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ORIGINAL RESEARCH

PERFECTRA: a pragmatic, multicentre, real-life study comparing treat-to-target strategies with baricitinib versus TNF inhibitors in patients with active rheumatoid arthritis after failure on csDMARDs

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ABSTRACT

Objective To compare the effectiveness of a strategy administering baricitinib versus one using TNF-inhibitors (TNFi) in patients with rheumatoid arthritis (RA) after conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) failure in a real-life treat-to-target (T2T) setting.

Methods Patients with biological and targeted synthetic DMARD (b/tsDMARD) naïve RA with disease duration ≤5 years without contraindications to b/tsDMARD were randomised to either TNFi or baricitinib when csDMARD failed to achieve disease control in a T2T setting. Changes in clinical and patient-reported outcome measures (PROMs) were assessed at 12-week intervals for 48 weeks. The primary endpoint was non-inferiority, with testing for superiority if non-inferiority is demonstrated, of baricitinib strategy in the number of patients achieving American College of Rheumatology 50 (ACR50) response at 12 weeks. Secondary endpoints included 28-joint count Disease Activity Score with C reactive protein (DAS28-CRP) <2.6, changes in PROMs and radiographic progression.

Results A total of 199 patients (TNFi, n=102; baricitinib, n=97) were studied. Both study groups were similar. Baricitinib was both non-inferior and superior in achieving ACR50 response at week 12 (42% vs 20%). Moreover, 75% of baricitinib patients achieved DAS28-CRP <2.6 at week 12 compared with 46% of TNFi patients. On secondary outcomes throughout the duration of the study, the baricitinib strategy demonstrated comparable or better outcomes than TNFi strategy. Although not powered for safety, no unexpected safety signals were seen in this relatively small group of patients.

Conclusion Up to present, in a T2T setting, patients with RA failing csDMARDs have two main strategies to consider, Janus Kinases inhibitor versus bDMARDs (in clinical practice, predominantly TNFi). The PERFECTRA study suggested that starting with baricitinib was superior over TNFi in achieving response at 12 weeks and resulted

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ European Alliance of Associations for Rheumatology and American College of Rheumatology (ACR) guidelines recommend using a TNF-inhibitor (TNFi) or a JAK-inhibitor (JAKi) for patients with rheumatoid arthritis (RA) failing to achieve target disease activity with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

⇒ Baricitinib showed significant clinical improvements in patients with RA with an inadequate response to methotrexate in comparison to adalimumab and placebo in pivotal trials.

WHAT DOES THIS STUDY ADD?

⇒ There is real-world evidence that a baricitinib strategy is superior to TNFi strategy in patients with csDMARD refractory RA in terms of ACR50 response at 12 weeks and secondary clinical endpoints, patient-reported outcome measures and drug survival over a 48-week period.

⇒ The pragmatic nature of PERFECTRA, including real-world, non-selected patients, generates results that are more easily generalisable and provides insight into results that can be achieved in daily clinical practice.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE OR FURTHER DEVELOPMENTS?

⇒ Baricitinib might be a better option as compared with TNFi in patients with RA with an inadequate reaction to methotrexate.

⇒ JAKis are a valuable addition to a rheumatologist's toolbox in treating patients with RA with an inadequate response to methotrexate.

in improved outcomes across all studied clinical measures and PROMs throughout the study duration in these patients.

INTRODUCTION

In recent decades, outcomes for rheumatoid arthritis (RA) have improved significantly, largely due to biological therapies and the treat-to-target (T2T) paradigm.[1 2] Despite these advances, a considerable number of patients in real-world clinical practice fail to achieve sustained disease control. Targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) have emerged as a new disease-modifying treatment option.[3–6] However, their effectiveness in comparison with other options within the current T2T strategies in the real world can still be better understood. Additionally, there is a need for real-world evidence of these treatment options within the T2T framework.

Baricitinib is an oral Janus Kinases inhibitor (JAKi) selectively for JAK-1 and JAK-2 available for the treatment of RA.[3 7 8] Even though European Alliance of Associations for Rheumatology (EULAR) guidelines present tsDMARDs, including JAKi such as baricitinib, as a treatment option next to biological disease-modifying antirheumatic drugs (bDMARD) after methotrexate (MTX) failure to reach the target with respect to disease activity: remission and low disease activity[2], physicians' extensive clinical experience with bDMARDs and specifically tumour necrosis factor inhibitors (TNFi) causes these to be more commonly used in practice. Other factors, like the availability of several TNFi biosimilars and costs, obviously also play a role in usage in practice.

However, tsDMARDs offer several clinically relevant benefits for patients compared with bDMARDs (TNFi), including convenient mode of administration, short half-life and improved suitability for monotherapy. Randomised controlled trials (RCTs) are extremely valuable in assessing efficacy and effectiveness of the compound of interest. However, due to strict inclusion and exclusion criteria and other factors, they may not always fully reflect how care is being conducted in all situations that the real world may bring. To add to the evidence that formal RCTs generate and to create a fuller picture of all scenarios, real-world studies are incredibly important and can complement results from RCTs to generate more information and further improve patient care. It is therefore important to study treatment options and strategies in relevant real-life settings, like in settings where T2T is fully implemented.[9 10] Obviously, compliance with safety precautions and recommendations surrounding the treatment of immune-mediated inflammatory diseases with JAKi have to be fully taken into account as outlined in Nash *et al*.[11]

PERFECTRA was designed as a pragmatic trial to inform clinical practice on the effectiveness of a strategy starting with the JAKi baricitinib compared with a strategy starting with a TNFi after conventional synthetic disease-modifying antirheumatic drug (csDMARD) failure in a real-life T2T setting. The pragmatic design of PERFECTRA yields several benefits; it better incorporates aspects of the population and its characteristics for which an intervention is intended and thus evaluates effectiveness in real-life situations whereas results from formal RCTs can be limited in generalisability.[12] The daily clinical practice setting and limited inclusion and exclusion criteria maximise applicability of the results of PERFECTRA. In this study, we report the findings of the 48-week multicentre randomised, open-label, pragmatic real-world PERFECTRA trial. The primary goal of PERFECTRA was to establish the non-inferiority (NI) of the tsDMARD baricitinib to TNFi in terms of American College of Rheumatology 50 (ACR50) response at 12 weeks. If NI was confirmed, assessment of superiority of baricitinib strategy at 12 weeks was included. Secondary objectives encompassed the comparison of patient-reported outcome measures (PROMs), safety assessments and radiological damage over the course of 48 weeks.

METHODS

Study design

The investigator-initiated PERFECTRA study was a 48-week multicentre randomised, open-label, pragmatic, real-world NI (including superiority) trial designed for 200 patients with active RA, despite adequate dosage of csDMARD. Included patients were treated open label, according the T2T principle[2] to either a strategy starting with TNFi (any TNFi as indicated and reimbursed for RA treatment in the Netherlands) or a treatment strategy starting with baricitinib.

Patients

Inclusion criteria were a clinical diagnosis of RA, active disease at the discretion of the rheumatologist, former treatment according to T2T principles (ie, past treatment decisions informed by disease activity measurements) and previous use of at least one csDMARD. Exclusion criteria included disease duration longer than 5 years, previous treatment with any bDMARD or tsDMARD, contraindications for TNFi and baricitinib, failure to provide written informed consent, or a refusal to use effective contraceptive during the study period when applicable.

Procedures

Fifteen centres, of which 14 were located in the Netherlands and 1 in Belgium, who had all fully implemented a T2T strategy for RA before this study, were enrolled. Consecutive patients with RA, not responding on or losing response on csDMARDs, were included after giving written informed consent. For all patients, a suggested treatment allocation to either to start with baricitinib or to start with a TNFi was provided by means of blockwise randomisation lists for each centre: final treatment decision was at the shared discretion of the attending physician and the patients, in compliance with the EULAR and national guidelines.[2] Both treatment

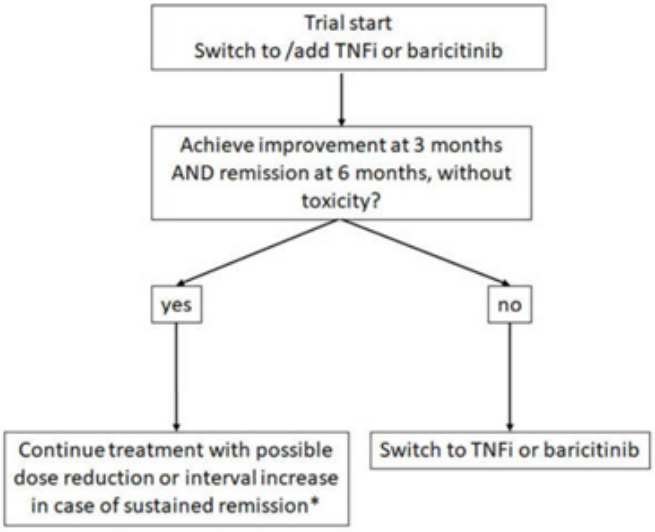

Figure 1 Treatment algorithm. TNFi, tumour necrosis factor inhibitor. *For at least 2 consecutive visits.

strategies completely conformed to EULAR guidelines, the only difference between the two being the first treatment step after inadequate response to csDMARD is a choice that the 2019 EULAR guidelines did not yet distinguish between.[10] The 2022 EULAR guidelines update has included a caution around JAKi, prompting to consider them after risk assessment.[13]

Patients were followed up over the course of 48 weeks with scheduled clinic visits at 0, 12, 24, 36 and 48 weeks and were encouraged to schedule visits if they experienced a disease flare or adverse events (AEs) in between scheduled visits. At each visit, disease activity-guided therapeutic adjustments were made as necessary in line with T2T principles, aiming to achieve clinical remission. Therapeutic adjustments included the option to taper or switch medication at the discretion of their attending physician. Patients were treated in accordance with the 2016 EULAR recommendations for RA treatment with synthetic and bDMARDs including more recent updates thereof.[2 10] The protocol under investigation in PERFECTRA recommended the use of defined registered and reimbursed products.

Figure 1 displays the study treatment algorithm. At baseline, patient characteristics including sex, age and disease duration were collected. Clinical characteristics, including anticyclic citrullinated peptide (anti-CCP) antibody, rheumatoid factor status, comorbidities and medication use were also recorded at baseline and updated throughout the study period. During each visit, patients underwent full clinical assessments including laboratory testing of acute phase response (C reactive protein (CRP)) and 28-joint count of tender and swollen joints (TJC and SJC). PROMs were completed online at 0, 4, 8, 12, 24, 36 and 48 weeks.

Measures

ACR50 response criteria served as a primary endpoint, defined as a reduction of at least 50% in both the TJC and SJC and a reduction of at least 50% in three of the five following ACR core measures: physician global assessment of disease activity, patient global assessment of well-being, patient-reported pain, patient-reported disability and CRP.[14]

The physician global assessment of current disease activity was measured using a visual analogue scale (VAS) ranging from 0 (not active at all) to 100 (extremely active). Patient global assessments of pain in the past week (no pain at all – unbearable pain), current well-being in the past week (very well – very poor) and fatigue in the past week (not fatigued at all – extreme fatigue) were also assessed at every measurement point using 0–100 VASs. Disability was measured with the Rapid Health Assessment Questionnaire-II Health Assessment Questionnaire.[15]

The composite 28-joint count Disease Activity Score with C reactive protein (DAS28-CRP) was computed as a secondary endpoint.[16] The Clinical Disease Activity Index (CDAI) was also computed as some bDMARDs and tsDMARDs, including baricitinib, directly influence the CRP production. The CDAI shows disease activity results independent from the acute phase response.[17]

Baseline and 48-week radiographs of hands and feet were scored according to the modified Sharp/van der Heijde method in random order by two trained readers independently.[18] 144 complete sets of radiographs were available, equally divided between both strategies. The readers were blinded to clinical information, chronological order and strategies assigned. After confirming acceptable inter-reader reliability, the average score of the two readers was considered the Sharp/van der Heijde Score (SHS) and used for analysis.

AEs and serious adverse events (SAE), as defined by the U.S. Food and Drug administration (FDA), were obtained continuously during follow-up. Patients were asked to report any side effects experienced to their treating rheumatologist. Reporting and procedures were aligned with national guidelines.[19]

Outcomes

The primary endpoint was NI, with subsequent superiority testing in case of NI with preservation of type 1 error rate,[20] of the strategy of starting with baricitinib versus the comparator strategy to start with a TNFi, in terms of ACR50 response at 12 weeks. Secondary objectives included to compare the proportions of patients achieving DAS28-CRP <2.6 at 12 weeks, changes in DAS28-CRP and CDAI scores and PROMs across the follow-up period, and radiological progression over 48 weeks. ACR response criteria and DAS28 both are composite outcome measures for RA. We chose to apply the ACR50 score as a realistic composite outcome measure since treatment decisions are usually driven by DAS28.

Drug survival

Switching from baricitinib to a TNFi or from TNFi to baricitinib was advised in case of no observed improvement or

in case of intolerable side effects after 12 weeks or thereafter. Kaplan-Meier analysis with log-rank testing was performed to explore drug survival over 48 weeks in both strategies.

Sample size calculation

The required sample size for the primary NI analysis was based on an expected 35% of the patients in the baricitinib arm and 25% of patients in the TNFi arm obtaining an ACR50 response at 12 weeks. These estimates were obtained by adjusting the ACR50 response rates observed in the RA BEAM trial[3] for differences in ACR50 response rates between clinical trial and clinical practice populations as described in previous studies.[21 22] The adjustment of ACR50 response rates was based on a random effects meta-analysis of the risk difference of obtaining ACR50 response in clinical practice versus clinical trial settings for biological medications in RA. To achieve 95% power for a NI test with a risk of type 1 error of 5%, 186 patients would need to be included to be sure that the lower limit of the 95% CI for the difference in proportions of patients achieving ACR50 at 12 weeks would be above the prespecified NI limit of −12%. To account for dropout, we aimed to include 200 patients. Since PERFECTRA is a real-world study, it was expected that the true difference between treatment arms might be lower than observed in RA BEAM. To assess robustness of the sample size calculations against deviations from our initial expectations, we tested a range of possible ACR50 response rates for the baricitinib arm ranging from 30% to 35% and the TNFi arm from 25% to 30%, with the difference between both arms ranging from 4% to 10%. The results showed that in all these scenarios power was ≥80% with the planned number of 200 included patients.

Populations and missing data

Primary endpoint analyses were performed for both the intention-to-treat (ITT) and per-protocol (PP) populations. The ITT population consisted of all subjects correctly included in the study, analysed based on assigned treatment. The PP population excluded all subjects that discontinued the study or had missing data for one or more assessments of the primary outcome at baseline or 12 weeks.

Assuming that any missing data occurred at random, missing values for the primary analyses were imputed for the ITT population using multiple imputation by chained equations (10 imputations with a maximum of 25 iterations) of the individual ACR50 components using predictive mean matching.[23] The imputation models were specified to include the individual component measures from which the ACR response criteria were calculated at baseline and 12 weeks as predictors along with baseline treatment group, sex, age, smoking status, disease duration, body mass index, erosion, RF and anti-CCP positivity, and concomitant MTX use, based on previously established predictors of disease activity remission[24–26] All secondary analyses were performed using the available (non-imputed) data of all correctly, according to study protocol inclusion and exclusion criteria, included patients.

Primary effectiveness analyses

For the primary analysis, the proportion of patients achieving ACR50 at week 12 in baricitinib strategy arm were compared with the TNFi strategy arm, using the 95% Wilson score CI for the difference in proportions using the Newcombe hybrid score.[27 28]

Following previous studies, a fixed NI margin of 12% was adopted for this study.[3 29 30] If the 95% CI for the difference in proportions of patients achieving ACR50 at 12 weeks (TNFi – Baricitinib) lies entirely to the right of −12%, baricitinib will be declared non-inferior. The prespecified NI margin of 12% was based on previous head-to-head trials in RA, including the RA BEAM baricitinib study.[3]

Secondary analyses

The difference in the proportion of patients achieving DAS28-CRP <2.6 was also compared using the 95% Wilson score CI method for the difference in proportions in those patients with available data at both baseline and 12 weeks. Continuous secondary endpoints were analysed using linear mixed-effect (LME) models with the endpoint as the dependent variable and time, treatment group and their interaction as fixed effects and random effects for patient intercepts and slopes over time. All LME models used restricted maximum likelihood estimation and the covariance structure was set to compound symmetry as unstructured or autoregressive structures did not provide significantly better fit according to likelihood ratio tests for disease activity and PROMs.

Radiological joint damage of hands and feet scores (SHS) was analysed by performing a Mann-Whitney U test for difference in progression scores at 48 weeks due to their non-normal distribution (zero-inflated or positively skewed) and was visualised in cumulative probability plots.[31 32]

Safety analyses

Safety was evaluated by tabulations of AE/SAE and presented with descriptive statistics for each treatment group.

Patient involvement

Patients were involved in the design of PERFECTRA. The Dutch patient association 'Nationale Vereniging Reuma-Zorg Nederland (RZN)' was involved with design of the study protocol and were consulted on design and feasibility.

RESULTS

Patients

Inclusion started on 25 September 2019, and the last patient was included on 2 February 2022. Last patient out took place one 4 April 2023. In total, 201 patients were

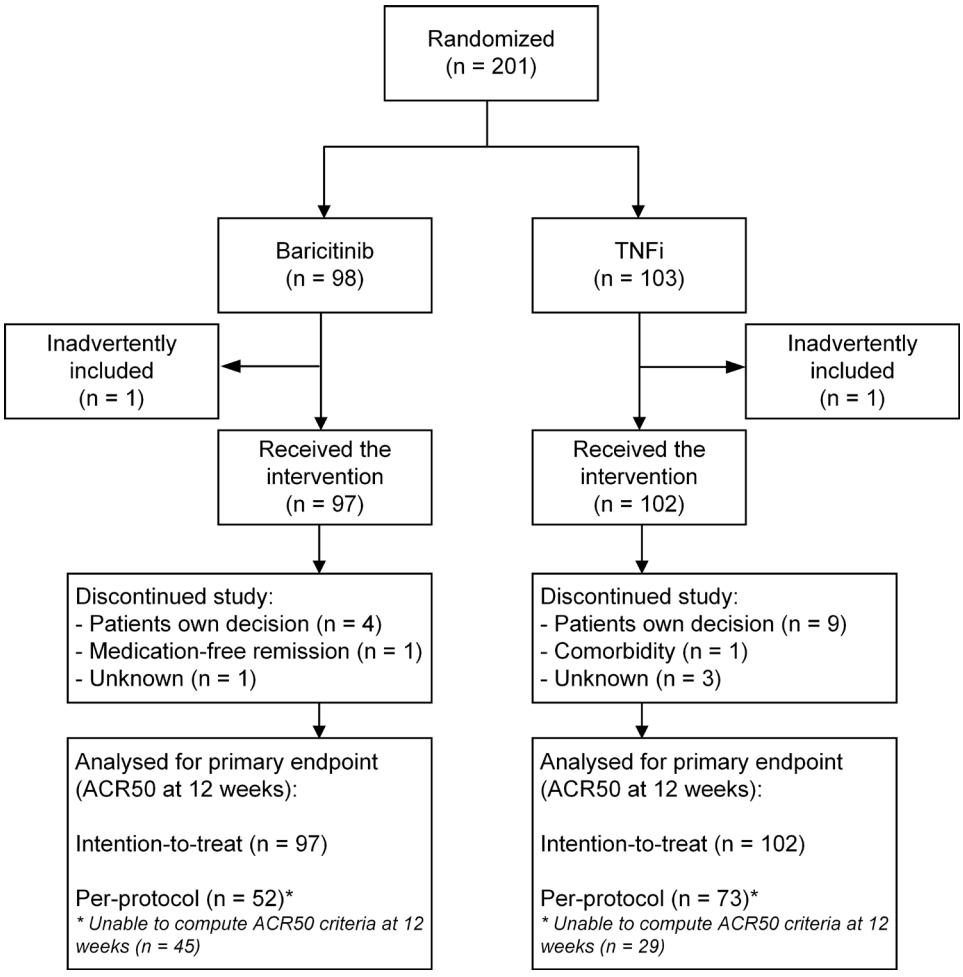

Figure 2 Study flow diagram. TNFi, tumour necrosis factor inhibitor.

included in the study of which 199 patients received the first dose. Figure 2 displays the Consolidated Standards of Reporting Trials flow chart.[33 34] After randomisation, 97 patients were assigned and started baricitinib strategy where 102 patients were assigned to and started TNFi strategy. Within the TNFi strategy, 64% of patients started on adalimumab, 33% used etanercept and the rest of the group used golimumab or infliximab.

Table 1 shows baseline characteristics for the study sample. Baseline characteristics were similar in both treatment groups. About two-thirds of the patients were female with an average disease duration of 2 years since diagnosis with RA. Disease activity as measured by DAS28-CRP scores, on average, match with moderate disease activity.[3 8] Concomitant MTX use and changes in dose of MTX are displayed in more detail in the online supplemental material.

Figure 3 displays the survival probability of baricitinib and TNFi in both strategies by Kaplan-Meier plots. Throughout the entire study period, approximately 70% of patients in TNFi strategy remained on their first treatment versus around 80% for baricitinib (p=0.04). During the study, 27 patients in the TNFi first strategy switched to baricitinib, while 4 switched to an interleukin 6 inhibitor. In the baricitinib strategy, 15 patients switched to a TNFi, while 2 switched to an IL6i, and 1 patient stopped baricitinib because of a stable clinical remission. At 12 weeks, only 7 patients in TNFi strategy and 4 patients in baricitinib strategy switched at that point.

Primary endpoint

Figure 4 shows the difference in proportions of ACR50 achievement at 12 weeks between the baricitinib strategy and TNFi first strategy (PP: Δ22%, 95% Wilson CI 5.7% to 38%, ITT: Δ22%, 95% Wilson CI 7.8% to 35%). In the PP population, 23/52 (44%) of baricitinib strategy patients reached ACR50 response at 12 weeks (ITT population: 42%), compared with 16/73 (22%) in the TNFi strategy group (ITT population: 20%). At 12 weeks, the lower bound of the 95% Wilson score interval for the difference in proportions of patients meeting the ACR50 response was to above the −12% NI margin and the right of zero in both the PP and ITT analysis. Hence, baricitinib was found to be not only non-inferior but also statistically superior to TNFi in the analysis of the primary endpoint in both the per-protocol and ITT analyses. Mean scores in individual ACR50 components can be found in online supplemental material.

Table 1 Baseline characteristics

	TNFi strategy	Baricitinib strategy
	n=102	n=97
Age (years), mean (SD)	55.2 (13.4)	54.8 (12.0)
Female, n (%)	68 (66.7%)	62 (63.9%)
Smoking, n (%)		
Never	38 (37.3%)	37 (38.9%)
Stopped	39 (38.2%)	36 (37.9%)
Yes	25 (24.5%)	22 (23.2%)
BMI, mean (SD) kg/m^2	27.4 (4.93)	26.5 (5.03)
Disease duration (years), median (IQR)	2.00(1.00; 3.00)	2.00(1.00; 3.00)
Erosions state, n (%)		
No	66 (64.7%)	69 (71.1%)
Unknown	19 (18.6%)	16 (16.3%)
Yes	17 (16.7%)	12 (12.4
CV		
No	74 (72.5%)	76 (78.4%)
Yes	28 (27.5%)	21 (21.6%)
Rheumatoid factor positive, n (%)	69 (67.6%)	70 (72.2%)
ACCP+, n (%)	65 (63.7%)	70 (72.2%)
Concomitant MTX, n (%)	69 (67.6%)	62 (63.9)
MTX dose, mg per week, mean (SD)	19.9 (5.06)	20.48 (5.42)
Glucocorticosteroid, n (average dose (mg)/day)	16 (6.3)	28 (7.7)
DAS28-ESR, mean (SD)	4.43 (1.06)	4.41 (1.14)
DAS28-CRP, mean (SD)	4.17 (1.03)	4.08 (1.05)
TJC, median (IQR)	4.00 (2.00; 7.00)	4.00 (2.00; 7.00)
SJC, median (IQR)	3.00 (1.00; 5.00)	3.00 (2.00; 4.00)
ESR, mm/hour, mean (SD)	24.0 (19.5)	25.1 (22.1)
CRP, mg/L mean (SD)	13.7 (19.1)	12.3 (17.5)
Physician global, mean (SD)	50.0 (21.3)	51.9 (16.9)
VAS wellbeing, mean (SD)	61.1 (21.5)	54.1 (22.5)
VAS pain, mean (SD)	61.5 (24.0)	55.6 (25.0)
RAPID 3 HAQ score, mean (SD)	12.2 (5.66)	10.9 (6.38)
CDAI, mean (SD)	19.9 (8.68)	19.6 (8.63)

.ACCP, anticyclic citrullinated peptide antibody; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; CV, increased CardioVascular risk as reported by attending physician; ESR, erythrocyte sedimentation rate; MTX, methotrexate; PG, physician global; RAPID 3 HAQ, Rapid Health Assessment Questionnaire-II Health Assessment Questionnaire; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitors; VAS, visual analogue scale.

Secondary endpoints

Of the patients in the baricitinib strategy, 65/87 (75%) (ITT population: 75%) reached DAS28-CRP <2.6 at 12 weeks. This was significantly more than the 45/97 (46%) (ITT population: 46%) in the TNFi strategy group (PP: Δ28%, 95% Wilson CI 14% to 41%, ITT: Δ28%, 95% Wilson CI 13% to 41%). Mean DAS28-CRP scores in both study groups showed a strong decline from baseline to 12 weeks and a gradual further decrease up to week 48, as shown in figure 5A. There was a more rapid decline in DAS28-CRP scores in the baricitinib strategy, compared with the TNFi strategy. Throughout the study period, the estimated marginal means remained lower in the baricitinib strategy. CDAI scores, which do not include an acute phase reactant, showed a comparable pattern (figure 5B). The individual DAS28 components all showed a comparable pattern in favour of baricitinib strategy (see online supplemental material).

All PROMs showed a clear improvement for both strategies, generally in favour of the baricitinib strategy. Differences in PROMs scores persisted over the full length of the study period. Plots for well-being, disease activity, pain, disability and fatigue can be found in the online supplemental material along with a table containing fixed effects estimates from the LME analyses.

Radiological damage was limited in both treatment strategies with the majority of patients showing no progression over 48 weeks. No significant difference was found in progression scores between the groups (p=0.246), although a small numerical benefit was noticeable for baricitinib. The SHS cumulative probability plot and median radiographic progression scores can be found in the online supplemental material.

Safety

The majority of SAEs were, according to the prescribing physician, not related to baricitinib/TNFi with the exception of three reported cases of infection. According to the prescriber, all three infection cases were possibly attributed to baricitinib. One reported case of gastrointestinal complication, that is 'diaphragmatic hernia after gastric bypass surgery', could be attributed to TNFi (etanercept) according to the physician. All other SAEs were according to the physician not attributed to used DMARDs. The overall incidence of AEs and their nature were comparable across the two strategies (see table 2; full AE table can be found in the online supplemental material).

DISCUSSION

The PERFECTRA study addressed the question of where we stand with a tsDMARD first versus a TNFi first treatment strategy for patients with RA failing to achieve DAS28-CRP <2.6 on csDMARDs.[35] This real-world study in a T2T setting applying EULAR guidelines[13] showed that after failing csDMARDs baricitinib is non-inferior and superior as compared with TNFi strategy with respect to clinical effectiveness, PROMs and drug survival. This study was not powered to address neither comparative safety nor radiological damage between baricitinib and TNFi. We did not observe AEs that have not previously reported with either therapy. When looking at the DAS28-CRP and CDAI graphs in figure 5 (and the individual component

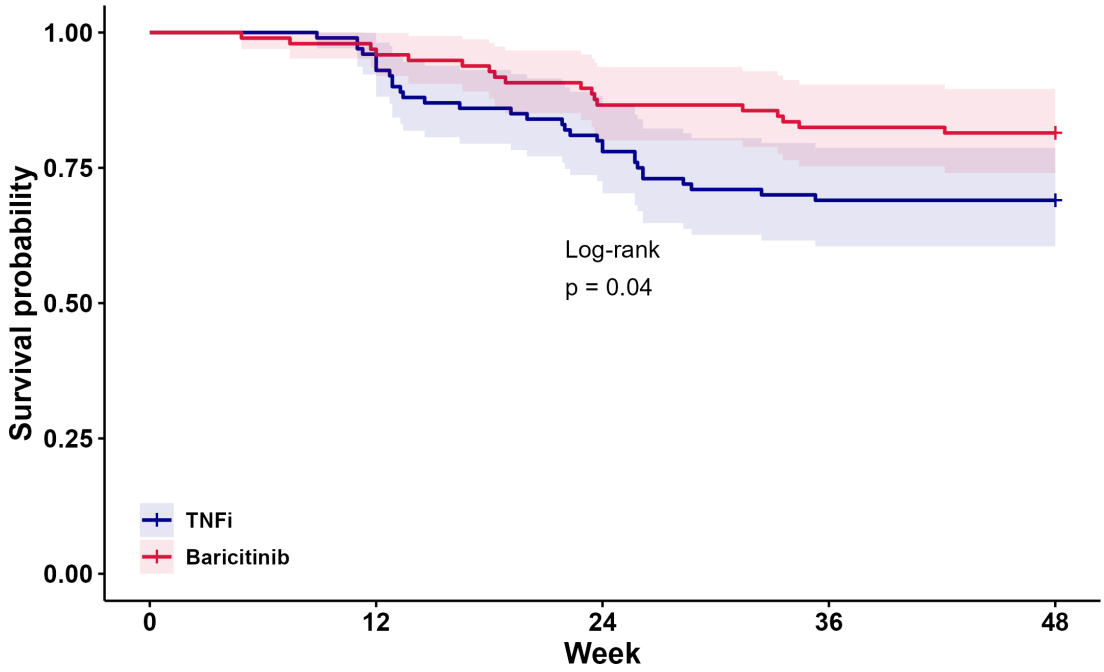

Figure 3 Drug survival in TNFi strategy and baricitinib strategy. TNFi, tumour necrosis factor inhibitors.

score in the online supplemental material), one should be aware that the real distinguishing moment is at 12 weeks. In line with the T2T principles, non-responders were encouraged to switch after 12 weeks, which could cause convergence between strategies. Progression of radiological damage was comparable for both treatment strategies, with only very few patients showing any progression over 48 weeks of treatment. Such zero-inflated data present extensive modelling challenges. It also should be noted that 144 complete radiographs sets were found indicating some patients had missing sets.

A preceding pivotal RCT compared baricitinib with adalimumab, RA BEAM.[3] PERFECTRA suggests that in a T2 setting, there is more likelihood of a response to baricitinib than adalimumab and possibly other TNFi, which

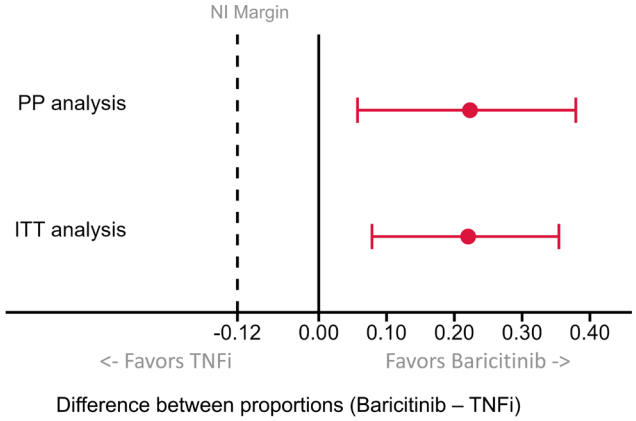

Figure 4 Difference between proportions in achieving American College of Rheumatology 50 at 12 weeks (baricitinib – TNFi). PP, per protocol; ITT, intention-to-treat; NI margin, non-inferiority margin; TNFi, tumour necrosis factor inhibitors.

is in line with findings from RA BEAM. In PERFECTRA, the TNFi strategy leads to 46% of patients being in remission after 12 weeks; this number adds up to 75% for the baricitinib strategy. These results seem high as compared with results RA BEAM; however, background of patients was vastly different between PERFECTRA and RA BEAM's patient populations. RA BEAM has an average prior disease duration of 10 years, whereas PERFECTRA average duration was 2 years. Prestudy treatment also differed significantly. PERFECTRA study patients were previously treated according T2T principles; this was not necessarily done in RA BEAM. Another major difference is that in RA BEAM all included patients had to have erosions. Composite disease activity scores are not only driven by inflammation alone but also by damage; this is illustrated by the average DAS score of >6 in RA BEAM at baseline. For all these reasons, achieving DAS28-CRP <2.6 in long-standing erosive RA, like in the RA BEAM study population, is more difficult than in the early RA population, like in the PERFECTRA study. Remission rates in the PERFECTRA study are in line with results from other T2T studies.[36–40]

Inhibitors of Janus Kinase other than baricitinib are also approved for the treatment of RA. For tofacitinib,[4 41] filgotinib[5 42]and upadacitinib,[6 43 44] formal RCTs were performed comparable to the RA BEAM study in non-T2T setting, showing comparable or even more favourable results for JAKi versus TNFi. Whether the additional evidence by the present study for baricitinib in the T2T setting can be extended to the other JAKi is yet to be determined. Not only are multiple JAKi available, but also many TNFi are approved for the treatment of RA. Most formal RCTs, as cited earlier, used adalimumab as their comparator. PERFECTRA allowed all

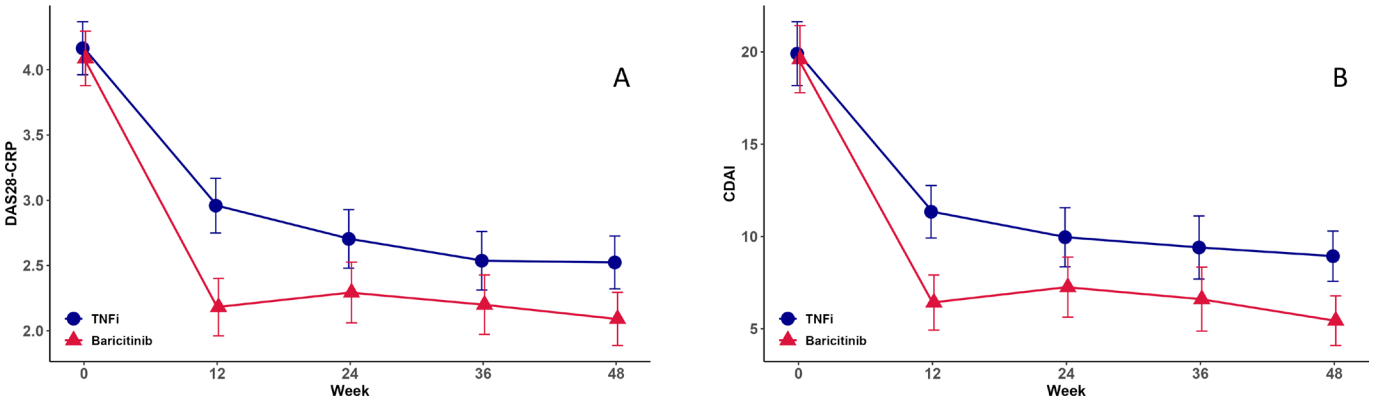

Figure 5 Estimated marginal means in 28-joint count Disease Activity Score with C-reactive protein (DAS28-CRP) and Clinical Disease Activity Index (CDAI) at weeks 0, 12, 24, 36 and 48. Error bars represent 95% Wald CI. TNFi, tumour necrosis factor inhibitors.

approved TNFi. The distribution of prescribed TNFi in our study reflects the market in the Netherlands meaning etanercept and adalimumab were predominantly used, combining to approximately 95%. We did not find any indication for different responses between TNFi used in the study, indicating that the conclusion of superior effectiveness of baricitinib strategy holds true for TNFi used.

The PERFECTRA study was designed for the currently relevant setting, where T2T is fully implemented. The rheumatological care preceding the inclusion of patients was according to this recommendation. The study was adequately powered for the primary outcome (ACR response at 12 weeks). For other clinical outcomes and PROMs over the study period of 48 weeks, consistent relevant differences between both strategies were found in favour of baricitinib. For a full picture on safety and joint damage, a larger population and a longer study period would be necessary.

PERFECTRA was performed during the COVID-19 pandemic. To the best of our knowledge, the consecutive inclusion and follow-up of patients was, although challenged, not jeopardised. The only exception was capturing ESR, since due to COVID-19 measuring ESR was because of an attempt to reduce the contamination risk, skipped in many centres.

One might question if the direct effect of baricitinib on CRP is responsible for the observed superior efficacy. Therefore, we also reported the CDAI scores, which showed similar results with respect to disease activity, independent from the acute phase reaction. The individual disease activity components also showed highly comparable results.

Oral glucocorticoid (<10 mg/day) and non-steroidal anti-inflammatory drugs (NSAID) use were limited. Switching and stopping throughout the study were not advised but always at the discretion of the attending physician. Consequently, this might not always be collected

Table 2 Safety

	Group analyses					Present treatment analyses		
	Baricitinib strategy	% of total	TNFi strategy	% of total	Total	Patients on baricitinib	Patients on TNFi	Total
SAE:	6	6.2	5	4.9	11	6	4	10
'cancer'	0	0.0	2	2.0	2	0	2	2
'GI complication'	0	0.0	2	2.0	2	0	1	1
'infections'	3	3.1	0	0.0	3	3	0	3
'total knee arthroplasty'	1	1.0	0	0.0	1	1	0	1
'MI'	1	1.0	0	0.0	1	1	0	1
'fracture'	0	0.0	1	1.0	1	0	1	1
'cerebral concussion'	1	1.0	0	0.0	1	1	0	1
AE	111		144		255	115	129	244

Present treatment analyses: (s)AE event developed while on either baricitinib of TNFi. N baricitinib strategy group: 97, N TNFi strategy group: 102, number of patients receiving baricitinib at any point during study: 124, number of patients receiving TNFi at any point during study: 117.
AE, adverse event; GI, gastrointestinal; MI, myocardial infraction; SAE, serious adverse events; TNFi, tumour necrosis factor inhibitors.

in the e-CRF resulting in limiting analysability of these factors.

Not all TNFi strategy patients used MTX at start and throughout the study. In the real world, MTX is increasingly perceived as poorly tolerated. Even though TNFi should preferably be used in combination with MTX, this is not always the case in practice. This study shows the comparative effectiveness of TNFi versus JAKi in daily clinical practice, including all nuances, contingencies and issues. Real-world adherence to MTX due to intolerance or other factors should be seriously considered when comparing treatment (sequences). MTX use at baseline and during the study was comparable in both groups.

DAS28-CRP, as used in PERFECTRA, can pose some challenges; it should be noted that DAS28-CRP scores tend to be slightly lower than DAS28-ESR scores.[45 46] Having said this, DAS28-CRP is frequently chosen as the proxy for measuring disease activity in daily clinical practice.

We designed PERFECTRA as a randomised, open-label controlled real-world strategy study. Although we acknowledge that in theory the compromises that have to be made in pragmatic studies may result in conclusions that are methodologically less rigorous than those resulting from formal RCTs. Randomisation by physician election could raise the question of physician bias. In order to mitigate, baseline characteristics were very carefully analysed and deemed appropriate; PERFECTRA showed nicely comparable groups at baseline. In terms of robustness and generalisability, pragmatic studies can add knowledge to pivotal trials. Generalisability of study results should always be carefully done. We think that the PERFECTRA study provides relevant information especially for the T2T setting of patients with early RA after failure of cs-DMARDs.

To this date, for good reasons, medical science and regular authorities heavily lean on formal RCTs. However, conclusions of these pivotal trials can not always be fully implemented in real world, where no preselection due to disease characteristics, age, comedication comorbidities and the challenges by the healthcare system are relevant factors. PERFECTRA addresses in a real-world T2T setting the clinical questions whether to start a JAKi (baricitinib) or any TNFi after csDMARDs failure. On one hand, a real-world open design may theoretically be methodologically less robust than a formal randomised and double-blinded RCT, the generalisability and applicability of this solid pragmatic real-life study complement the formal RCTs by demonstrating the effectiveness in a real-world setting in daily clinical practice, something which formal RCTs can lack. PERFECTRA not only confirms previous suggestions by preceding RCTs and registry data that baricitinib, and probably JAKi in general, has increased efficacy as compared with TNFi (adalimumab), but illustrates that, in combination with a fully implemented T2T approach to the target of DAS28-CRP<2.6, the decision to start with baricitinib after failure of csDMARDS is a valid option for patients. Results from a real-world setting not only complement formal RCTs, but can also assist in identifying proper application in specific situations for physicians.

Although not powered for safety, no unexpected safety signals were seen in this relatively small group of patients. Prescribers have to be aware that cardiovascular and malignant SAEs are more frequently reported in JAKis than TNFis. Obviously, this has to be considered carefully in risk–benefit discussions with any individual patient. Nonetheless, there are well-known safety warnings for both JAKi[47 48] and TNFi.[49] For treatment with JAKi, full history and physical examination and testing, among other things as recommended, outlined fully in Nash *et al*.[11] Rheumatologists should be well aware and are educated to take into account the individual patient's safety profile as well as the patient's preferences in order to minimalise the risk of complications and to balance these risks with the expected efficacy. Rheumatologists learnt to effectively manage the complication risks of TNFi (among others, cardiovascular events, congestive heart failure and infections, especially tuberculosis)[50 51] As of more recently, they manage the warnings for JAKi (among others, herpes zoster, major arterial cardiovascular events and thromboembolism).

CONCLUSIONS

In the setting of real-world T2T treatment for RA, as advised by professional societies like EULAR, after failure on csDMARDs, PERFECTRA suggests that the strategy to start baricitinib is a feasible alternative to starting with TNFi with respect to disease activity and PROMs. Baricitinib also showed beneficial drug survival compared with that of TNFi. The limited number of patients and study duration do not allow for conclusions on differences in safety and radiological damage which need to be established in larger and longer studies.

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Data availability statement Data are available upon reasonable request. Data are available upon reasonable request. Underlying data from this manuscript may be requested by qualified researchers. Investigators may request access to anonymised individual patient-level data and/or (redacted) trial documents. Prior to use of the data, proposals need to be approved by the PERFECTRA study group and a signed data sharing agreement will need to be executed. Requests can be made via the corresponding author.

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