14 (8)
Seropositivity (ACPA and/or RF), n (%)	90 (73.2)	41 (75.9)	49 (71)
Treatment history			
Concomitant csDMARD (%) Any (%) MTX other	 73 (59.3) 54 (43.9) 19 (15.4)	 34 (62.9) 27 (50) 7 (13)	 39 (56.5) 27 (39.1) 12 (17.4)
Number of previous TT(median, range)	3 (0-9)	4 (0-8)	3 (0-9)
Number of previous classes of TTs (%)			
Targeted therapy naïve (%)	11(9)	1 (1.9)	10 (14.5)
TNFi Only	13 (10.6)	4 (7.4)	9 (13)
1 Non-TNFi TT only	8 (6.5)	3 (5.6)	5 (7.2)
2 classes	20 (16.3)	7 (13)	13 (18.8)
3 classes	39 (31.7)	21 (38.9)	18 (26.1)
4 classes	26 (21.1)	18 (33.3)	8 (11.6)
5 classes	6 (4.9)	0 (0)	6 (8.7)
Previous anti-IL-6 therapy	76 (61.8)	39 (72.2)	37 (53.6)
Reason for failure of previous TTs			
Primary non-response only	16 (13)	8 (15.1)	8 (11.6)
Secondary loss of response only	20 (16.3)	6 (11.3)	14 (20.3)

Mixed primary non-response/secondary loss of response	22 (17.9)	15 (28.3)	6 (8.7)
Adverse effects	8 (6.5)	2 (3.8)	6 (8.7)
Mixed primary/secondary/adverse events	48 (39)	23 (40.4)	25 (36.2)

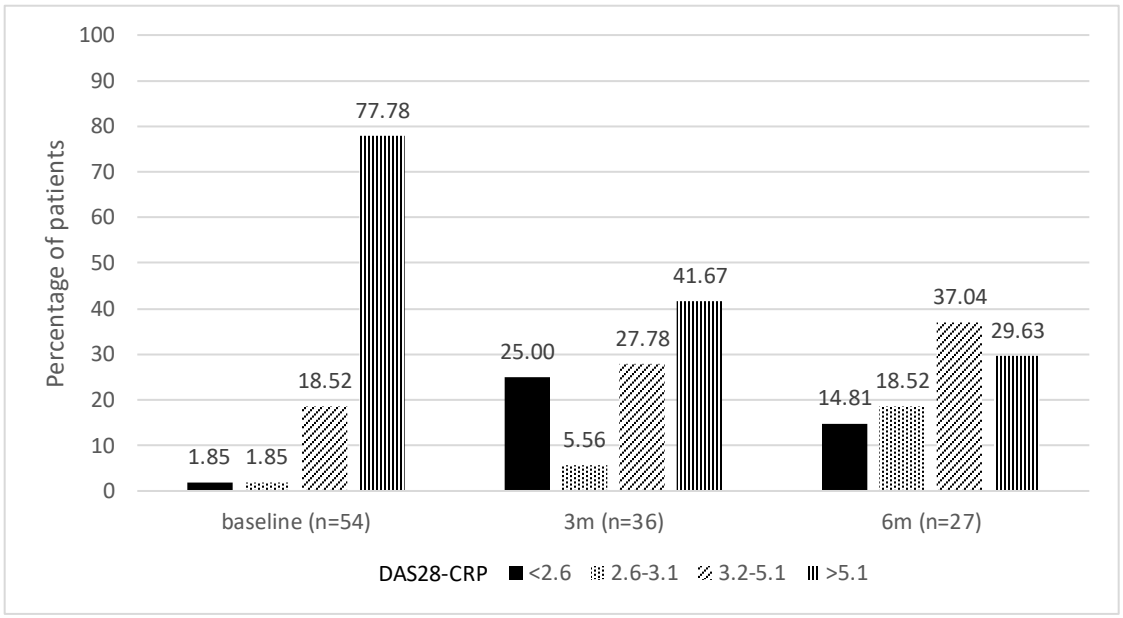
JAK – Janus Kinase inhibitor, ACPA – Anti-Citrullinated protein antibody, RF – Rheumatoid factor, TNFi – Tumour necrosis factor inhibitor, TT – Targeted therapy.

Table 2: Mean (SD) DAS28-CRP score and change in DAS28-CRP components at baseline, 3 and 6 months

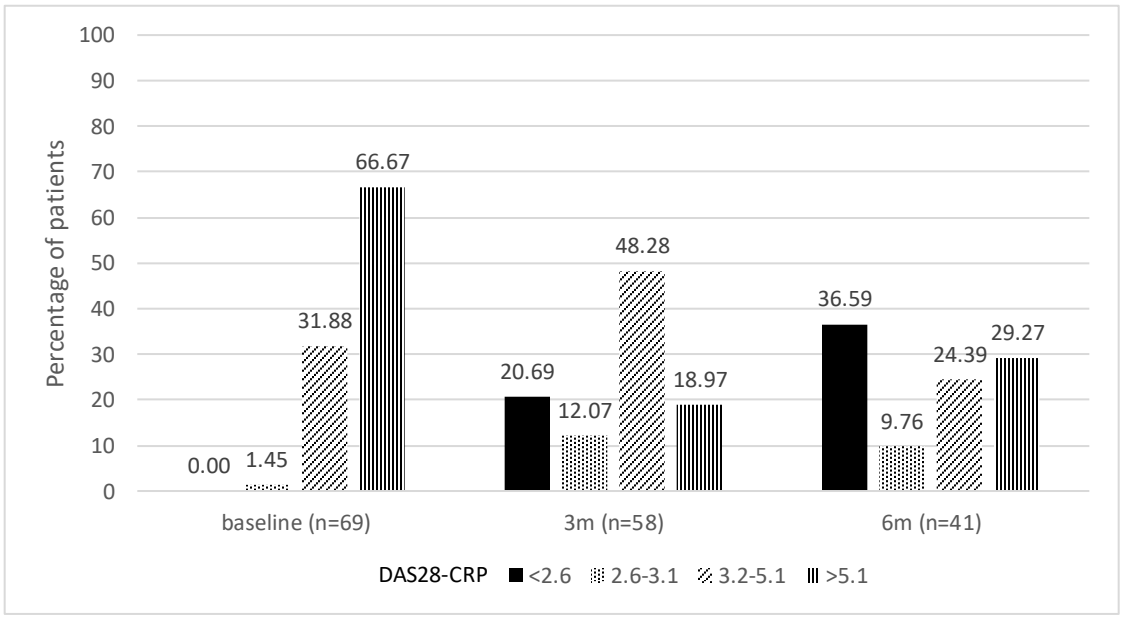
	Baseline	3 months	6 months
Combined JAKi group	n=123	n=94	n=68
DAS28	5.62 (1.14)	-1.49 (1.44)	-1.67 (1.61)
TJC	14.30 (7.84)	-6.73 (9.24)	-7.31 (9.71)
SJC	6.50 (5.13)	-3.31 (5.54)	-3.49 (5.39)
VAS GH	77.01 (17.97)	-26.34 (26.47)	-23.32 (26.92)
CRP	26.33 (39.81)	-10.93 (37.06)	-16.74 (47.69)
Tofacitinib	n=54	n=36	n=27
DAS28	5.85 (1.23)	-1.71 (1.78)	-1.81 (1.77)
TJC	15.13 (8.46)	-8.0 (10.50)	-8.56 (8.33)
SJC	7.45 (5.26)	-4.35 (5.94)	-5.11(5.49)
VAS GH	79.63 (18.87)	-27.55 (26.55)	-23.86 (26.50)
CRP	31.58 (47.12)	-18.98 (53.08)	-32.62 (69.11)
Baricitinib	n=69	n=58	n=41
DAS28	5.45 (1.04)	-1.35 (1.19)	-1.57 (1.50)
TJC	13.65 (7.32)	-5.96 (8.39)	-6.44 (10.58)
SJC	5.77 (4.95)	-2.68 (5.25)	-2.28 (5.05)
VAS GH	74.89 (17.06)	-25.86 (26.71)	-22.97 (27.59)
CRP	22.3 (33.05)	-6.81 (21.64)	-5.7 (17.85)

DAS – Disease activity score, TJC – tender joint count, SJC – swollen joint count, VAS GH – Visual analogue score general health, CRP – C-reactive protein.

Figure 1: DAS28-CRP categories at baseline, 3 and 6 months of (A) Tofacitinib and (B) Baricitinib.



A

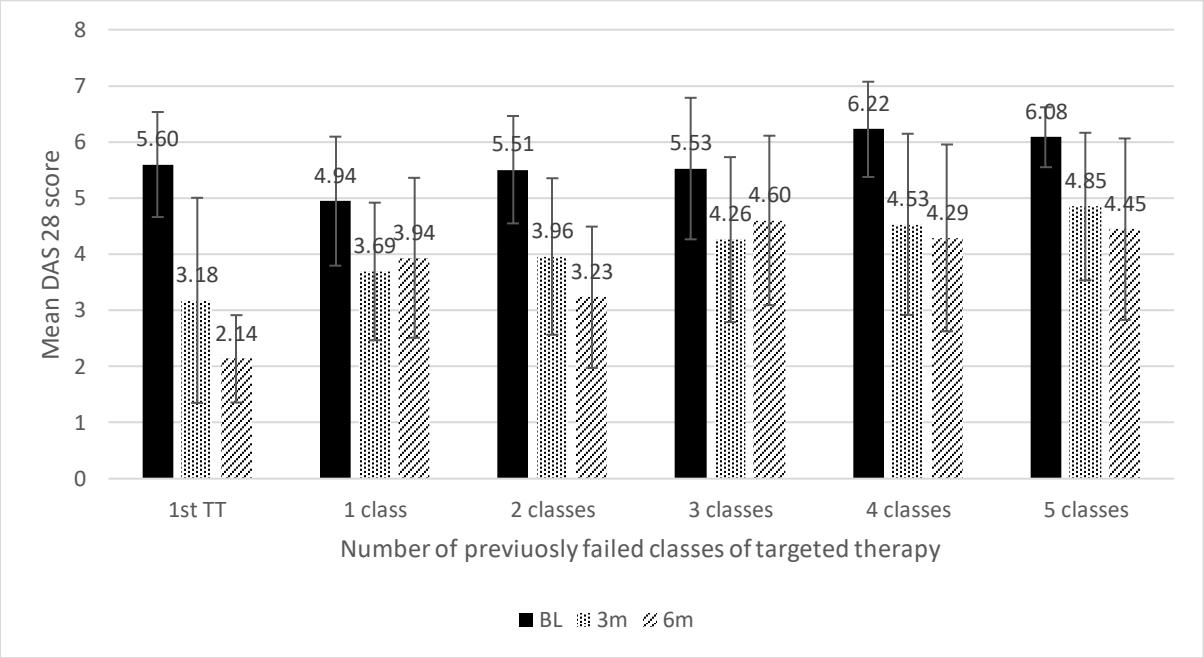


B

Percentage of patients in each DAS28-CRP cut-off category at baseline, 3 and 6 months treated with A. Tofacitinib; B. Baricitinib.

DAS28-CRP: Disease activity score 28-joint C-reactive protein

Figure 2: Response to JAKi based on prior number of classes of targeted therapy (combined group tofacitinib and baricitinib).



DAS28-CRP: Disease activity score 28-joint C-reactive protein; JAKi: Janus Kinase inhibitor