How effective are JAK-inhibitors? Perspectives from clinical trials and real-world studies

Lauper, Kim; Hyrich, Kimme L

How to cite

LAUPER, Kim, HYRICH, Kimme L. How effective are JAK-inhibitors? Perspectives from clinical trials and real-world studies. In: Expert review of clinical immunology, 2021, vol. 18, n° 3, p. 207–220. doi: 10.1080/1744666X.2021.1982383

This publication URL: https://archive-ouverte.unige.ch/unige:159653
Publication DOI: 10.1080/1744666X.2021.1982383

How effective are JAK-inhibitors? Perspectives from clinical trials and real-world studies

Kim Lauper, 1,2,3, Kimme L. Hyrich 1,4

1: Centre for Epidemiology Versus Arthritis, Centre for Musculoskeletal Research, University of Manchester, Manchester, UK.

2: Division of Rheumatology, Geneva University Hospitals, Geneva, Switzerland.

3: Faculty of Medicine, University of Geneva, Geneva, Switzerland

4: NIHR Manchester Biomedical Research Centre, Manchester Foundation NHS Trust, Manchester, UK

Corresponding author: Kim Lauper, Division of Rheumatology, Geneva University Hospitals, 26 av. Beau-Séjour, 1206 Genève, Switzerland, kim.lauper@hcuge.ch

Keywords: comparative effectiveness, JAK-inhibitors, Janus kinase, rheumatoid arthritis, rheumatology, trials.

How effective are JAK-inhibitors? Perspectives from clinical trials and real-world studies

World count: 4775

Structured abstract

Introduction:

JAK-inhibitors have emerged as a new treatment option for rheumatoid arthritis, with five molecules currently available in different parts of the world: tofacitinib, baricitinib, upadacitinib, peficitinib and filgotinib. These molecules have been the subject of numerous trials looking at their efficacy (how well they perform in controlled conditions) but also some observational studies from the general population to assess their effectiveness (how well treatment perform under real conditions). With each their own weaknesses and strengths, they give different but complementary information.

Areas covered: We will review what we can learn from trials and real-world studies on how effective JAK-inhibitors are in the treatment of rheumatoid arthritis.

Expert opinion:

Trials of JAK-inhibitors have shown that JAK-inhibitors are efficacious for the treatment of rheumatoid arthritis. However, their main outcomes are not clinically meaningful as their aim is mainly the regulatory authorisation of the product. Real-world studies are important as they evaluate the real-life effectiveness of the compounds, however, they are scarce at the moment, mainly evaluating tofacitinib and of variable quality. Future high-quality studies are needed to assess the real-world effectiveness of JAK-inhibitors in a more complete manner.

Keywords: comparative effectiveness, JAK-inhibitors, Janus kinase, rheumatoid arthritis, rheumatology, trials.

Article highlights:

- This review shows that substantial trials have evaluated the efficacy of JAK-inhibitors.
- We learn from trials that JAK-inhibitors seems to be more efficacious than csDMARDs and placebo and as efficacious as adalimumab or etanercept for the treatment of rheumatoid arthritis.
- Trials conclusions are difficult to translate in the real world, as the patient population is different and the outcomes are not clinically meaningful.
- Only a few real-world studies have evaluated the effectiveness of JAK-inhibitors. Their outcomes are more relatable to routine clinical practice than trials. Of various quality and small sample size, overall these studies point to similar effectiveness of tofacitinib compared to bDMARDs.
- More high-quality real-world studies are needed to evaluate the effectiveness of JAK-inhibitors and their place in the treatment landscape of rheumatoid arthritis.

1. Introduction

Since the 1990s, the treatment landscape of rheumatoid arthritis (RA) has changed significantly with the advent of biologic therapies. Even more recently, Janus kinase(JAK)-inhibitors, small oral compounds targeting specific signal transduction molecules, have emerged as a new treatment option for RA. Five molecules are currently available: tofacitinib, baricitinib, upadacitinib, peficitinib and filgotinib. These molecules have been the subject of numerous randomised controlled trials (RCTs) looking at their efficacy (how well they perform in controlled conditions) in different types of settings and disease stage. The gold standard when studying causal relationships, RCTs may however lack generalisability with their selected population based on strict inclusion criteria, which may not be representative of the target population. In contrast, observational studies from the general population allow the assessment of effectiveness (how well treatment perform under real conditions). Yet, they also carry their limitations, which are more related to internal validity (truth of the causal relationship). In this review, we will evaluate what perspectives can be derived from RCTs and real-world studies on how effective JAK-inhibitors are, starting with some definitions of clinical research phases.

2. Clinical research and real-world data to evaluate new treatments

Clinical research phases

After the preclinical testing phase, clinical research for the evaluation of a new treatment will potentially go through four phases [1,2]:

- Phase I is generally a “human pharmacology” phase, where the pharmacokinetics, pharmacodynamics, safety and sometimes early measurement of disease activity are evaluated in healthy volunteers or people with the disease in very small groups during a few months (<100 participants).

- Phase II is a “therapeutic exploratory” phase, where the efficacy is first evaluated in people with the disease (usually a few hundred participants) and dose and regimen for phase III studies are determined.
- Phase III is usually a “therapeutic confirmatory” phase where the safety and efficacy of a drug evaluated in previous phases are confirmed in the target population for its intended use. The efficacy is generally compared to treatments currently available, or alternatively with placebo.
- Phase IV comprises all studies performed after therapeutic approval (“therapeutic use” phase).

In all phases, adverse events are evaluated. Randomised controlled trials usually are phase II or phase III studies and real-world studies will be classified as phase IV studies. Many JAK-inhibitors have completed phase III and reached phase IV, on which we will focus later.

Why RCTs are the gold standard when looking at efficacy

RCTs are interventional studies (as opposed to observational studies) where subjects are randomly allocated to different treatment groups, including a control group. In RA RCTs, the control group can be a placebo, but this is less and less ethically acceptable in the early treatment and treat-to-target era, and most recent studies use an active comparator.

Participants and assessors may be blinded to the treatment group, to minimise biases when assessing the outcome. Usually, endpoints are well-specified and the study is powered accordingly. RCTs also generally have very strict inclusion criteria to obtain a homogeneous population. For RA, trials will generally use classification criteria such as the 1987 Rheumatoid Arthritis Classification of American College of Rheumatology[3] or the collaborative 2010 Rheumatoid Arthritis Classification Criteria of the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) [4].

When appropriately conducted (i.e., in terms of randomisation, blinding and allocation), treatment groups should be similar, allowing the evaluation of the sole effect of the treatments in a prospective manner. If all these parameters are adequate, the internal validity (the level of confidence in the causal relationship) of the study is very high, which is why they are the gold standard for the evaluation of the efficacy of a drug.

What are real-world data and why do we need them?

According to the definition of the European Medicines Agency, real-world data are "routinely collected data relating to a patient's health status or the delivery of health care from a variety of sources other than traditional clinical trials."[5]. They can be issued from different sources (e.g. diseases or treatment registers, claims data, electronic health records…) but are all observational. They can be classified as primary data, such as questionnaires or research registers, where data are actively collected for research purposes, and secondary data, such as electronic health records or health insurance claims data, where data are collected for other reasons (e.g. administrative reasons).

Generally, observational data are easier to obtain, allowing for larger populations, longer follow-up time and comparison of more treatments at the same time than in RCTs.

However, as they are observational, there is an increased risk of bias and more issues of confounding compared to RCTs. In contrast to RCTs, in the real world, the patient population is very diverse and heterogeneous. When comparing different drugs, treatment groups are not randomised and thus may not be similar. In the population with RA, it has been shown numerous times that patients treated with TNF-inhibitors differ on several aspects to patients with non-TNFi-bDMARDs such as age, functional status and the number of previous treatments [6]. These may lead to confounding if there are factors that influence treatment choice and the effectiveness outcome simultaneously, wrongly attributing an effect to the treatment when it is associated with another factor associated with the treatment. Additionally, there is a risk of prevalent user bias if patients are recruited sometime after the start of treatment, which can lead to missed early events. The treatment may

also have influenced the characteristics at study entry which are therefore no longer suitable to be used for adjustment. There may also be more issues of missing data or losses-to-follow up.

However, real-world studies are also generally less burdened by volunteer bias (representativeness of the sampled population compared to the general population due to the need to volunteer to be included in the study), although not completely immune [7]. They can have many uses that are not possible with RCTs: help evaluate treatment practice, register rare events or describe the prognosis of a particular disease, for example. In RA, real-world studies were able to capture the increased mortality associated with the condition[8], linked tuberculosis infections with TNF-inhibitors which could not be detected in RCTs [9,10]and showed the effectiveness of methotrexate, which had never been assessed in a randomised controlled trial [11].

When looking particularly at how effective treatments are, these studies can help to assess whether the findings of RCTs are translated into practice in a less selected population.

3. Randomised controlled trials of JAK-inhibitors

Multiple phase III RCTs have been published, evaluating the efficacy of all JAK-inhibitors for the treatment of RA. Eight trials for tofacitinib [12–19], four trials for baricitinib: [20–23], five trials for upadacitinib [24–28], three for filgotinib [29–31] and three with peficitinib [32–34] (Table 1 to 5). These trials aimed to evaluate different study populations including patients (a) naïve to any treatment [12,20,24,29,32], (b) with insufficient response to csDMARDs [13–16,21,22,25–27,30,32], (c) with insufficient response to previous csDMARDs or bDMARDs [17,18,34] or (d) with insufficient response to bDMARDs [19,23,28,31]. One study with peficitinib included any patients with moderate disease activity independent of their treatment history [33]

Inclusion and exclusion criteria

Compared to real-world data, which generally only requires exposure to a specific drug and/or diagnosis of a specific disease for patient inclusion, the inclusion criteria of RCTs are more stringent. In JAK-inhibitors trials, as in most RA studies, inclusion involved a diagnostic of rheumatoid arthritis

according to classification criteria: the ACR 1987 criteria [3] in some of the older studies with tofacitinib and ACR/EULAR 2010 criteria [4] in more recent studies with tofacitinib and with other JAK-inhibitors (Table 1 to 5). In some studies, the presence of bone erosions was mandatory [21,30,32,35]. All patients were required to have active disease, generally defined by ≥4 to 6 tender joints and ≥4 to 6 swollen joints and an increase in acute phase reactants. Exclusion criteria were also very strict, with the exclusion of patients receiving more than 10 mg of prednisone, recent intra-articular injection corticosteroids or unstable dose of NSAIDs in the previous weeks in almost every RCTs.

Efficacy outcomes

Efficacy was assessed mainly using the ACR response in JAK-inhibitors trials (Table 1 to 5). The ACR response is a binary outcome (responder vs non-responder) that evaluates relative improvement in tender joint count, swollen joint count and 5 core measures: patient global assessment of disease activity, physician global assessment of disease activity, patient pain scale, disability (Health Assessment Questionnaire Disability Index) and acute phase reactants (ESR or CRP) [36]. Subjects are defined as responders if they improve in the tender and swollen joint count and at least 3 of the 5 core measures. The ACR response can be then classified by the percentage of improvement: at least 20% of improvement in the joints counts and 3 or the core measures for ACR20, 50% for ACR50, 70% for ACR70.

Most of the studies used ACR20 as one of the main outcomes, and only a few used ACR50 or ACR70. The main outcome was generally evaluated at 12 weeks, but sometimes at 24 weeks. Several other outcomes were also evaluated as secondary outcomes such as reaching a specific low disease state (e.g. SDAI or DAS28CRP remission), changes in functional status or absence of radiographic progression.

Radiographic progression, using the modified total Sharp score, was one of the main outcome in 2 trials of tofacitinib [12,13], and both trials showed superiority of tofacitinib versus their comparator (methotrexate or placebo). It was also an important endpoint in 3 studies with baricitinib [20–22], 2

with upadacitinib[24,27], 1 with filgotinib [30] and 1 with peficitinib [32].In all studies, they showed superiority for preventing radiographic damage compared to placebo or csDMARDs. There was no direct comparison between dosages or comparison to TNF-inhibitors.

Comparison group

JAK-inhibitor studies evaluated the efficacy of the molecules compared either to placebo, methotrexate or TNF-inhibitors (adalimumab or etanercept). There are no head-to-head trials between JAK-inhibitors. In the phase III studies, even when different dosage of the treatment were evaluated, there were no direct comparisons between dosages of the JAK-inhibitors.

Results of main phase III RCTs

Principal trials of JAK-inhibitors and their main results are presented in Tables 1 to 5. As we can see, studies have shown that all JAK-inhibitors are more efficacious than placebo in all trials in RA, and more efficacious when compared to csDMARDs in patients with inadequate response to csDMARDs. There were 5 studies comparing the JAK-inhibitors to TNF-inhibitors (adalimumab), 2 with tofacitinib [14,15], 1 with baricitinib [21], 1 with upadacitinib [27], 1 with filgotinib[30]. One of the peficitinib studies included an open-label arm of patients with etanercept, but no statistical comparisons were made. In the 3 studies with tofacitinib and filgotinib [14,15,30], the JAK-inhibitors have shown to be non-inferior, but there are no signs of superiority. For filgotinib, the dose of 200 mg was non-inferior compared to adalimumab, but not the dose of 100 mg [30]. In patients with inadequate response to methotrexate, there were signs of superiority for baricitinib compared to adalimumab in combination therapy in the RA-BEAM study [21] and of upadacitinib 15mg/day compared to adalimumab, both given in combination with methotrexate, in the SELECT-COMPARE study [27] for the main outcome and some secondary outcomes. In the RA-BEAM study, the main outcome of ACR20 response was 70% for baricitinib and 61% for adalimumab. The difference of DAS28-CRP was also significant with -2.24 for baricitinib vs -1.95 for adalimumab at week 12. The ACR50, ACR70 at different time points and the change of HAQ-DI were also in favour of baricitinib. However, this was

not reflected in the inhibition of radiographic progression, which was numerically slightly lower with adalimumab (least square mean change from baseline of 0.41 vs 0.33 for mTSS, 0.29 vs 0.24 for erosion score and 0.12 vs 0.10 for joint-space narrowing for baricitinib and adalimumab respectively). In the SELECT-COMPARE study[27], upadacitinib was superior to adalimumab when looking at the main outcome of ACR20 at week 12 (71% for upadacitinib vs 63% for adalimumab) and also for some secondary endpoints such as ACR50, ACR70, DAS28-CRP remission at week 12 and/or 26. Numerically, changes in radiographic scores were slightly in favour of upadacitinib.

4. JAK-inhibitors in real-world studies

JAK inhibitors have only recently been licensed for clinical use, so there are only a few real-world studies published so far, and mainly on tofacitinib, which was available before the other JAK-inhibitors and earlier in North America (2012) than Europe (2017).

When looking at treatment effectiveness in RA, the same outcomes as in clinical trials can be used. However, as discussed before, some biases may be more frequent in real-world studies, which can hamper the interpretation of the results. Also, real-world studies generally use scores that are more commonly used in routine clinical practice, such as DAS28 and CDAI and less often ACR responses.

In addition, real-world studies often include drug retention (also called persistence or maintenance) which is defined as the "duration of time from initiation to discontinuation of therapy"[37]. Retention evaluates effectiveness but also drug tolerance and is thought to be more representative of clinical practice. In addition, it also takes attrition into account in studies of comparative effectiveness. Finally, the date of treatments starts and stops are often well recorded in real-world datasets.

USA - MarketScan

One of the first published studies evaluating the effectiveness of JAK-inhibitors in the real world, this US study used insurance claims data from the MarketScan database. The aim was to evaluate the effectiveness and safety of tofacitinib (164 patients) compared to csDMARDs (5399 patients), TNFi

(13,367 patients) and non-TNFi bDMARDs (2902 patients)[38]. As this database is not a clinical database, there was no possibility of evaluating disease activity. Effectiveness was thus evaluated using a validated claims-based algorithm comprising 6 elements: high adherence (defined as a certain percentage of pharmacy claims or number of treatment procedures), no bDMARD or tsDMARD switch or addition, no csDMARD switch or addition, no increase in dose or frequency of index drug, no more than one glucocorticoid joint injection, and no new or increased oral glucocorticoid dose. This study found a low rate of effectiveness with less than 20% of patients reaching the criteria for effectiveness from the algorithm in every group, mainly because of the adherence component of the score. This item evaluated if patients had pharmacy claims or insurance claims pertaining to their therapy. It can thus not discriminate why the treatment was stopped e.g. nonadherence, ineffectiveness or adverse events. Although this algorithm has been validated in two databases [39,40], it was not validated in Marketscan nor with the use of tofacitinib and the question remains about its meaningfulness from a clinical point of view. Additionally, the tofacitinib group was small thus introducing issues of power.

USA - CORRONA

In this study using the US Corrona (now CorEVITAS) register data, the effectiveness of treatment with tofacitinib (N=558) was compared to TNFi (N=8014). The main outcome was CDAI low disease activity (LDA) or remission at 6 months, but they evaluated other outcomes such as the modified ACR 20% (mACR20) response and pain [41], which were available for 402 patients with tofacitinib and 6241 patients with TNFi. Patients were stratified by line of therapy, and comparison between tofacitinib and TNFi was only made on the third or fourth lines of therapy because there were not enough tofacitinib patients in earlier lines of therapy. There was no statistically significant difference in the tofacitinib monotherapy and tofacitinib combination therapy with csDMARDs in terms of mACR20, CDAI LDA and pain at 6 months nor between tofacitinib monotherapy and TNFi in combination with csDMARDs for patients in their third and fourth lines of therapy. As in the previous study, the numbers of patients in tofacitinib groups are quite low and 20% of the patients had no outcome

measures available at 6 months. These patients were classified as non-responders for binary outcomes (e.g. CDAI LDA and mACR20), but it is not clear how they were assessed for continuous outcomes.

Switzerland - SCQM

In a study using data from the Swiss Clinical Quality Management in Rheumatoid Arthritis (SCQM-RA) register, the retention of tofacitinib was compared to TNF-inhibitors and other bDMARDs [42]. The study included 4023 treatment courses in 2600 patients: 806 on tofacitinib, 1862 on TNFi, 1355 on other bDMARDs. As with bDMARDs other than TNFi, this study showed that tofacitinib was prescribed to older patients with more previous treatments than TNFi. Tofacitinib was also more often prescribed in monotherapy (47% vs 29%) than TNFi. In this study, tofacitinib retention was shown to be comparable with other bDMARDs (adjusted hazards ratio (aHR) of discontinuation bDMARDs vs JAK-inhibitors 1.09, 95% CI 0.96 to 1.24) and slightly higher than TNFi (aHR TNFi vs JAK-inhibitors 1.29, 95% CI 1.14 to 1.47). The presence of concomitant treatment with a csDMARD did not influence retention, in contrast to TNFi. Overall, the retention of all treatments was rather short with a median time to discontinuation of 1.86 years (95% CI 1.52 to 2.3 years) for tofacitinib, 1.32 (1.15 to 1.6) years for TNFi and 1.69 (1.48 to 2.1) for other bDMARDs. This was attributed by the authors to the fairly liberal practice of prescription in Switzerland where treatments can be easily switched, without any binding guidelines for treatment reimbursement. A secondary outcome was the evaluation of CDAI at 1 year, which was available in around two-third of the patients. The odds of attaining CDAI low disease activity at 1 year was not significantly different between groups, with 40% of tofacitinib users., 40% of TNFi users, and 46% of other bDMARD users reaching low disease activity.

Japan - Tsurumai Biologics Communication Registry (TBCR)

In a multicentre registry of patients with RA starting tsDMARDs, the retention of baricitinib and the DAS28 –CRP were evaluated at 24 weeks[43]. In this study of 113 patients, 86.5% of the patients

were still under treatment at 24 weeks. The authors describe a decrease of DAS28-CRP from a mean of 3.55 ± 1.21 at baseline to 2.65 ± 1.06 at 4 weeks and 2.32 ± 1.03 at 24 weeks, with a proportion of patients in LDA increasing significantly from 26.7 to 68.2% from baseline to 24 weeks. However, it is unclear how patients no longer under treatment and lost of follow-up were evaluated for these outcomes. The absence of previous tsDMARDs use and a lower DAS28-CRP score at baseline were associated with the achievement of LDA at 24 weeks.

Australia - OPAL

In a study from the Optimizing Patient outcome in Australian rheumatoLogy (OPAL) study using medical records, Bird et al. evaluated the effectiveness, retention and treatment patterns of tofacitinib (650 patients) and bDMARDs (1300 patients)[44]. Patients were included only if they had at least 1 year of follow-up since starting the index treatment. At baseline, 17.3% (53/300) of patients in the tofacitinib group and 16.1% (16/539) in the bDMARDs group were in DAS28-ESR remission. After 3 month, 49.7% (73/147) and 49.1% (157/320) had achieved remission and, after 18 months of treatment, 57.8% (48/83) and 52.4% (89/170), respectively. The median retention was 34.2 months for patients with tofacitinib and 33.8 months for patients with bDMARDs. The most common reason for discontinuation was “completion of treatment” which was not clearly defined, followed by ineffectiveness. The conclusions of this study were limited by the small number of patients, missing data on DAS28 and probably an important selection bias as only patients with complete follow-up were included.

UK - Leeds Teaching Hospitals NHS Trust

This recent study evaluated the effectiveness of tofacitinib (n=54) and baricitinib (n=69) in a single centre [45], looking at DAS28-CRP at 3 and 6 months. As in other cohorts, most of the patients received previous bDMARDs with only 9.6% that were bionaïve. Eighty-five per cent of the patients were still on their JAK-inhibitor at 3 months and 73.2% at 6 months. The DAS28-CRP decreased by a

mean of -1.48 at 3 months and -1.67 at 6 months. Again, it is not clear how the outcome was evaluated in patients lost-to-follow-up or no longer under treatment, which was not described.

Overview of the analyses in real-world studies of JAK-inhibitors

Of the 6 studies that we found that evaluated JAK-inhibitors in the real world, 1 used retention, 1 used a claim algorithm and 4 used diseases activity score commonly used in routine clinical practice as the main outcome (see Table 6). Four of the studies compared JAK-inhibitors to other treatments (generally bDMARDs) and adjusted the analysis for potential confounding factors. However, the adjustment factors were very different between studies and for example, two studies were not able to adjust for disease activity at baseline, although this is known to be associated with effectiveness[38,44]. It was also not always clear how patients lost of follow-up were taken into account for the evaluation of effectiveness or how missing data were managed, making it sometimes difficult to evaluate the validity of the conclusions.

5. Comparison of results between RWE and RCTs

To directly compare results between RCTs and real-world data is problematic. First, the populations are very different. In a study of the German biologics register RABBIT, it was found that only 21% to 33% of patients receiving TNF-inhibitors in clinical practice would have been eligible for major trials of TNF-inhibitors[46]. These “ineligible” patients had lower disease activity, more comorbidities and lower functional status compared to trial eligible patients. As we have seen, in real-world studies with JAK-inhibitors, most patients already had several previous lines of therapy, which was less often the case in clinical trials. Second, the outcomes are different, with clinical trials reporting ACR response rates and real-world studies evaluating retention or disease activity scores. Finally, the analyses in terms of outcome and statistical management were very different between real-world studies and clinical trials, and also among real-world studies, rendering direct comparisons difficult. However, so far real-world studies seem to confirm the effectiveness of JAK-inhibitors in the

unselected RA population with no major differences between JAK-inhibitors and other treatments in terms of retention or disease activity.

6. Discussion

Numerous RCTs have evaluated the efficacy of JAK-inhibitors. The main outcome was principally the ACR20. The use of similar outcomes in RA RCTs is advantageous as they can be compared between trials, although it is still difficult to make a direct comparison as inclusion and exclusion criteria differ between studies. That said, the primary outcome in most trials was the ACR20. ACR20 is often chosen as the primary outcome in RA clinical trials as more patients will have an ACR20 response than an ACR50 or ACR70 response, or clinical remission. This allows smaller required sample sizes to detect statistically significant differences between treatment arms; however, it is argued that ACR20 is not a clinically meaningful outcome as patients who only achieve a 20% improvement but not a higher response score will still have significant symptoms, including joint inflammation, and thus be at risk of joint damage [47]. Outcomes in RCTs were also often evaluated very rapidly (e.g. after 12 weeks), which may be fitting in the treat-to-target era but does not allow the evaluation of long-term outcomes. Finally, patients in RCTs are not always representative of the current population treated with JAK-inhibitors, for example when looking at the number of previous DMARD treatments. For these reasons, the usefulness of RCTs is limited when we want to extrapolate results to our clinical population of patients. However, it should be remembered that the main aim of most of the RCTs presented has been regulatory authorisation of the product and the RCT design is very successful in demonstrating differences between therapies for this purpose and thus facilitating access to a wider range of therapies for our patients.

There were only a few studies comparing JAK-inhibitors to TNF-inhibitors, all showing non-inferiority and less than a half pointing maybe to superiority on certain outcomes, although the clinical significance is difficult to determine. There were no studies comparing JAK-inhibitors. In a network meta-analysis looking at the comparative efficacy of tofacitinib, baricitinib and upadacitinib,

upadacitinib had a numerically higher point estimate for ACR response and DAS28 remission, but the confidence intervals were wide and crossed the other JAK-inhibitors (except for DAS28-CRP remission at week 24 between upadacitinib 15 mg and tofacitinib 5 mg) [48].

When looking at current real-world data on the effectiveness of JAK-inhibitors, presently the number of studies is scarce with generally a low number of patients in the JAK-inhibitors groups. Although all studies adjusted for potential baseline confounders, most studies did not clearly explain how they evaluated patients that were no longer under treatment and how many were lost to follow-up. There are thus potential issues of internal validity. However, all studies point to the effectiveness of JAK-inhibitors in the unselected RA population, which is then reassuring. Well-designed studies with greater samples and longer follow-up are needed to confirm the effectiveness of JAK-inhibitors in the unselected population.

RCTs and observational studies have each their flaws and strengths but both are necessary to draw a comprehensive picture on how effective a treatment is, and this is not different with JAK-inhibitors.

Expert Opinion

Trials of JAK-inhibitors have shown that they are a treatment option for rheumatoid arthritis patients as they are at least as effective as currently available treatments. This is reflected in the most recent EULAR recommendations for the treatment of rheumatoid arthritis, were JAK-inhibitors are placed at the same level than bDMARDs in the treatment strategy [49]. However, the main RCT outcomes are not clinically meaningful and the trials were generally not powered to evaluate more clinically meaningful outcomes, although there were also assessed most of the time. Additionally, the population included in these trials is noticeably different to the population of rheumatoid arthritis patients in the real world. The effectiveness of JAK-inhibitors for patients that we see in routine clinical practice is thus not clear at the moment. Real-world studies evaluating the effectiveness of JAK-inhibitors in rheumatoid arthritis are presently scarce, including small numbers of patients and

are of variable quality. It is then difficult to evaluate the validity of their conclusions. However, the fact that no studies so far seem to find major differences in efficacy or effectiveness between JAK-inhibitors and other treatments of rheumatoid arthritis is reassuring. There might be some signals pointing to a greater efficacy of upadacitinib (JAK-1 selective) and baricitinib (JAK-1/2 selective), however, this is driven by only 2 trials and the clinical significance is unclear. As such, the choice between the different tsDMARDs in terms of efficacy should primarily be done considering the availability, the price and the frequency of use.

Independent of the effectiveness, we must also acknowledge that for the patient, the option of an oral advanced therapy for rheumatoid arthritis can bring a dramatic change in day-to-day life, with no need for treatment refrigeration or injection. At the same time, the daily posology may be fastidious and decrease adherence to the treatment. This potential decrease in adherence is not taken into account in clinical trials where patients generally strictly follow the drug regimen. In this aspect, real-world studies can bring light on how effective these treatments are, even with imperfect adherence.

As physicians, we should also take into consideration that the price of these molecules can be high, and with the increasing availability of biosimilars, the cost-effectiveness must be taken into account. However, considering the manufacturing process, they are still generally cheaper than bDMARDs.

Treatment cycling is also an area that should be explored. Are these molecules more effective than bDMARDs after a bDMARD failure or are they at least as efficacious as other non-Interleukin (IL)-6 bDMARDs after IL-6 failure, considering their high effect on IL-6?

In addition, safety has not been discussed in our review, but this aspect is very important in the shared-making decision process. Currently, it is not very clear if the safety profile of these compounds is similar to other treatment options. Most of the safety data are issued from tofacitinib studies as they have longer follow-up time and are more numerous because this molecule was developed earlier.

Many questions are still unanswered about the use of JAK-inhibitors in routine clinical use for rheumatoid arthritis and we are looking forward to seeing more real-world studies in the next years, with all types of JAK-inhibitors and also in other rheumatologic diseases. However, these studies will need to take into account as much as possible the frequent issues that occur when analysing real-world data for effectiveness studies.

In any case, as with all aspects of the management of rheumatoid arthritis, communication with the patient of the current state of knowledge about these molecules and areas of uncertainty is essential so that they can take an active part in the decision-making process when discussing treatment options.

Funding: None

References

[1] U.S. Food & Drug administration. Step:3 Clinical Research. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research. Accessed the 21.05. 2021.

[2] European Medicines Agency. ICH E8 General considerations for clinical studies. 1998. https://www.ema.europa.eu/en/ich-e8-general-considerations-clinical-studies. Accessed the 21.05 2021.

[3] Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

[4] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.

[5] Cave A, Kurz X, Arlett P. Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe. Clin Pharmacol Ther 2019;106:36–9.

[6] Lauper K, Mongin D, Alpizar-Rodriguez D, Codreanu C, Iannone F, Kristianslund EK, et al. Drug retention of biological DMARD in rheumatoid arthritis patients: the role of baseline characteristics and disease evolution. Rheumatology (Oxford) 2019.

[7] Monti S, Grosso V, Todoerti M, Caporali R. Randomized controlled trials and real-world data: differences and similarities to untangle literature data. Rheumatology (Oxford) 2018;57:vii54–8.

[8] Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994;37:481–94.

[9] Gómez-Reino JJ, Carmona L, Rodríguez Valverde V, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: A multicenter active-surveillance report. Arthritis Rheum 2003;48:2122–7.

[10] Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis Associated with Infliximab, a Tumor Necrosis Factor α–Neutralizing Agent. N Engl J Med 2001;345:1098–104.

[11] Pincus T, Marcum SB, Callahan LF. Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatol 1992;19:1885–94.

[12] Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014;370:2377–86.

[13] Van Der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib

(CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: Twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum 2013;65:559–70.

[14] van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al. Tofacitinib or Adalimumab versus Placebo in Rheumatoid Arthritis. N Engl J Med 2012;367:508–19.

[15] Fleischmann RM, Mysler EF, Hall S, Kivitz AJ, Moots RJ, Luo Z, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet 2017;390:457–68.

[16] Cohen SB, Pope J, Haraoui B, Irazoque-Palazuelos F, Korkosz M, Diehl A, et al. Methotrexate withdrawal in patients with rheumatoid arthritis who achieve low disease activity with tofacitinib modified-release 11 mg once daily plus methotrexate (ORAL Shift): a randomised, phase 3b/4, non-inferiority trial. Lancet Rheumatol 2019;1:e23–34.

[17] Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-Controlled Trial of Tofacitinib Monotherapy in Rheumatoid Arthritis. N Engl J Med 2012;367:495–507.

[18] Kremer J, Li Z-G, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in Combination With Nonbiologic Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis. Ann Intern Med 2013;159:253.

[19] Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: A randomised phase 3 trial. Lancet 2013;381:451–60.

[20] Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, et al. Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or

Limited Prior Disease-Modifying Antirheumatic Drug Treatment. Arthritis Rheumatol 2017;69:506–17.

[21] Taylor PC, Keystone EC, van der Heijde DD, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. N Engl J Med 2017;376:652–62.

[22] Dougados M, Van Der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: Results from the RA-BUILD study. Ann Rheum Dis 2017;76:88–95.

[23] Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in Patients with Refractory Rheumatoid Arthritis. N Engl J Med 2016;374:1243–52.

[24] van Vollenhoven R, Takeuchi T, Pangan AL, Friedman A, Mohamed MEF, Chen S, et al. Efficacy and Safety of Upadacitinib Monotherapy in Methotrexate-Naive Patients With Moderately-to-Severely Active Rheumatoid Arthritis (SELECT-EARLY): A Multicenter, Multi-Country, Randomized, Double-Blind, Active Comparator–Controlled Trial. Arthritis Rheumatol 2020;72:1607–20.

[25] Burmester GR, Kremer JM, Van den Bosch F, Kivitz A, Bessette L, Li Y, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391:2503–12.

[26] Smolen JS, Pangan AL, Emery P, Rigby W, Tanaka Y, Vargas JI, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. Lancet 2019;393:2303–11.

[27] Fleischmann R, Pangan AL, Song IH, Mysler E, Bessette L, Peterfy C, et al. Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial. Arthritis

Rheumatol 2019;71:1788–800.

[28] Genovese MC, Fleischmann R, Combe B, Hall S, Rubbert-Roth A, Zhang Y, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet 2018;391:2513–24.

[29] Westhovens R, Rigby WFC, Van Der Heijde D, Ching DWT, Stohl W, Kay J, et al. Filgotinib in combination with methotrexate or as monotherapy versus methotrexate monotherapy in patients with active rheumatoid arthritis and limited or no prior exposure to methotrexate: The phase 3, randomised controlled FINCH 3 trial. Ann Rheum Dis 2021:1–12.

[30] Combe B, Kivitz A, Tanaka Y, Van Der Heijde D, Simon JA, Baraf HSB, et al. Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. Ann Rheum Dis 2021:1–11.

[31] Genovese MC, Kalunian K, Gottenberg JE, Mozaffarian N, Bartok B, Matzkies F, et al. Effect of Filgotinib vs Placebo on Clinical Response in Patients with Moderate to Severe Rheumatoid Arthritis Refractory to Disease-Modifying Antirheumatic Drug Therapy: The FINCH 2 Randomized Clinical Trial. JAMA - J Am Med Assoc 2019;322:315–25.

[32] Takeuchi T, Tanaka Y, Tanaka S, Kawakami A, Iwasaki M, Katayama K, et al. Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to methotrexate: Results of a phase III randomised, double-blind, placebo-controlled trial (RAJ4) in Japan. Ann Rheum Dis 2019;78:1305–19.

[33] Takeuchi T, Tanaka Y, Iwasaki M, Ishikura H, Saeki S, Kaneko Y. Efficacy and safety of the oral Janus kinase inhibitor peficitinib (ASP015K) monotherapy in patients with moderate to severe rheumatoid arthritis in Japan: A 12-week, randomised, double-blind, placebo-controlled phase IIb study. Ann Rheum Dis 2016;75:1057–64.

[34] Tanaka Y, Takeuchi T, Tanaka S, Kawakami A, Iwasaki M, Song YW, et al. Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to

conventional DMARDs: A randomised, double-blind, placebo-controlled phase III trial (RAJ3). Ann Rheum Dis 2019;78:1320–32.

[35] van der Heijde D, Strand V, Tanaka Y, Keystone E, Kremer J, Zerbini CAF, et al. Tofacitinib in Combination With Methotrexate in Patients With Rheumatoid Arthritis: Clinical Efficacy, Radiographic, and Safety Outcomes From a Twenty-Four–Month, Phase III Study. Arthritis Rheumatol 2019;71:878–91.

[36] Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American college of rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.

[37] Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: Terminology and definitions. Value Heal 2008;11:44–7.

[38] Machado MA de Á, Moura CS de, Guerra SF, Curtis JR, Abrahamowicz M, Bernatsky S. Effectiveness and safety of tofacitinib in rheumatoid arthritis: a cohort study. Arthritis Res Ther 2018;20:60.

[39] Curtis JR, Chastek B, Becker L, Harrison DJ, Collier D, Yun H, et al. Further evaluation of a claims-based algorithm to determine the effectiveness of biologics for rheumatoid arthritis using commercial claims data. Arthritis Res Ther 2013;15:2010–1.

[40] Curtis JR, Baddley JW, Yang S, Patkar N, Chen L, Delzell E, et al. Derivation and preliminary validation of an administrative claims-based algorithm for the effectiveness of medications for rheumatoid arthritis. Arthritis Res Ther 2011;13.

[41] Reed GW, Gerber RA, Shan Y, Takiya L, Dandreo KJ, Gruben D, et al. Real-World Comparative Effectiveness of Tofacitinib and Tumor Necrosis Factor Inhibitors as Monotherapy and Combination Therapy for Treatment of Rheumatoid Arthritis. Rheumatol Ther 2019;6:573–86.

[42] Finckh A, Tellenbach C, Herzog L, Scherer A, Moeller B, Ciurea A, et al. Comparative effectiveness of antitumour necrosis factor agents, biologics with an alternative mode of action and tofacitinib in an observational cohort of patients with rheumatoid arthritis in

Switzerland. RMD Open 2020;6:1–7.

[43] Takahashi N, Asai S, Kobayakawa T, Kaneko A, Watanabe T, Kato T, et al. Predictors for clinical effectiveness of baricitinib in rheumatoid arthritis patients in routine clinical practice: data from a Japanese multicenter registry. Sci Rep 2020;10:21907.

[44] Bird P, Littlejohn G, Butcher B, Smith T, da Fonseca Pereira C, Witcombe D, et al. Real-world evaluation of effectiveness, persistence, and usage patterns of tofacitinib in treatment of rheumatoid arthritis in Australia. Clin Rheumatol 2020;39:2545–51.

[45] Fitton J, Melville AR, Emery P, Nam JL, Buch MH. Real-world single centre use of JAK inhibitors across the rheumatoid arthritis pathway. Rheumatology 2020:1–7.

[46] Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: Comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum 2006;54:3399–407.

[47] Pincus T, Stein CM. ACR 20: Clinical or statistical significance? Arthritis Rheum 1999;42:1572–6.

[48] Pope J, Sawant R, Tundia N, Du EX, Qi CZ, Song Y, et al. Comparative Efficacy of JAK Inhibitors for Moderate-To-Severe Rheumatoid Arthritis: A Network Meta-Analysis. Adv Ther 2020;37:2356–72.

[49] Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:annrheumdis-2019-216655.

Tables

Table 1 Phase III studies with tofacitinib

Population studied	**MTX naïve**	**Inadequate response to MTX**				**Inadequate response to at least one conventional synthetic or biological DMARD**		**Inadequate response to a TNFi**
Study name	ORAL START[12]	ORAL SCAN[13]	ORAL STANDARD[14]	ORAL STRATEGY[15]	ORAL SHIFT[16]	ORAL SOLO[17]	ORAL SYNC[18]	ORAL STEP[19]
	Lee *et al*, 2014	van der Heijde *et al*, 2013	Vollenhoven *et al*, 2012	Fleischmann *et al*, 2017	Cohen et al 2019	Fleischmann *et al*, 2012	Kremer *et al*, 2013	Burmester *et al*, 2013P
Main inclusion criteria	ACR1987, ≥6 TJ, ≥6 SJ, ESR>28mm or CRP >7 mg/l, ≥3 erosions or RF/ACPA	ACR1987, ≥6 TJ, ≥6 SJ, ESR>28mm/h, CRP >7mg/l, ≥3 erosions or RF/ACPA	ACR1987, ≥6 TJ, ≥6 SJ, >ESR>28mm/h or CRP >7 mg/l	2010 ACR/EULAR, ≥4 TJ , ≥4 SJ, CRP≥3 mg/l,	2010 ACR/EULAR, ≥4 TJ, ≥4SJ , CDAI>10, DAS28-4-ESR≥3.2	ACR1987, ≥6 TJ & ≥6 SJ, ESR>28mm/h or CRP >7mg/l	ACR1987, ≥4 TJ, ≥4 SJ, ESR > 28 mm/h or CRP > 7 mg/l	ACR1987, ≥6 TJ, ≥6 SJ, ESR>28mm/h or CRP >7 mg/l
Tofacitinib group (monotherapy /combination)	Monotherapy	Combination with MTX	Combination with MTX	Monotherapy and combination with MTX	Monotherapy and combination	Monotherapy. Antimalarial agents allowed	Combination with csDMARD	Combination with MTX. Antimalarial agents allowed
Treatment arms	MTX	Placebo + MTX	Placebo + MTX	Adalimumab + MTX	Tofacitinib 11mg ER qd + MTX	Placebo	Placebo	Placebo
	Tofacitinib 5 bid	Tofacitinib 5 mg bid	Adalimumab + MTX	Tofacitinib 5 mg bid + MTX	Tofacitinib 11mg ER qd + PBO	Tofactinib 5 mg bid	Tofacitinib 5 mg bid	Tofacitinib 5 mg bid
	Tofacitinib 10 bid	Tofacitinib 10 bid	Tofacitinib 5 mg bid	Tofacitinib 5 mg bid + PBO		Tofacitinib 10 mg bid	Tofacitinib 10 mg bid	Tofacitinib 10 mg bid

			Tofacitinib 10 bid					
Principal outcome(s)	ACR70 at month 6,, mTSS at months 6	ACR20, mTSS, DAS28-4(ESR)<2.6 at month 6, HAQ-DI at month 3	ACR20 and DAS28-4(ESR) < 2.6 at month 6, HAQ-DI at month 3	ACR50 at month 6	DAS28-4(ESR) change between week 24 and week 48	ACR20, HAQ-DI, DAS28-4(ESR) <2.6 at month 3	ACR20 andDAS28-4(ESR) <2.6 at month 6, HAQ-DI at month 3	ACR20, HAQ-DI, DAS28-4(ESR) <2.6 at month 3
Evaluation of radiographic progression as an important endpoint	Yes (mTSS, coprimary end point)	Yes (mTSS, coprimary end point)	No	No	No	No	No	No
Duration	2 years	2 years	1 year	1 year	2 years	6 months	1 year	6 months
Randomized population	956	797	717	1146	533	611	795	399
Previous treatments received	No previous csDMARDs	100% previously treated with MTX, 15.9% with TNFi and 4.6% with another bDMARD.	100% previously treated with MTX, 7.1% with TNFi and 2.1% with another bDMARD	100% previously treated with MTX, 31 to 37% with another csDMARD, 4-7% with a TNFi, 4-5% with another bDMARD	100% previous MTX, 30% previous TNFi, 14.4% other bDMARDs, 0.7% tsDMARDs	84.9% previously treated with MTX, 66.4% with another csDMARD, 16.2% with TNFi and 6.7% with another bDMARD	99.8% treated with csDMARD, of which 84.3% with MTX, 6.6% with TNFi and 2.9% with another bDMARD	98.5% previously treated with MTX, 30.8% with another csDMARD, 99.2% with a TNFi and 11.5% with another bDMARD
Main results for efficacy	Both dosage demonstrated superiority versus MTX on the X-rays	Superiority demonstrated versus placebo+ MTX on ACR 20 for both doses, on	Demonstrated superiority vs placebo + MTX on all outcomes.	Non-inferiority tofacitinib+MTX vs adalimumab+ MTX demonstrated	Non inferiority of tofacitinib monotherapy compared to tofacitinib	Superiority demonstrated versus placebo on ACR20 and HAQ, but not	Superiority demonstrated versus placebo+csDMARD on all outcomes	Superiority demonstrated versus placebo + MTX on ACR20 and HAQ-DI but

	(mTSS) and on the ACR 70	radiography (mTSS), HAQ-DI and DAS28 for the dose 5mg bid only			combined to MTX	on DAS28 remission		not on the DAS28 remission
	No direct comparison of the dosages of tofacitinib	No direct comparison of the dosages of tofacitinib	No conclusion vs adalimumab	Non-inferiority of tofacitinib alone vs tofacitinib+MTX or adalimumab + MTX not demonstrated		No direct comparison of the dosages of tofacitinib	No direct comparison of the dosages of tofacitinib	No direct comparison of the dosages of tofacitinib
			No direct comparison of the dosages of tofacitinib					
bid:twice a day, mTSS: modified Sharp score, MTX: methotrexate, SJ: swollen joints, TJ: tender / painful joints, RA: rheumatoid arthritis								

Table 2 Phase III studies with baricitinib

Population studied	**MTX naïve**	**Inadequate response to conventional synthetic DMARDs**		**Inadequate response or intolerance to TNFi**
		Inadequate response to MTX	Inadequate response to csDMARDs	
Study name	RA-BEGIN[20]	RA-BEAM[21]	RA-BUILD[22]	RA-BEACON[23]
Main inclusion criteria	ACR/EULAR 2010, ≥6/68 TJC, ≥6/66 SJC, CRP > 3.6 mg/l, RF/ACPA	ACR/EULAR 2010, ≥6/68 TJC, ≥6/66 SJC, CRP > 6 mg/l, 3	ACR/EULAR 2010, ≥6/68 TJC, ≥6/66 SJC, CRP > 3.6 mg/l	ACR/EULAR 2010, ≥6/68 TJC, ≥6/66 SJC, CRP > 3 mg/l

		erosions or RF/ACPA and 1 erosion		
Baricitinib group (monotherapy/combination)	Monotherapy and combination with MTX	Combination with MTX	Monotherapy or combination with csDMARDs	Combination with csDMARDs
Treatment arms	Baricitinib 4 mg/day	Baricitinib 4 mg/day	Baricitinib 4 mg/day	Baricitinib 4 mg/day
	Baricitinib 4mg/day + MTX	Adalimumab 40mg SC/2weeks	Baricitinib 2 mg/day	Baricitinib 2 mg/day
	MTX	Placebo	Placebo	Placebo
Duration	52 weeks	52 weeks	24 weeks	24 weeks
Principal outcome	ACR20 response at week 24	ACR20 response at week 12	ACR20 response at week 12	ACR20 response at week 12
Evaluation of radiographic progression as an important endpoint	Yes (mTSS at week 24)	Yes (mTSS at week 24)	Yes (mTSS at week 24)	No
Randomized population	584	1305	684	527
Previous treatments	No previous treatment	100% previous MTX, 0% previous bDMARDs	100% previous csDMARDs, 0% previous bDMARDs	100% previous bDMARDs (46% 1, 27% 2, 27% ≥ 3)
Main results for efficacy	Non-inferiority of baricitinib 4mg/day in monotherapy vs MTX monotherapy for ACR20 response at week 24 (main objective achieved)	Superiority of baricitinib vs placebo for ACR20 at week 12	Superiority of baricitinib 2 and 4 mg vs placebo for ACR20 and radiographic progression	Superiority of baricitinib 2 and 4 mg vs placebo
	Superiority of baricitinib 4mg/d monotherapy vs MTX monotherapy on ACR20	Superiority of baricitinib compared to adalimumab for ACR20 at week 12.		
	No comparison possible of baricitinib monotherapy or combination with MTX (not	Superiority of baricitinib and adalimumab for radiographic progression at week 24 and 54 compared to placebo.		

	methodologically designed to assess this question)			
	Superiority of bartiinib + MTX (but not as monotherapy) for radiographic progression vs placebo			
mTSS: modified total Sharp score, MTX: methotrexate, SJC: swollen joints count, TJC: tender / painful joints count, RA: rheumatoid arthritis, RF/ACPA: rheumatoid factor and/or anti-citrullinated protein antibodies				

Table 3 Phase III studies with upadacitinib

Population studied	**MTX naïve**	**Inadequate response to csDMARDs**	**Inadequate response to MTX**		**Inadequate response to a bDMARD**
Study name	SELECT-EARLY[24]	SELECT-NEXT[25]	SELECT-MONOTHERAPY[26]	SELECT-COMPARE[27]	SELECT-BEYOND[28]
Treatment arms	MTX	placebo +/- csDMARDs	MTX	Adalimumab + MTX	placebo +/- csDMARDs
	Upadacitinib 15mg/d	Upadacitinib 15mg/d	Upadacitinib 15mg/d	Updacitinib 15 mg/d+ MTX	Updacitinib 15 mg/d+/- csDMARDs
	Upadacitinib 30mg/d	Upadacitinib 30mg/d	Upadacitinib 30mg/d	Placebo	Upadacitinib 30mg/d+/- csDMARDs
Main inclusion criteria	ACR/EULAR 2010, ≥6 TJ, ≥6 SJ, CRP > 5 mg/l, 1 bone erosion or RF/ACPA	ACR/EULAR 2010, ≥6 TJ, ≥6 SJ, CRP > 3 mg/l	ACR/EULAR 2010, ≥6 TJ, ≥6 SJ, CRP > 3 mg/l	ACR/EULAR 2010, ≥6 TJ, ≥6 SJ, CRP > 5 mg/l, 3 erosions or 1 erosion and RF/ACPA	ACR/EULAR 2010, ≥6 TJ, ≥6 SJ, CRP > 3 mg/l

Upadacitinib group (monotherapy/combination)	Monotherapy	Monotherapy and combination with csDMARDs	Monotherapy	Combination with MTX	rheumatoid arthritis.
Principal outcome(s)	ACR50 at week 12 / DAS28CRP≤ 2.6 at week 24	ACR20 / DAS28CRP≤3.2	ACR20 / DAS28CRP≤3.2 at week 12	ACR20 / DAS28CRP≤3.2 at week 12	ACR20 / DAS28≤3.2 at week 12
Duration	24 weeks	12 weeks	14 weeks	48 weeks	24 weeks
Evaluation of radiographic progression as an important endpoint	Yes (mTSS at week 24)	No	No	Yes (mTSS at week 26)	No
Randomized population	945	1083	648	1629	499
Previous treatments received	100% MTX-naïve	100% previously treated with 1 to 2 csDMARDs, 13% previously treated with bDMARDs	100% previously treated with MTX, 0% previously treated with bDMARDs or JAKi	100% previously treated with MTX, 10% previously treated with bDMARDs	100% previously treated with bDMARDs (47% 1, 28% 2, 25% ≥3)
Main results for efficacy	Superiority demonstrated for both dosage versus MTX on ACR50 at 12 weeks and DAS28CRP < 2.6 at 24 weeks	Superiority demonstrated for both dosage versus placebo on ACR20 and DAS28≤3.2	Superiority demonstrated for both dosage versus MTX on ACR20 and DAS28≤3.2	Superiority demonstrated versus placebo and adalimumab on ACR20 and DAS28≤3.2	Superiority demonstrated versus placebo on ACR20 and DAS28≤3.2
	Superiority of both dosage versus MTX for radiographic progression at week 24			Superiority demonstrated versus placebo on radiographic progression at week 26	
	No direct comparison of the dosage	No direct comparison of the dosage	No direct comparison of the dosage		No direct comparison of the dosage
JAKi: JAK-inhibitors, MTX: methotrexate, SJ: swollen joints, TJ: tender / painful joints, RA: rheumatoid arthritis, RF/ACPA: rheumatoid factor and/or anti-citrullinated protein antibodies					

Table 4 Phase III studies with filgotinib

Population studied	**MTX naïve**	**Inadequate response to MTX**	**Inadequate response to a bDMARD**
Study name	FINCH 3[29]	FINCH 1[30]	FINCH 2[31]
Treatment arms	MTX	placebo	placebo
	Filgotinib 100 mg/d + MTX	adalimumab 40 mg biweekly	filgotinib 100mg/d
	Filgotinib 200 mg/d + MTX	filgotinib 100 mg/d	filgotinib 200 mg/d
	Filgotinib 200 mg/d	filgotinib 200 mg/d	
Main inclusion criteria	ACR/EULAR 2010, ≥6 TJ, ≥6 SJ, CRP ≥ 4 mg/l or FR/ACPA or ≥ 1 erosion	ACR/EULAR 2010, ≥6 TJ, ≥6 SJ, CRP ≥ 4 mg/l, ≥ 3 erosions or FR/ACPA and ≥ 1 erosion	ACR/EULAR 2010,≥6 TJ, ≥6 SJ, CRP ≥ 4 mg/l
Filgotinib group (monotherapy/combination)	MTX or monotherapy	MTX	stable csDMARDs
Principal outcome(s)	ACR20 at week 24	ACR20 at week 12	ACR20 at week 12
Duration	52 weeks	52 weeks	24 weeks
Evaluation of radiographic progression as an important endpoint	No	Yes (mTSS at week 24)	No
Randomized population	1252	1755	449
Previous treatments received	18% previous csDMARDs (<3 doses), 0% previous bDMARDs	100% previous csDMARDs, 3% previous bDMARDs	100% previous bDMARDs (77% <3 bDMARDs)
Main results for efficacy	Superiority of both doses of filgotinib in combination therapy over MTX	Superiority of filgotinib 200 and 100 mg vs placebo for ACR20 at week 12 and radiographic progression at week 24	Superiority of both dosage of filgotinib vs placebo

	Superiority of filgotinib 200 mg/d monotherapy over MTX not demonstrated	Non-inferiority of filgotinib 200 mg vs adalimumab	No direct comparison of the dosages of filgotinib
	No direct comparison of the dosages of filgotinib	Filgotinib 100 mg did not achieve non-inferiority vs adalimumab	
		No direct comparison of the dosages of filgotinib	
MTX: methotrexate, SJ: swollen joints, TJ: tender / painful joints, RA: rheumatoid arthritis			

Table 5 Phase III studies with peficitinib

Population studied	**Inadequate response to MTX**	**Naive or inadequate response to csDMARDs or bDMARDs**	**Inadequate response to at least one conventional synthetic or biological DMARD**
Study name	RAJ4[32]	RAJ1[33]	RAJ3[34]
Treatment arms	Placebo + csDMARDs	Placebo	Placebo +/- csDMARDs
	Peficitinib 100 mg/d	Peficitinib 25 mg/d	Etanercept +/- csDMARDs
	Peficitinib 150 mg/d	Peficinitib 50 mg/d	Peficitinib 100 mg +/- csDMARDs
		Peficinitib 100 mg/d	Peficitinib 150 mg +/- csDMARDs
		Peficitinib 150 mg/d	
Main inclusion criteria	ACR1987 or ACR/EULAR2010, ≥6/68 TJC, ≥6/66 SJC, CRP ≥10 mg/l, ≥1 erosion	RA > 10 yrs ACR 1987, ≥6/68 TJC, ≥6/66 SJC, CRP ≥5 mg/l	ACR1987 or ACR/EULAR2010, ≥6/68 TJC, ≥6/66 SJC, CRP ≥5 mg/l
Peficitinib group (monotherapy/combination)	Combination with MTX	Monotherapy	Monotherapy and combination with MTX
Principal outcome(s)	ACR20 at week 12	ACR20 at week 12	ACR20 at week 12
Duration	52 weeks	12 weeks	52 weeks

Evaluation of radiographic progression as an important endpoint	Yes (mTSS at week 28)	No	No
Randomized population	519	281	507
Previous treatments received	100% previously treated with MTX, 15.5% to 22.4% previously treated with bDMARDs	85.5% to 93.1% previously treated with MTX, 25.3% previously treated with TNFi	89.5% previously treated with MTX, 7.1% previously treated with bDMARDs (0%≥3)
Main results for efficacy	Superiority demonstrated for both doses versus placebo on ACR20	Superiority demonstrated of all dosage versus placebo on ACR20	Superiority demonstrated for both dosage versus placebo on ACR20
	Superiority of both dosage vs placebo for radiographic damage	Statistically significant dose response on ACR 20 response rates at week 12	No direct comparison of both dosage of peficitinib
	No direct comparison of both dosage of peficitinib		Etanercept was set as an open-label anti-TNF reference arm and was not included in statistical comparisons with other arms
MTX: methotrexate, SJC: swollen joints count, TJC: tender / painful joints count, RA: rheumatoid arthritis			

Table 6 Real world effectiveness studies of JAK-inhibitors

Database	**Marketscan**[38]	**Corrona/CorEvitas**[41]	**SCQM** [42]	**TBCR**[43]	**OPAL**[44]	**Leeds Teaching Hospitals NHS Trust**[45]
Database type	Insurance claims	Disease register	Disease register	Treatment register	Electronic health record	Treatment register completed with medical records
Country	USA	USA	Switzerland	Japan	Australia	UK (single centre)
Main inclusion criteria	RA code, previous MTX treatment claim, new	RA diagnose, new treatment with tofacitinib or TNFi	RA diagnose, new treatment with	RA diagnose, new treatment by bDMARD or	RA diagnose in the clinical record, new treatment with	RA diagnose, treatment with

	treatment claim with other csDMARDs, bDMARDs or tofacitinib	and follow-up for at least 6 months	TNFi, JAKi or other bDMARDs	tsDMARD and followed for at least 24 weeks	bDMARD and tofacitinib, at least 1 year of follow-up	tofacitinib or baricitinib
JAKi group (monotherapy /combination)	Monotherapy and combination with csDMARDs	Monotherapy and combination with csDMARDs	Monotherapy and combination with csDMARDs	Monotherapy and combination with csDMARDs	Monotherapy and combination with csDMARDs	Monotherapy and combination with csDMARDs
Treatment arms	csDMARDs	Tofacitinib alone	Tofacitinib	Baricitinib	Tofacitinib	Tofacitinib and baricitinib
	TNFi	Tofacitinib + csDMARDs	TNFi		bDMARD	
	Other bDMARDs	TNFi alone	Other bDMARDs			
	Tofacitinib	TNFi + csDMARDs				
Principal outcome(s)	Effectiveness according to a claim-based algorithm including high adherence (medications claims or treatment-related procedures claims), no new treatment during follow-up, no csDMARD switch or addition, no increase in dose or frequency of index drug, no more than 1 glucocorticoid joint injection between month 4	CDAI low disease activity or remission at 6 months	Drug retention	DAS28CRP in 4 categories at 4, 12, 24 and 52 weeks	DAS28-ESR, CDAI and SDAI remission/low disease activity at 18 months	DAS28-CRP change

	and 12 of follow-up, no new/increased oral glucocorticoid dose during the first year after inclusion					
Duration	4 years	3.5 years	6 years	24 to 52 weeks	3.5 years	5 years
Observed	164 tofacitinib, 13367 TNFi, 2902 other bDMARDs, 5399 csDMARDs	558 tofacitinib, 8014 TNFi	793 tofacitinib, 1847 TNFi, 1338 other bDMARDs	113 baricitinib	650 JAKi, 1300 bDMARDs	123 JAKi (54 tofacitinib, 69 baricitinib)
Previous treatments received in the JAKi group	100% previous MTX, not described for other previous treatments	89% at least 1 previous bDMARDs, most patients in third or fourth line of therapy	26% bio-naïve, 22% 1 bDMARDs, 20% 2 bDMARDs, 32% ≥ 3 bDMARDs	Mean of 2 previous b or tsDMARDs	Not described	Median of 3 previous treatment, 17.1% 1 previous treatment, 20% 2, 39% 3, 26%4, 6% 5
Main results for effectiveness	Adjusted risk ratio for effectiveness similar to non-TNF biologics (not directly compared to TNFi)	Matched odds ratio of achieving CDAI LDA/remission similar between tofacitinib mono and combo in third and fourth lines of therapy	Adjusted hazard ratio of discontinuation higher with TNFi compared with tofacitinib and similar between other bDMARDs and tofacitinib	Significant decrease of the DAS28-CRP score from a mean of 3.55 ± 1.21 at baseline to 2.65 ± 1.06 at 4 weeks and 2.32 ± 1.03 at 24 weeks	No significant differences in the DAS28-ESR remission and LDA proportion between bDMARD and tofacitinib groups in the matched comparison	Only descriptive: decrease of DAS28 by a mean of -1.48 at 3 months and -1.67 at 6 months
		Matched odds ratio of achieving CDAI LDA/remission similar between tofacitinib combo and TNFi combo in third and fourth lines of therapy	Adjusted hazard ratio of discontinuation similar between tofacitinib mono and combo	Significant increase of the proportion of patient in DAS28-CRP low disease activity from 26.7% to 68.2% at 24 weeks	No significant differences in the SDAI or CDAI remission proportion between bDMARD and tofacitinib groups in the matched comparison	

		Matched odds ratio of achieving CDAI LDA/remission similar between tofacitinib mono and TNFi combo in third and fourth lines of therapy				
Lost to follow-up management	The algorithm would classify them as non-responder	Not included if not at least 6 months of follow-up	Retention takes into account lost to follow-up	Not included if not at least 24 months of follow-up	Not described	Not included
Missing data management	The algorithm would classify them as not present	Not described	Multiple imputation	Not described	Not clearly described but probably complete case analysis	Not described
Confounding factors taken into account	Sex, age, year, previous glucocorticoid use, NSAID use, COX-2 inhibitor use, Charlson comorbidity index, infection related hospitalisation, emergency department visit, physician visit, rheumatology visit and number of hospitalisations in the year prior to cohort entry	Tofacitinib mono vs combo: race, work status, insurance, patient global assessment, and CDAI	Line of therapy, DAS28, disease duration, seropositivity (RF or ACPA) and patient characteristics, namely sex, age, tobacco smoking and body mass index (BMI).	No adjusted analysis but not comparative	Age, sex, concomitant treatment	No adjusted analysis but not comparative

		Tofacitinib combo vs TNFi combo: gender, age, duration of RA, work status, insurance, patient global assessment and morning stiffness				
		Tofacitinib mono vs TNFi combo: gender, age, race, duration of RA, work status, smoking status, insurance, body mass index,				
JAKi: JAK-inhibitors, LDA: low disease activity, RA: rheumatoid arthritis						