Comparative effectiveness of improvement in pain and physical function for baricitinib versus adalimumab, tocilizumab and tofacitinib monotherapies in rheumatoid arthritis patients who are naïve to treatment with biologic or conventional synthetic disease-modifying antirheumatic drugs: a matching-adjusted indirect comparison

B Fautrel, B Zhu, P C Taylor, M van de Laar, P Emery, F De Leonardis, C L Kannowski, C Nicolay, Z Kadziola, I De La Torre, R Fleischmann

ABSTRACT

Objective To compare improvement in pain and physical function for patients treated with baricitinib, adalimumab, tocilizumab and tofacitinib monotherapy from randomised, methotrexate (MTX)-controlled trials in conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)/biologic (bDMARD)-naïve RA patients using matching-adjusted indirect comparisons (MAICs).

Methods Data were from Phase III trials on patients receiving monotherapy baricitinib, tocilizumab, adalimumab, tofacitinib or MTX. Pain was assessed using a visual analogue scale (0–100 mm) and physical function using the Health Assessment Questionnaire-Disability Index (HAQ-DI). An MAIC based on treatment-arm matching, an MAIC with study-level matching and Bucher’s method without matching compared change in outcomes between therapies. Matching variables included age, gender, baseline disease activity and baseline value of outcome measure.

Results With all methods, greater improvements were observed in pain and HAQ-DI at 6 months for baricitinib compared with adalimumab and tocilizumab (p<0.05). Differences in treatment effects (TEs) favouring baricitinib for pain VAS for treatment-arm matching, study-level matching and Bucher’s method, respectively, were −12.−12 and −12 for baricitinib versus adalimumab and −7, −7 and −7 for baricitinib versus tocilizumab; the difference in TEs for HAQ-DI was −0.28, −0.28 and −0.30 for adalimumab and −0.23, −0.23 and −0.26 for tocilizumab. For baricitinib versus tofacitinib, no statistically significant differences for pain improvement were observed except with one of the three methods (Bucher method) and none for HAQ-DI.

Conclusions Results suggest greater pain reduction and improved physical function for baricitinib monotherapy compared with tocilizumab and adalimumab monotherapy. No statistically significant differences in pain reduction and improved physical function were observed between baricitinib and tofacitinib with the MAIC analyses.

Key messages

What is already known about this subject?

► Large, randomised clinical trials have demonstrated the efficacy of baricitinib, adalimumab, tocilizumab and tofacitinib monotherapy in pain reduction and HAQ-DI improvement compared with methotrexate monotherapy, but there are no head-to-head trials between these treatments in patients with RA who are naïve to treatment with conventional synthetic or biologic disease-modifying antirheumatic drugs.

What does this study add?

► The results from this study add evidence, through indirect comparison, that suggest greater pain reduction and improved physical function for baricitinib monotherapy compared with tocilizumab and adalimumab monotherapy.

How might this impact on clinical practice or future developments?

► The findings from this study will help clinicians evaluate different therapies to reduce pain and improve physical function in the treatment of RA patients.

INTRODUCTION

Despite substantial improvements over the last two decades in the management of patients with rheumatoid arthritis (RA), the treat-to-target approach has led rheumatologists to focus on inflammatory disease activity, whereas patients generally consider the reduction of pain and fatigue and improvement of physical function a matching-adjusted indirect comparison.

RMD Open: first published as 10.1136/rmdopen-2019-001131 on 5 May 2020. Downloaded from http://rmdopen.bmj.com/ on July 2, 2020 at Universiteit Twente. Protected by copyright.
function to be more important. Their assessment, in addition to healthcare provider (HCP)-reported disease activity measures, should help physicians determine the best treatment management for the patient. In the RA-BEAM randomised controlled trial (RCT), with concomitant methotrexate (MTX), baricitinib 4 mg one per day demonstrated greater improvements in pain and physical function compared with adalimumab 40 mg every other week in a population of patients who had had an insufficient response to MTX. There is an absence, however, of prospective, head-to-head trials between different biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in MTX-naïve RA patients, a population that could be considered more sensitive to change in PROs because they had not yet experienced the irreversible consequences of the longstanding disease.

In the absence of data from RCT, indirect comparison methodologies, such as Network Meta-Analysis (NMA) and, in more recent years, Matching-Adjusted Indirect Comparison (MAIC), have been proposed to compare the efficacy of different therapies based on aggregate data from different RCTs, and they are commonly used for the purposes of health technology appraisal. Compared with an NMA, which is based on the assumption that treatment effects (TEs) are only relative to a common comparator (eg, placebo) with no additional difference between the trials in the distribution of effect-modifying variables, MAIC builds upon the indirect comparison through additional adjustment of effect-modifying variables.

An MAIC analysis uses patient-level data of a drug to match with published data from comparators. Specifically, individual patient data from one or more studies for one treatment are reweighted to match with the baseline characteristics, which are known to be TE modifiers, from a published study of another treatment. To have an appropriate analysis, the study with patient-level data and the study with published data must have a common reference arm for matching. After the matching with the individual patient data, the weighted difference in mean values of an outcome measure between the active arm and the reference arm of one study is calculated and compared with the difference from the other published study.

The objective of this analysis was to compare improvement in pain and physical function between baricitinib, adalimumab, tocilizumab and tofacitinib monotherapy with an MAIC using data from randomised, MTX-controlled trials in conventional synthetic DMARD (csDMARD)/bDMARD-naïve RA patients.

**METHODS**

**Study eligibility**

The studies included in this analysis were derived from a prior systematic literature review (SLR) that was designed for a NMA conducted by Eli Lilly. The SLR synthesised the evidence of treatments on measures of treatment response and effectiveness, disease activity, physical function, radiographic outcomes, safety and other key measures for adult patients with moderate-to-severe RA among studies conducted from 1999 to 2016. The criteria for selection in the SLR and a flow chart describing the screening for inclusion are in online supplementary figure 1. For the purposes of the current analysis, we focused on the population of patients with limited or no treatment with csDMARDs in the SLR; 27 studies met this criterion. Of these studies, 12 included monotherapy and an MTX treatment arm, which constitutes the common comparator; and of these 12 studies, 5 reported on pain and physical function, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI), at 6 months or 24±2 weeks, depending upon the time points reported in the studies. These five studies were included in the current analysis (table 1). The study designs and inclusion and exclusion criteria for the studies have been previously reported.

The doses of the medications included in the analysis were oral 4 mg of baricitinib daily, subcutaneous 40 mg of adalimumab every other week, intravenous 8 mg/kg of tocilizumab every 4 weeks and oral 5 mg tofacitinib two times per day.

**Outcome measures**

Pain was measured with the patient’s assessment of pain, a visual analogue scale (VAS), ranging from 0 to 100 mm. Physical function was measured with the HAQ-DI.

The HAQ-DI consists of 24 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities. The score for the HAQ-DI ranges from 0 to 3, with lower scores reflecting better physical function and thus, less disability.

**Matching-adjusted indirect comparisons (MAICs) and sensitivity analyses**

The primary MAIC in this analysis was based on the Signorovitch method with weights applied to treatment arms. Specifically, data from the baricitinib 4 mg treatment arm from the RA-BEGIN trial were weighted to match the baseline characteristics that are TE modifiers (age, gender, Disease Activity Score-28 erythrocyte sedimentation rate [DAS28-ESR], pain VAS and HAQ-DI) from the adalimumab arm from PREMIER, tofacitinib 5 mg twice a day arm from ORAL-START twice a day and tocilizumab 8 mg/kg arm from FUNCTION. For reference, the MTX monotherapy arms were also matched between the trials. Analyses were conducted on patients from RA-BEGIN who met the inclusion and exclusion criteria of the respective comparator trials. Sensitivity analyses were conducted with the inclusion of disease duration as an additional matching variable. Two other approaches, an MAIC based on the Signorovitch method with study-level matching (matching on the entire study, rather than by treatment arm) and Bucher’s method without matching adjustment, were also conducted as sensitivity analyses to determine the consistency of the findings. Because of the prior experience patients in the AMBITION study had with MTX, we also conducted...
Table 1  Study design and characteristics

| Study | Study design and dosage information | Inclusion criteria | Key exclusion criteria |
|-------|------------------------------------|--------------------|------------------------|
| Baricitinib (RA-BEGIN, NCT01711359)\(^9\) | Patients were randomised 4:3:4 to oral MTX one time per week (N=210), baricitinib 4 mg (monotherapy) one time per day (N=159), or the combination of baricitinib+MTX (N=215) | ▶ Patients were ≥18 years  
▶ Moderately-to-severely active RA  
▶ Patients had active disease (TJC ≥6 and SJC ≥6)  
▶ Serum CRP level ≥3.6 mg/L  
▶ Seropositive for RF or ACPA  
▶ No prior csDMARD therapy and no prior bDMARD | ▶ Recent clinically significant infection and select laboratory abnormalities |
| Tocilizumab (AMBITION, NCT00109408)\(^10\) | Patients were randomised to tocilizumab (TCZ) 8 mg/kg intravenously every 4 weeks (N=286), or to MTX oral capsules, weekly together with folate (>5 mg/week) (N=284) | ▶ Patients were ≥18 years  
▶ ≥3 months of moderately-to-severely active RA  
▶ SJC of ≥6, TJC ≥8, CRP level ≥1.0 mg/dL or ESR ≥28 mm/h at baseline  
▶ Oral glucocorticoids and NSAIDs were permitted if stable >6 weeks | ▶ Clinically unstable concurrent illnesses  
▶ Active or untreated latent TB  
▶ Unsuccessful treatment with TNFi  
▶ Received MTX within 6 months of randomisation or discontinued MTX previously |
| Tocilizumab (FUNCTION, NCT01007435)\(^8\) | Patients were randomised to 4 mg/kg TCZ+MTX (N=288), 8 mg/kg TCZ+MTX (N=290), 8 mg/kg TCZ +placebo (N=292) or placebo+MTX (N=287); TCZ or placebo were administered intravenously every 4 weeks | ▶ Patients were ≥18 years  
▶ ≥2 years of moderate-to-severe RA  
▶ SJC of ≥4, TJC of ≥6, CRP level ≥1.0 mg/dL or ESR ≥28 mm/h at baseline  
▶ Positive RF or ACPA or ≥1 erosion of hands, wrists or feet attributable to RA based on a central radiographic reading | ▶ Clinically unstable concurrent illnesses and screened according to local standards  
▶ Active or untreated latent TB  
▶ Had been unsuccessfully treated with TNFi  
▶ Had received MTX 6 months prior to randomisation or had discontinued MTX |
| Tofacitinib (ORAL-START, NCT01039688)\(^11\) | Patients were randomised to tofacitinib 5 mg two times per day (BID, N=373) or tofacitinib 10 mg BID (N=397) or MTX (N=186) | ▶ Patients were ≥18 years  
▶ ≥3 months of moderately-to-severely active RA  
▶ SJC of ≥6, TJC of ≥6, CRP level >7.0 mg/L or ESR >28 mm/h at baseline  
▶ ≥3 distinct joint erosions on radiographs, positive test for IgM RF or ACPA | ▶ Prior treatment with lymphocyte-depleting or alkylating agents  
▶ Select lab abnormalities  
▶ History of: another autoimmune rheumatic disease except Sjögren's syndrome  
▶ Serious infection  
▶ Lymphoproliferative disorder  
▶ Malignancy except adequately treated non-metastatic basal/squamous cell cancer of the skin or cervical carcinoma in situ  
▶ Evidence of active, latent or inadequately treated Mycobacterium TB infection |
| Adalimumab PREMIER, NCT00195663\(^6,7\) | Patients were randomised to adalimumab 40 mg subcutaneously every other week + weekly oral MTX (N=268); adalimumab 40 mg subcutaneously every other week (adalimumab + placebo; N=274); or weekly oral MTX (N=257) | ▶ Patients were ≥18 years  
▶ <3 years of RA  
▶ SJC of ≥8, TJC of ≥10, CRP level ≥1.5 mg/dL or ESR ≥28 mm/h at baseline | Patients who had received treatment with MTX, cyclophosphamide, cyclosporine, azathioprine or >2 other DMARDs |

ACPA, anti-citrullinated protein antibodies; bDMARD, biologic disease-modifying antirheumatic drugs; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IgM, immunoglobulin M; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; TB, tuberculosis; TCZ, tocilizumab; TJC, tender joint count; TNFi, tumour necrosis factor inhibitor.
separate MAICs between baricitinib and tocilizumab, one with data from AMBITION alone and the second from AMBITION and FUNCTION combined.8–10

Statistical analyses

Differences between weighted TE in mean change in pain VAS and HAQ-DI from baseline to 6 months for baricitinib and the reported TE for adalimumab, tocilizumab or tofacitinib were compared. For adalimumab, mean changes in pain and HAQ-DI were based on the mean pain and HAQ-DI values reported at Week 26.7 The variance of the weighted TE was estimated with the bootstrap method with 1000 iterations.16 17 The differences and their associated 95% CIs are presented and a p<0.05 was considered statistically significant. Analyses were not adjusted for multiplicity, and they were conducted with SAS version 9.4 (Cary, NC) and R (version 3.3.3).

RESULTS

Baseline characteristics

Baseline characteristics are presented in table 2. For the MTX arms across trials, the mean baseline pain VAS ranged from 59 to 65 mm and the 6-month mean change in pain ranged from −28.3 to −33.5 mm. Likewise, for the MTX arm, the mean baseline HAQ-DI values ranged from 1.5 to 1.7, and the 6-month mean change in HAQ-DI ranged from −0.5 to −0.74 (table 3). The similarity of the baseline pain and HAQ-DI scores and the similar change in pain and HAQ-DI from the MTX control arm across studies suggest comparability between the trials.

The baseline values of the variables used in matching for all the trials are shown in table 4, which includes the baseline variables for RA-BEGIN after the matching on those variables. Because of the matching, the baseline values for baricitinib are the same as those from the published data for the respective comparator drugs. The effective sample sizes from RA-BEGIN, with individual patient-level data, are reduced as the consequence of weighting and matching.

Pain

For the primary MAIC analysis, baricitinib-treated patients showed greater improvement in pain at 6 months compared with adalimumab (treatment difference: −12.3, 95% CI −17.9 to −6.6) and tocilizumab (treatment difference: −7.3, 95% CI −14.2 to −0.38) (figure 1). Consistent results were observed with the other indirect comparison methods. There were numerical, but no statistically significant, differences in pain improvement between baricitinib and tofacitinib with the primary analysis. With the sensitivity analyses, no statistically significant differences were observed using the MAIC with study-level matching; there were, however, significant differences with Bucher method (treatment difference: −7.1; −13.5 to −0.65). (figure 1)

Physical function

For the primary MAIC analysis (figure 1), baricitinib-treated patients were shown to have greater improvement in physical function at 6 months compared with adalimumab (treatment difference: −0.28, 95% CI −0.44 to −0.13) and tocilizumab (treatment difference: −0.23, 95% CI −0.39 to −0.07). Similar results were observed with the other indirect comparisons. There were no differences between baricitinib and tofacitinib with all methods (figure 1).

Sensitivity analyses

To confirm the robustness of these results, we conducted sensitivity analyses in which disease duration was an additional matching variable, and when data from AMBITION and FUNCTION were analysed together. These sensitivity analyses were generally consistent with the direction and magnitude of the primary results, except for the comparison with the AMBITION data (figures 2a,b). The different patient characteristics from AMBITION from those in the FUNCTION and RA-BEGIN studies may have contributed to the differences, as described in the discussion below.

DISCUSSION

The gold standard for assessing the relative effectiveness of one medication compared with another is a properly powered head-to-head study using an appropriate metric as the primary endpoint. There has not been a study conducted comparing one JAK inhibitor with another, or with a bDMARD, in MTX-naive patients, as monotherapy. In the absence of a head-to-head RCT, we applied an MAIC to compare improvement in pain and physical function for patients treated with baricitinib, adalimumab, tocilizumab and tofacitinib monotherapy from randomised, MTX-controlled trials in RA patients who were naïve to csDMARDs and bDMARDs. The MAIC enables greater flexibility to adjust for patient characteristics and TE modifiers and should provide a more robust indirect comparison than other traditional indirect comparison methods, such as a network meta-analysis.18 This MAIC analysis has been used in the indirect comparison of efficacy in other rheumatic diseases, such as psoriatic arthritis.19 20 The results of the current analysis suggest greater pain reduction with improved physical function for baricitinib monotherapy compared with tocilizumab and adalimumab monotherapy with the primary MAIC and sensitivity analyses. For comparisons between baricitinib and tofacitinib monotherapy, greater pain reduction with baricitinib was not consistently observed across the MAIC analyses, which did not allow for a robust conclusion on a difference between the two molecules. There were no differences observed between the two JAK inhibitors for HAQ-DI. Similar observations were also observed with models in which disease duration was an additional matching variable and with models in which the AMBITION and FUNCTION data were analysed together.
Table 2  Baseline characteristics from trials in the indirect comparisons

| Characteristics | RA-BEGIN\(^9\) | AMBITION\(^10\) | FUNCTION\(^8\) | PREMIER\(^6\,\,7\) | ORAL-START\(^11\) |
|-----------------|----------------|----------------|----------------|----------------|----------------|
| MTX (N=210)     | MTX (N=284)    | MTX (N=287)    | MTX (N=257)    | MTX (N=186)    | MTX (N=373)    |
| Baricitinib 4mg (N=159) | Tocilizumab 8mg/kg (N=286) | Tocilizumab 8mg/kg (N=292) | Adalimumab 40mg (N=274) | Tofacitinib 5mg (N=373) |
| **Mean duration of RA, years** | 1.3 | 1.9 | 6.2 | 6.4 | 0.4 | 0.5 | 0.8 | 0.7 | 2.7 | 2.9 |
| **SJC, 66 joints** | 16.4 | 16.1 | 19.2 | 19.1 | 16.2 | 16.5 | 22.1 | 21.8 | 16.8 | 16.3 |
| **TJC, 68 joints** | 27 | 26 | 31.1 | 31.8 | 27.4 | 28.7 | 32.3 | 31.8 | 25.4 | 25.7 |
| **CRP, mg/L** | 22 | 24 | 31 | 30 | 23 | 25 | 40 | 41 | 26 | 23 |
| **DAS28-ESR** | 6.6 | 6.6 | 6.8 | 6.8 | 6.6 | 6.7 | 6.3 | 6.4 | 6.6 | 6.6 |
| **Mean MTX dosing achieved, mg/week** | 17.7 | 15.5 | N/A (81% achieved 20 mg/week) | 16.9 | 18.5 |

CRP, C reactive protein; DAS28, Disease Activity Score for 28 joints; ESR, erythrocyte sedimentation rate; MTX, methotrexate; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Fautrel B, et al. RMD Open 2020;6:e001131. doi:10.1136/rmdopen-2019-001131
### Table 3  Pain and HAQ-DI for studies included in the MAIC

| Endpoint values at baseline and either change from baseline or mean values at 6 months | RA-BEGIN⁹ | AMBITION¹⁰ | FUNCTION⁸ | PREMIER⁶ ⁷ | ORAL-START¹¹ |
|---|---|---|---|---|---|
| **Patient’s assessment of pain, 0–100 mm VAS** | | | | | |
| Baseline | MTX (N=210) | MTX (N=284) | MTX (N=287) | MTX (N=257) | MTX (N=186) |
| | Baricitinib 4 mg (N=159) | Tocilizumab 8 mg/kg (N=286) | Tocilizumab 8 mg/kg (N=292) | Tocilizumab 8 mg/kg (N=292) | Tocilizumab 8 mg/kg (N=292) |
| 6 months | 65 | 62 | 60 | 60 | 65 |
| | −30 | −31 | −34 | −30 (vs MTX) | −28 |
| | 64 | 59 | −36 | Adjusted absolute mean*: 31 | −32 |
| **HAQ-DI, 0-3** | | | | | |
| Baseline | 1.7 | 1.5 | 1.5 | 1.5 | 1.5 |
| | MTX (N=186) | Tocilizumab 8 mg/kg (N=292) | Tocilizumab 8 mg/kg (N=292) | Tocilizumab 8 mg/kg (N=292) | Tocilizumab 8 mg/kg (N=292) |
| 6 months | 1.6 | 1.6 | 1.6 | 1.6 | 1.5 |
| | −0.7 | −0.5 | −0.7 | −0.04 (vs MTX) | −0.6 |
| | 1.0 | 0.7 | Adjusted absolute mean*: 0.9 | Adjusted absolute mean*: 0.9 | −0.8 |

*Adjusted mean scores, rather than change from baseline, were reported in Strand et al.⁷

HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; VAS, visual analogue scale. Pain and HAQ-DI were collected at 6 months or 24±2 weeks.
| Study              | Sample size | Age, mean (years) | Gender (%) | DAS28-ESR | Pain VAS | HAQ-DI | MTX and baricitinib effective sample size, pain/HAQ-DI | Age, mean (years) | Gender (%) | DAS28-ESR | Pain VAS | HAQ-DI |
|-------------------|-------------|-------------------|------------|-----------|----------|--------|-------------------------------------------------------|------------------|------------|-----------|----------|--------|
| RA-BEGIN<sup>6</sup> |             |                   |            |           |          |        |                                                       |                  |            |           |          |        |
| MTX               | 210         | 51                | 70%        | 6.6       | 65       | 1.7    |                                                       |                  |            |           |          |        |
| Baricitinib 4 mg  | 159         | 51                | 76%        | 6.6       | 64       | 1.6    |                                                       |                  |            |           |          |        |
| AMBITION/ FUNCTION<sup>8,10</sup> |             |                   |            |           |          |        |                                                       |                  |            |           |          |        |
| MTX               | 571         | 50                | 80%        | 6.7       | 61       | 1.49   | 179.4/160.9                                           | 50               | 80%        | 6.7       | 61       | 1.49   |
| Tocilizumab 8 mg/ kg | 578       | 50               | 79%        | 6.8       | 61       | 1.59   | 142.7/147.6                                           | 50               | 79%        | 6.8       | 61       | 1.59   |
| PREMIER<sup>6,7</sup> |             |                   |            |           |          |        |                                                       |                  |            |           |          |        |
| MTX               | 257         | 52                | 74%        | 6.3       | 60       | 1.5    | 181.4/180.1                                           | 52               | 74%        | 6.3       | 60       | 1.5    |
| Adalimumab 40 mg  | 274         | 52                | 77%        | 6.4       | 65       | 1.6    | 151.5/153.4                                           | 52               | 77%        | 6.4       | 65       | 1.6    |
| ORAL-START<sup>11</sup> |            |                   |            |           |          |        |                                                       |                  |            |           |          |        |
| MTX               | 186         | 49                | 78%        | 6.6       | 59       | 1.5    | 177.8/172.8                                           | 49               | 78%        | 6.6       | 59       | 1.5    |
| Tofacitinib 5 mg  | 373         | 50                | 77%        | 6.6       | 59       | 1.5    | 146.5/148.9                                           | 50               | 77%        | 6.6       | 59       | 1.5    |

*Effective sample size and values for baricitinib or MTX from RA-BEGIN decreased after matching with different studies.

DAS28, Disease Activity Score for 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; VAS, visual analogue scale.
To our knowledge, this is the first systematic analysis that compares patients receiving different csDMARD and bDMARD monotherapies in MTX-naïve patients with RA. This analytic approach offers many advantages over other conventional pairwise meta-analyses. Of note, the inclusion of active comparators provides more clinically relevant information compared with meta-analyses with only placebo. We also included data from well-designed RCTs that included large enough sample sizes to allow for more reliable estimations of differences between treatments.

There are, however, limitations intrinsic to the MAIC approach and, for this reason, our results should be interpreted with caution. The MAIC analysis matches based on observed TE modifiers, but it is not possible to control for variables that are unobserved. Additionally, the application of the MAIC reduces the effective sample size for the study with patient-level data, RA-BEGIN in the current analysis, which subsequently results in reduced power and capability to detect differences between medications. Importantly, the RCTs in the current analysis were conducted at different time periods during which more aggressive therapy was being introduced, with different patients and investigators in different regions of the world. These factors have the potential to increase the variations in baseline characteristics among the included studies, with consequent challenges in matching patients accurately. Of note, the AMBITION trial included 33% of patients who had been previously treated with MTX, but who had stopped MTX >6 months. Patients from AMBITION had a longer duration of disease, higher tender and swollen joint counts and higher CRP levels than the other studies included in this MAIC analysis; whereas, patients from FUNCTION tended to show more similar characteristics to those in RA-BEGIN; the other studies included patients who were naïve to treatment. Because of this, we included the AMBITION trial only as a sensitivity analysis. Also, parameters, such as race and geographic location, were not included in the analysis, because these parameters were not widely reported in the original trial publications. Additionally, these variables and the inclusion of geographic location have rarely been explored in indirect comparisons. Lastly, the baricitinib RCT in the MAIC was conducted before the drug and dosage for baricitinib received regulatory approvals; a monotherapy study with a 2 mg dose of baricitinib was not conducted.

In conclusion, this MAIC suggests that among RA patients who are naïve to csDMARDs and bDMARDs, baricitinib 4 mg provides statistically significant greater pain reduction and improvement of physical function compared with adalimumab 40 mg and tocilizumab 8 mg/kg. No difference in pain reduction was observed between baricitinib and two times per day tofacitinib 5 mg with two of the three analyses employed, and no difference was observed in improving physical function. Well-designed, properly powered, head-to-head clinical trials are needed to confirm whether there is a class effect for JAK inhibitors over bDMARDs.
Figure 2  Sensitivity analyses with (a) disease duration included in the model and (b) with data from AMBITION and FUNCTION analysed separately. HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; VAS, visual analogue scale.
support and Julie A Sherman of Eli Lilly and Company for her assistance in creating the figures.

Contributors All authors participated in the interpretation of data, provided critical comments and input and reviewed and approved the final manuscript. B. Zhu, C. Nicolay and K. Kadziola additionally conducted the analyses.

Funding This study was funded by Eli Lilly and Company and Incyte Corporation.

Competing interests B. Fautrel: Grant/research support from: AbbVie, Lilly, MSD, Pfizer; Consultant and consultancy fees from: AbbVie, Biogen, BMS, Celgene, Janssen, Lilly, Medac, MSD, NORDIC Pharma, Novartis, Pfizer, Roche, Sanofi-Aventis, SOBI, UCB; P. C. Taylor: Research grants from Celgene, Galapagos, Janssen, Lilly, Consultation fees from AbbVie, Biogen, Galapagos, Gilead, GlaxoSmithKline, Janssen, Lilly, Novartis, Pfizer, Roche, Sanofi, Nordic Pharma, Fresenius and UCB. M. van de Laar: Grant/research support from: Abbvie; Eli Lilly and Company, Sanofi-Genzyme, Pfizer; Janssen-Cilag. Consulting and consulting fees for: Eli Lilly and Company, Sanofi Genzyme, Abbvie. P. Emery: Consultant and consulting fees for: Pfizer, MSD, Abbvie, BMS, UCB, Roche, Novartis, Samsung, Sanodiz, Eli Lilly and Company, R. Fleischmann: Grant/research support from: AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Centrexion, Genentech, GlaxoSmithKline, Janssen, Eli Lilly and Company, Merck, Pfizer, Regeneron, Roche, Sanofi, Aventis, UCB; Consultant and consulting fees for: AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Celltrion, GSK, Janssen, Eli Lilly and Company, Novartis, Pfizer, Samsung, Sanofi-Aventis, B. Zhu, F. De Leonardis, C.L. Kannowski, C. Nicoley, Z. Kadziola, and I. De La Torre: employees and shareholders of Eli Lilly and Company.

Patient consent Not required.

Ethics approval Not applicable.

Data sharing statement Lilly provides access to relevant anonymised patient-level data from studies on approved medicines and indications as defined by the sponsor-specific information on clinicalstudytdatarequest.com. For details on submitting a request, see the instructions provided at clinicalstudytdatarequest.com.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use and license their derivative works on different terms, provided the original work is

REFERENCES

1 Fautrel B, Afton R, Kirkham B, et al. Call for action: how to improve use of patient-reported outcomes to guide clinical decision making in rheumatoid arthritis. Rheumatol Int 2018;38:935–47.

2 Taylor PC, Moore A, Vasilescu R, et al. A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective. Rheumatol Int 2016;36:685–95.

3 Oude Voshaar M, Das Gupta Z, Van de Laar MA, et al. Op0329-hpr outcomes that matter to people living with inflammatory arthritis; a global standard set, developed by the international consortium for health outcome measurement (ichom) working group for inflammatory arthritis. Ann Rheum Dis 2018;77:211.

4 Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med 2017;376:652–62.

5 Signorovitch JE, Wu EQ, Yu AP, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. Pharmacoeconomics 2010;28:935–45.

6 Breedveld FC, Weisman MH, Kavanaugh AF, et al. The premier study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus metotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheumatol 2012;64:2393–404.

7 Strand V, Rentz AM, Cifaldi MA, et al. Health-related quality of life outcomes of adalimumab for patients with early rheumatoid arthritis: results from a randomized multicenter study. J Rheumatol 2012;39:63–72.

8 Burmester GR, Rigby WF, van Vollenhoven RF, et al. Tocilizumab in early progressive rheumatoid arthritis: function, a randomised controlled trial. Ann Rheum Dis 2016;75:1081–91.

9 Fleischmann R, Schiff M, van der Heijde D, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis Rheumatol 2017;69:986–97.

10 Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the ambition study. Ann Rheum Dis 2010;69:88–96.

11 Lee EB, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014;370:2377–86.

12 Bruce B, Fries JF. The health assessment questionnaire (HAQ). Clin Exp Rheumatol 2005;23:S14–8.

13 Ramey D, Fries J, Singh G. The health assessment questionnaire 1995–2000 and review. In: Spilker B, ed. Health Outcomes Measurement (ICHOM) Working Group for Rheumatoid Arthritis: a Current Perspective. Philadelphia, Lippincott-Raven, 1996: 227–37.

14 Petto H, Kadziola Z, Brnabic A, et al. Alternative weighting approaches for anchored matching-adjusted indirect comparisons using a common comparator. Value Health 2019;22:85–91.

15 Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1999;52:683–91.

16 Ender MH, Xie J, Signorovitch JE, et al. Cost effectiveness of guanfacine extended-release versus atomoxetine for the treatment of attention-deficit/hyperactivity disorder; application of a matching-adjusted indirect comparison. Appl Health Econ Health Policy 2012;10:381–95.

17 Sikiciva V, Findling RL, Signorovitch J, et al. Comparative efficacy of guanfacine extended-release versus atomoxetine for the treatment of attention-deficit/hyperactivity disorder in children and adolescents: applying matching-adjusted indirect comparison methodology. CNS Drugs 2013;27:943–53.

18 Strand V, McNees I, Mease P, et al. Matching-adjusted indirect comparison: secukinumab versus infliximab in biologic-naive patients with psoriatic arthritis. J Comp Eff Res 2019;8:497–510.

19 Nash P, McNees IB, Mease PJ, et al. Secukinumab versus adalimumab for psoriatic arthritis: comparative effectiveness up to 48 weeks using a matching-adjusted indirect comparison. Rheumatol Ther 2018;5:99–122.

20 Strand V, Betts KA, Mittal M, et al. Comparative effectiveness of adalimumab versus secukinumab for the treatment of psoriatic arthritis: a matching-adjusted indirect comparison. Rheumatol Ther 2017;4:349–62.

21 Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. BMJ 2013;346:f2914.