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REVIEW

JAK Inhibitors in Rheumatoid Arthritis: An Evidence-Based Review on the Emerging Clinical Data

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Abstract: Janus kinase (JAK) Inhibitors are the latest drug class of disease-modifying medication to emerge for the treatment of rheumatoid arthritis (RA). They are a small molecule-targeted treatment and are the first oral option to compare favourably to existing biologic disease-modifying anti-rheumatic drugs (DMARDs). Tofacitinib, baricitinib and upadacitinib are the first 3 JAK inhibitors to become commercially available in the field and are the core focus of this review. To date, they have demonstrated comparable efficacy to tumour necrosis factor (TNF) inhibitors in terms of American College of Rheumatology (ACR) response rates and disease activity (DAS28) scores with similar cost to the benchmark adalimumab. This narrative review article aims to synthesise and distil the key available trial data on JAK inhibitor efficacy and safety, along with their place in the ACR and European League Against Rheumatism (EULAR) guidelines for RA. The novel mechanism of action of the JAK/STAT pathway is highlighted along with the potential effects of modulating each pathway. The rapid onset of action, role in attenuation of central pain processing and effect on structural damage and radiographic progression are also all examined in detail. We also explore the latest meta-analyses and comparative performance of each of the 3 available JAKs in an effort to determine which is most efficacious and which has the most favourable safety profile. Post marketing concerns regarding thromboembolism risk and herpes zoster infection are also discussed. Additionally, we review the cost-benefit analyses of the available JAK inhibitors and address some of the pharmacoeconomic considerations for real-world practice in the UK and US by detailing the raw acquisition cost and the value they provide in comparison to the benchmark biologic adalimumab and the anchor DMARD methotrexate.

Keywords: rheumatoid arthritis, immunosuppressive therapies, JAK inhibitors, targeted synthetic DMARD, tsDMARD

Introduction

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease, causing progressive damage to the synovial lining of joints. Left untreated RA can cause significant pain, deformity, loss of manual function and deterioration in overall quality of life. Since the late 1990s, methotrexate (MTX) has been the anchor disease-modifying anti-rheumatic drug (DMARD) for RA.[1] While MTX was an undoubted breakthrough in treatment options, not all patients achieve the desired response with approximately 30% discontinuing treatment within the 1st year due to a lack of efficacy or side effects.[2] As a result, there has been a continued drive to better understand the

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pathophysiology of RA and explore other potential therapeutic targets in an effort to develop and bring to market more viable treatments and alternatives.

The past two decades have seen the introduction of multiple biologic DMARDs (bDMARDs) which were seen as a less crude and more targeted form of immunosuppression than the broader effects of MTX, which was originally developed as a form of chemotherapy in the 1950s. Despite the arrival of tumour necrosis factor (TNF) inhibitors, B cell depletion of CD20 cells and interleukin 6 (IL-6) inhibition, there remains a sizeable cohort of RA patients with suboptimal control, loss of response or intolerability to the existing bDMARDs.

The newest class of drugs in RA treatment are the Janus kinase (JAK) inhibitors. JAK inhibitors are small-molecule oral treatments which have become widely available and they offer the first truly clinically efficacious long-term oral biologic option in RA. The discovery of the role of the JAK and the signal transducer and activator of transcription (STAT) constituents in cytokine signalling and RA pathogenesis has resulted in firstly, a novel targeted therapy and secondly, a targeted low molecular mass drug that can pass the lipid bilayer of the cellular membrane. As such JAK inhibitors were initially heralded for their targeted "smarter" mechanism of action and their oral route of delivery which was perceived as being very appealing to patients. However, in contrast, much has been written about herpes zoster infection rates, venous thromboembolism (VTE) risk, comparative clinical efficacy with established biological disease-modifying anti-rheumatic drugs (bDMARDs), radiographic structural progression over time, and the role of the JAK/STAT pathway on pain perception in central pain syndromes. This review will focus on the Jaki currently available for use in rheumatic diseases, tofacitinib, baricitinib and upadacitinib. Other Jaki that are in late-phase clinical trials or used in other diseases (peficitinib decernotinib, itacitinib, ruxolitinib) will not be the focus of this review.

The JAK/STAT Pathway

The JAK family is comprised of several different subtypes, notably JAK1, JAK2, JAK3 and TYK2 in addition to a multitude of STAT proteins, STAT 1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6. The pathway is initiated by a ligand/cytokine acting as an extracellular signal and binding to a receptor on the cell membrane which in turn causes a structural or conformational change and thus consequent activation of the implicated JAK isoforms that are either homodimers or heterodimers. Via a process of JAK auto-phosphorylation, a docking site is created for the STAT protein which itself undergoes phosphorylation upon binding. The JAKs facilitate transportation or translocation of the STAT proteins into the cell nucleus whereby gene expression is initiated followed by protein synthesis.

The main cytokines that operate through the JAK/STAT pathway include interleukins IL4, IL-6, IL 10, IL-12, IL-23, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), erythropoietin (EPO), thrombopoietin (TPO), leptin and growth hormone (GH), Table 1.[3–5]

Figure 1 demonstrates a simplified illustration of the functional effect of the JAK/STAT signalling pathway. Various different combinations of JAKs and STATs assemble into complex multimers with a wide range of resultant biochemical and biophysiological effects within the cell and on the host at a broader systemic level, Table 1. Deficiencies of certain JAKs, or indeed genetic gain of functions of other JAKs, are the aberrant pathological basis of a broad spectrum of disease states. Gain of function genetic mutations in JAK1 can cause lymphoid neoplasms while gain of function mutations in JAK2 can cause myeloproliferative neoplasms.[6–9] JAK3 genetic loss of function is strongly linked to Severe Combined Immunodeficiency (SCID) while STAT3 deficiency is associated with Hyper-IgE syndrome and interestingly chronic activation of JAK2-STAT3 by leptin and IL−6

Table 1 JAK/STAT and Cytokine Interactions

Cytokine	JAKs	Broad Effect
IFNα, IFNβ, IL-10	JAK1 & TYK2	Antiviral Immunity
IFNγ	JAK1 & JAK2	Antiviral Immunity
IL-6, IL-11	JAK1, JAK2 & TYK2	Acute Phase Inflammatory Response
IL-12, IL-23	JAK2 & TYK2	Th17 Cell Differentiation
IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-19, IL-21	JAK1 & JAK3	White Cell Differentiation
G-CSF, GM-CSF, EPO, TPO, IL-3, IL-5 Growth hormone, prolactin Leptin	JAK2 & JAK2	Myeloid Cell Differentiation Metabolic homeostasis

Note: Data from references 13 and 14.

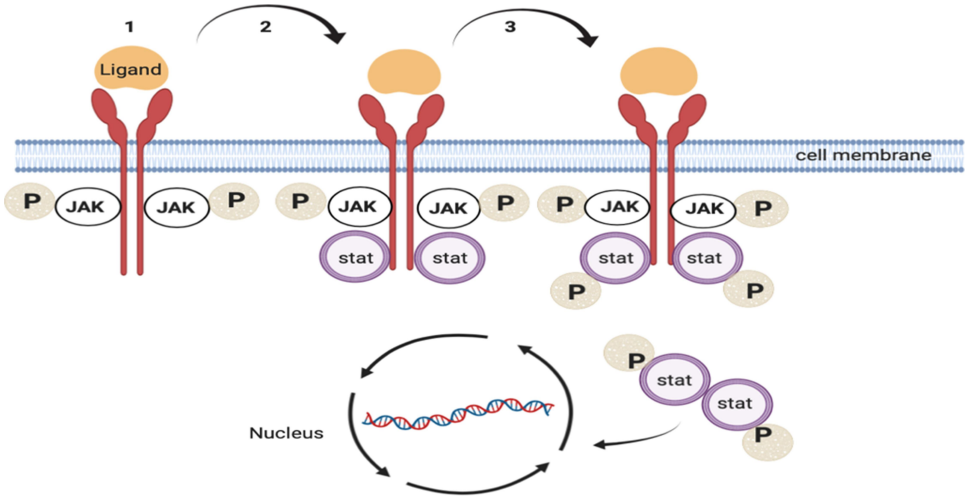


Figure 1 Simplified representation of the JAK/STAT signalling pathway: 1. Ligand binding to the extra-cellular domain of the homodimer or heterodimer cytokines receptor, the latter is activated and auto-phosphorylation occurs, 2. STAT proteins bind to the activated receptor, 3. STAT proteins are phosphorylated followed by nucleus translocation and protein synthesis.

has been linked with obesity due to impair proper leptin and insulin action.[10–12]

JAK Inhibitors in Rheumatoid Arthritis

Tofacitinib was the first commercially available JAK inhibitor developed and brought to market for the treatment of RA. Its development was undertaken in the mid-1990s by a joint public–private partnership between the National Institute of Health (NIH) and Pfizer.[13] It was approved by the Food and Drug Administration (FDA) in November 2012 at 5mg BD dose and brought to market under the brand name Xeljanz. The original target cohort was intended to be adults with moderately to severely active RA who have had an inadequate response to, or who are intolerant of methotrexate.[14] Tofacitinib was finally approved by the European Medicines Agency (EMA) in March 2017 after over 4 years of post-marketing safety surveillance in North America.

Further interest in the JAK pathway within the pharmaceutical industry resulted in the development of Baricitinib (Oluminant) by Eli Lilly and Upadacitinib (Rinvoq) by AbbVie, receiving FDA approval in May 2018 and August 2019, respectively. There are a few key differences in the therapeutic targets of each of JAK inhibitor. Tofacitinib is a pan JAK inhibitor with greater selectivity for JAK1/JAK3 with minor activity on JAK2 and TYK2. Baricitinib is a JAK1/JAK2 inhibitor with moderate activity against TYK2 and minimal activity against JAK3.[15,16] Upadacitinib aims to solely target the JAK1 pathway. The rationale here being that more specific selectivity of JAK inhibition may reduce dose-related toxicity and side effects without a significant loss of efficacy.[17] Currently, commercially available JAK inhibitors are detailed in Table 2.

Tofacitinib Efficacy and Radiographic Progression

During the FDA approval process, all 7 of tofacitinib's Phase III randomised control trials (RCTs) showed the efficacy of inhibiting JAK1/JAK3 in RA. ORAL-START demonstrated significantly higher ACR20, ACR50 and ACR70 response rates in tofacitinib 5mg and 10mg BD dosing than MTX monotherapy at both 6 and 24 months.[18] A post hoc study of ORAL-SCAN highlighted tofacitinib's efficacy versus placebo regardless of the background methotrexate dose.[19] In ORAL-STRATEGY, tofacitinib + MTX was noninferior to adalimumab + MTX. However, tofacitinib monotherapy did not fare as favourably as the combination of adalimumab + MTX. This suggests that the synergistic effect of tofacitinib + MTX is preferable to tofacitinib monotherapy in moderate to severe RA in terms of disease control, if the combination is tolerable for the patient.[20] Progression of structural joint damage was also assessed using the modified van der Heijde Total Sharp Score. In ORAL-START, tofacitinib monotherapy was shown to be superior to MTX monotherapy in limiting progression of structural damage.[18]

Baricitinib Efficacy and Radiographic Progression

Baricitinib successfully progressed through 4 global phase III RCTs during the approval process. In RA-BEGIN,

Table 2 Commercially Available JAK Inhibitors

JAK Inhibitors in RA							
JAK Inhibitor	**Pharma Company**	**Target (Selectivity)**	**Trials**	**Recommended Dose**	**FDA Approval**	**EMA Approval**	**Japan Approval**
Tofacitinib (Xeljanz)	Pfizer	JAK1 & JAK3 (strong/high) JAK2 (minor) TYK2 (minor)	ORAL Solo[63] ORAL Standard[64] ORAL Scan[65] ORAL Step[66] ORAL Sync[67] ORAL Start[68] ORAL Strategy[20] ORAL Sequel[69]	5mg BD 11mg OD	November 2012	March 2017	March 2013
Baricitinib (Olumiant)	Lilly	JAK1 & JAK2 (strong/high) TYK2 (moderate) JAK3 (minor)	Phase 2 NCT00902486 Phase2b NCT01185353[70] Phase 2b NCT01469013[71] RA-Beacon[72] RA-Build[73] RA-Begin[21] RA-Beam[74] RA-Balance[75] RA-Beyond[76]	2mg OD 4mg OD	May 2018	February 2017	July 2017
Upadacitinib (Rinvoq)	AbbVie	JAK1 (strong/high)	SELECT-Beyond[77] SELECT-Next[78] SELECT-Monotherapy[79] SELECT-Choice[80] SELECT-Compare[81] SELECT-Early[82] NCT02955212	15mg OD	August 2019	December 2019	January 2020
Filgotinib (Jyseleca)	Gilead & Galapagos	JAK1 (strong/high)	DARWIN1[83] DARWIN2[84] DARWIN3 NCT02065700 FINCH1 NCT02889796 FINCH2[85] FINCH3 NCT02886728 FINCH4 NCT03025308	100mg OD 200mg OD	–	–	–
Peficitinib (Smyraf)	Astellas Pharma	JAK3 (moderate) JAK1 (minor) JAK2 (minor) TYK2 (minor)	RAJ1[86] RAJ2[87] RAJ3[88] RAJ4[89]	100mg OD 150mg OD	–	–	March 2019
Decernotinib	Vertex	JAK3 (strong/high)	Discontinued			–	

(*Continued*)

Table 2 (Continued).

JAK Inhibitors in RA							
JAK Inhibitor	**Pharma Company**	**Target (Selectivity)**	**Trials**	**Recommended Dose**	**FDA Approval**	**EMA Approval**	**Japan Approval**
Itacitinib	Incyte	JAK1 (strong/high)	NCT01626573[90]	100 mg BID 300 mg QD 200 mg BID 600 mg QD	–	–	–
Ruxolitinib (Jakavi)	Incyte Corp (US) Novartis	JAK1 & JAK2 (strong/high)	NCT00550043[91]	5 mg BID 15mg BID 25mg BID 50mg QD	–	–	–

Note: Data from references 17–21.

baricitinib monotherapy and baricitinib + MTX was compared with MTX monotherapy in RA patients with little to no prior conventional DMARD use. Comparison was favourable with baricitinib monotherapy demonstrating superior efficacy to MTX monotherapy at 24 weeks with a p-value of less than 0.01. Statistically significant improvements were consistently observed in baricitinib monotherapy and baricitinib + MTX compared to MTX monotherapy for ACR20, ACR50 and ACR70 response rates.[21]

In RA-BEAM, baricitinib, both as monotherapy and in combination with MTX, was compared with adalimumab and placebo in biologic naïve RA patients with poor response to prior MTX treatment. Baricitinib was found to be non-inferior to adalimumab at week 12 for the ACR20 response with a noninferiority margin of 12% (70% vs 61%, 95% confidence interval for the difference between groups, 2% to 15%). The authors note that according to the statistical analysis plan, it can be deduced that baricitinib was as a result significantly superior to adalimumab ($p<0.01$). Furthermore, baricitinib was superior to adalimumab with respect to the mean change in DAS28-CRP score at week 12 (−2.24 for baricitinib and −1.95 for adalimumab, $p<0.001$). Baricitinib's time to effect is also noted as a strength of the medication, with significant superiority to placebo after 1 week and to adalimumab at 2 to 4 weeks.

Reduction in radiographic progression using the modified van der Heijde score was seen at week 24 for both baricitinib and adalimumab when compared with placebo.[22] Baricitinib + MTX also demonstrated statistically superior reduction in radiographic progression when compared with MTX monotherapy.[23]

Upadacitinib Efficacy and Radiographic Progression

As a JAK1 inhibitor, upadacitinib tested the hypothesis that selective inhibition of only JAK1 could obtain the same clinical efficacy in RA treatment as a more non-selective JAK inhibitor such as tofacitinib and baricitinib, while achieving a better safety profile. In the SELECT-EARLY and SELECT-MONOTHERAPY RCTs, upadacitinib showed a significantly greater clinical response at 15mg and 30mg compared to MTX in ACR50 response (52.1%, 56.4%, and 28.3%, $p<0.001$) and DAS28-CRP <2.6 rate (35.6%, 40.8%, and 13.7%) at week 12.[24,25]

In SELECT-COMPARE, upadacitinib + MTX was compared with adalimumab + MTX in RA patients with previous inadequate response to MTX. At week 12 superiority was achieved for upadacitinib + MTX versus adalimumab + MTX with ACR 20 (70.5% vs 63%, $p<0.05$), ACR50 (45.2% vs 29.1%, $p<0.01$) and DAS28-CRP ≤3.2 (45.0% vs 28.7%). Using the modified van der Heijde score, erosion score, and joint space narrowing as metrics of radiographic progression, upadacitinib and adalimumab performed similarly. Significantly more patients randomised to upadacitinib (86%) or adalimumab (88%) had no radiographic progression versus placebo (74%) ($p\leq0.001$).[26]

Comparative Efficacy of the Approved JAK Inhibitors for RA

To date, there has not been a head-to-head trial for any of the available JAK inhibitors approved in RA. In attempting to answer this question Lee & Song performed a network meta-analysis.[27] This meta-analysis included 4

RCTs; namely ORAL Strategy, RA-BEAM, FINCH1 & Fleischman 2019.[22,26,28,29]

This meta-analysis showed that in RA patients with an inadequate response to MTX, baricitinib 4mg + MTX and upadacitinib 15mg + MTX showed the highest ACR response rates. Additionally, it demonstrated a significantly higher ACR20 response rate with both baricitinib 4mg + MTX and upadacitinib 15mg + MTX when compared to adalimumab 40mg + MTX. With regard to the issue of herpes zoster infection (HZV), placebo + MTX ranked as the safest treatment in terms of risk of HZV infection, with baricitinib + MTX carrying the highest risk of infection. Interestingly, filgotinib 200mg + MTX ranked as the 2nd safest combination strongly suggesting that discrete targeting of JAK1 alone carries similar efficacy with an improved safety and side effect profile compared to non-specific JAK inhibition. The authors do note however that adalimumab + MTX carries the lowest risk or probability of a severe adverse event (SAE) while baricitinib + MTX carries the highest risk.[27]

Given adalimumab is the common comparator in all 4 RCTs and it is also the most commonly prescribed bDMARD in our country, we have used these trials for our own meta-analysis (Figure 2). Using Cochrane's RevMan 5 meta-analysis software and a Mantel Haenszel test with fixed effects, the following forest plots for multiple JAK inhibitors and the comparator adalimumab were created for the odds ratio of achieving ACR20, 50 and 70 response rates. The results of this analysis would suggest that both baricitinib 4mg OD + MTX and upadacitinib 15mg OD + MTX are superior to adalimumab 40mg + MTX in terms of achieving a meaningful ACR70 response rate.

Side Effect Profile

The most frequently reported adverse events with JAK inhibitor treatment in RA patients are infections.[30] While the incidence of common infections such as upper respiratory tract, lower respiratory tract, and urinary tract infections are higher compared with the general population, the incidence is still similar to bDMARDs.[30,31] It is notable that trials to date suggest a lower risk of infection with tofacitinib in comparison to TNF inhibitors, rituximab and tocilizumab, JAK inhibitors carry a slightly lower rate of severe infection with a frequency of (2.7–3.1) per 100 patient-years as compared to between 3 and 5 per 100 patient-years in bDMARDs. Tuberculosis was seen at a frequency of 1.5 per 1000 patient-years. As a result, quantiferon testing should still be performed as part of screening prior to introduction of JAK inhibitors.[30–32]

Herpes Zoster Infection

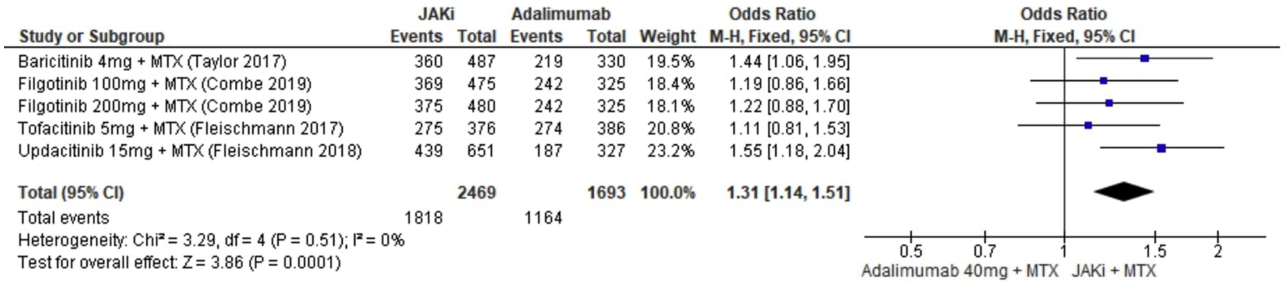
Herpes zoster (HZV) infection is seen more frequently in RA patients compared with the background population. Much of the risk can be attributed to age and the immunosuppression secondary to chronic use of corticosteroids.[33] However, the exploration and development of drugs acting on the JAK pathway raised concern of markedly increased risk of HZV infection. Pooling data from tofacitinib RCTs revealed an incidence rate of HZV 1.5 to 2 fold higher than normally seen in the RA population and higher than the observed rate in those on bDMARDs. Some of the risks can be explained by geographic distortion or ethnicity as rates of HZV were increased in Asia at 9.2 per 100 patient-years and India at 8.9 patients. Rates were significantly lower in Western Europe and North America at 2.7 and 3.3 per 100 patient-years respectively. This may reflect the effect of downregulation of interferons and IL−15 responsible for viral elimination. Reassuringly, multi-dermatomal, and disseminated herpes zoster were uncommon, with no cases of visceral disease or death with tofacitinib treatment.[34,35]

Cytopenias

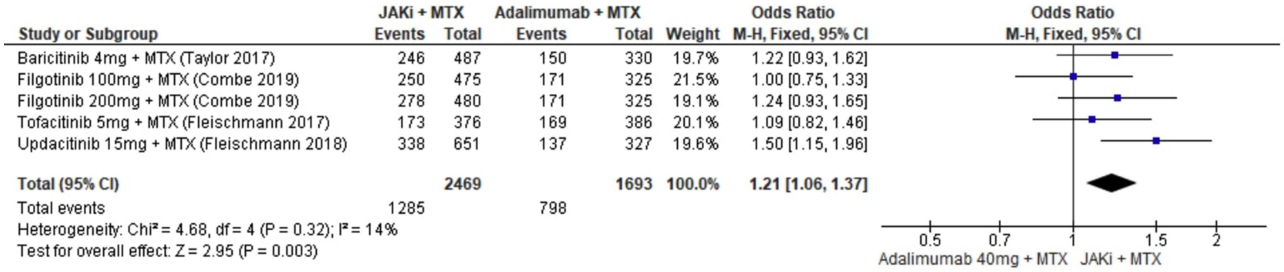
Cytopenias can be seen with all JAK inhibitors in clinical use in RA. It is this cytopenic effect that is the mechanism of action of the JAK inhibitor Ruxolitinib which is used in myeloproliferative disorders. As mentioned previously, it is well known that the JAK2 pathway is implicated in lymphomas and leukaemias, so while JAK inhibitors may have a protective effect in this regard, the physician needs to remain vigilant of cytopenia, particularly the effects of neutropenia and lymphopenia and the risk of infection this confers.[32,36,37] Although cytopenia is a common adverse effect of JAKi, there are multiple reasons for anaemia in RA, and tofacitinib can slightly increase haemoglobin level due to less inhibitory effect on JAK2 which is responsible for erythropoietin signalling. Paradoxical transient modest elevation of platelets has been noticed with baricitinib at 2 weeks, hypothesised to be due to suboptimal dosing, but no negative consequences of this have been reported.[34,38,39]

Thrombosis

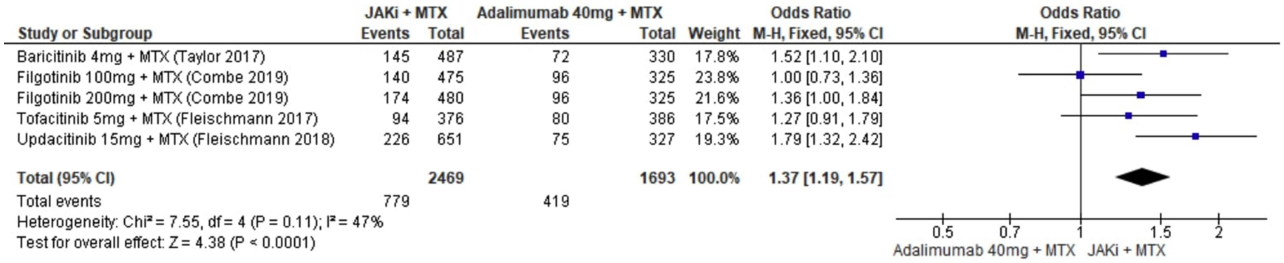
The FDA and post-marketing safety surveillance have revealed an increase in risk of pulmonary embolism (PE) and death with the 10mg twice daily dose of tofacitinib in



ACR20 Response Rate Forest Plot



ACR50 Response Rate Forest Plot



ACR70 Response Rate Forest Plot

Figure 2 Forest plot comparing the JAKs to adalimumab.

RA patients. This dose is not approved in RA and is only approved for ulcerative colitis. Discovery of this increased risk of PE over time is in contrast to the initial reassuring data derived from pooled analyses of RCTs. As a result, rheumatologists must be cognisant of a history of prior venous thromboembolism before considering commencing a JAK inhibitor. From the mechanism of action of JAK inhibitors, this risk is not immediately obvious since these medications can cause predominantly thrombocytopenia rather than thrombocytosis.[30,40]

Malignancy

To date, extensive meta-analyses have revealed no significantly increased risk of malignancies in patients treated with either tofacitinib or bDMARDs when compared to treat with cDMARDs or placebo.[30,41]

Lipid Levels and Cardiovascular Events

It is well established that tofacitinib and baricitinib increase LDL cholesterol in RA patients.[34] It is believed chronic inflammation in the setting of RA causes falsely low levels of LDL which do not correlate with the increased atherosclerotic risk seen in RA and chronic inflammation. As a result, the current thinking is that both JAK inhibitors and bDMARDs correct these low levels of LDL without negatively impacting cardiovascular risk. The LDL/HDL ratio remains stable with JAK inhibitor treatment suggesting negligible impact on long-term

cardiovascular risk. This is consistent with lipid profiles seen in psoriasis patients on tofacitinib treatment.[32,37,42] Pooled studies on cardiovascular risk in RA patients on the approved doses of tofacitinib or baricitinib have not demonstrated an increase in risk compared with placebo.[43]

Weight/Adiposity

There is conflicting information on the effects of JAK inhibitors on adiposity in RA patients.

It is known than JAK2 is a component of the intracellular insulin-like growth factor 1 (IGF−1) and growth hormone (GH) signalling axis. Weight gain is clearly demonstrated for ruxolitinib which is used in myeloproliferative disorders, but the same effect has also been observed with both tofacitinib and baricitinib.[32,36,44,45] Conversely, a 2014 study discovered that tofacitinib was able to convert white adipocytes into the more metabolically active brown adipocytes, suggesting a possible mechanism of action that may have potential in the treatment of obesity.[46] In younger RA patients, there is an argument that better disease control with JAK inhibitors will result in improved exercise capacity, and subsequent weight loss, due to reduced stiffness, pain and fatigue.

Pain

The measure or metric of effective RA disease control from the perspective of the rheumatologist and the patient are not necessarily one and the same. With bDMARDs becoming ubiquitous and the more recent introduction of the JAK inhibitor class, there has been a strict focus on the treat-to-target approach of inflammatory disease activity. The principal concerns of the patients however are the reduction of pain and fatigue and restoration of physical function and vitality.[47–49]

In a survey of 1204 RA patients, 68.6% reported pain as the most important area required for health improvement.[50] From the physician's perspective, a lot of focus is directed at markers of inflammation and radiographic progression as the proxies for adequate disease control, while the patient's focus remains on pain reduction.

Pain in RA has generally been attributed to peripheral nociceptive aetiologies such as ongoing inflammation and synovial damage.[51] However, patient reports of pain persistence after achieving strict disease activity targets are common. Despite normalisation of inflammatory markers, halting of radiographic progression and absence of synovitis clinically, pain often persists and subjective measures of quality life such as energy and fatigue levels do not improve.[52,53] This strongly suggests that peripheral and central pain-processing mechanisms that are upregulated by repeated stimulus through inflammation are not effectively downregulated by traditional cDMARDs or bDMARDs, despite control of disease at the level of the synovium. It has been demonstrated that RA patients demonstrate heightened sensitivity to nociceptive stimuli. In conjunction with this, studies in rat models suggest that JAK/STAT signalling can promote mechanical pain sensitivity.[54] Blocking IL-6 by targeting JAK-STAT3 activity in these animal models substantially reduces mechanical allodynia and suggests a potential role for JAK inhibitor use in humans for downregulating central pain processing pathways which are firing aberrantly due to prior chronic inflammation.

In terms of mechanism of action, tofacitinib blocks multiple cytokines via JAK3 but it also inhibits IL-6 via JAK1 inhibition. Indeed, some patients report pain relief within the first 24 hours of commencing JAK inhibitors, long before there is any biochemical improvement in CRP or ESR.[55] The goal of determining differences between JAK inhibitors, TNF inhibitors, and IL-6 inhibitors in improvement in pain and physical function was achieved through an extensive matching adjusted indirect comparison (MAIC) using data from RCTs. It determined that among patients naïve to cDMARDs and bDMARDs, baricitinib 4mg provides statistically significant greater pain reduction and improvement in physical function compared with adalimumab 40mg and tocilizumab 8mg/kg. There was no discernible difference between baricitinib and tofacitinib with respect to pain or physical function in 2 of 3 of these analyses.[56]

An important learning point to consider here is that baricitinib shows superior improvement in pain compared to adalimumab. One hypothesis suggests a role of GM-CSF and IL6 in osteoarthritic and neuropathic pain, respectively. By targeting JAK2 signalling pain pathways are attenuated and downregulated.[57] However, baricitinib does not show superior efficacy to adalimumab in terms of halting or retarding radiographic progression of structural damage. In fact, the modified van der Heijde score for adalimumab is superior to baricitinib at week 24. Longitudinal studies over many years would be required to determine if there is a true difference in effect on structural damage between the two drugs. What can be said at this point is that in RA patients baricitinib is superior to adalimumab in pain improvement yet it is inferior to adalimumab in terms of the modified van der Heijde score

at week 24. This in conjunction with the fact that some patients report pain reduction within the first 1 to 2 doses of tofacitinib or baricitinib implies that JAK inhibitors not alone decrease systemic inflammation in RA, but may also be efficacious in central pain syndromes.

ACR and EULAR Guidelines

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have produced congruent guidelines for the treatment of RA. While both the ACR 2015 and EULAR 2019 guidelines affirm MTX monotherapy as the 1st line treatment, JAK inhibitors are now considered a viable option as 2nd line treatment in moderate or high disease activity refractory to MTX monotherapy. JAK inhibitors are now viewed on equal footing with TNF inhibitors and non-TNF biologics such as abatacept, tocilizumab and rituximab. While it may take some time for physician prescribing practices to change, the availability of an equally efficacious oral option is particularly appealing to many patients. Figure 3 demonstrates a simplified flowchart of the existing treatment guidelines.[58,59]

Pharmacoeconomic Considerations

Drug class availability within public healthcare systems may differ from country to country and is based on robust cost-benefit analysis. Quality adjusted life years (QALYs) gives a useful metric for such pharmacoeconomic considerations within a healthcare system. Referral to the report on JAK inhibitors for RA by the Institute for Clinical and Economic Review (ICER) shows the relative cost of each treatment, Table 3. New treatments are benchmarked against the anchor cDMARD MTX and the most commonly prescribed bDMARD adalimumab.[60]

Using the raw wholesale acquisition cost (WAC) as the comparator, tofacitinib and baricitinib are approximately 68 and 32 times more expensive per annum than MTX monotherapy in the US. While both tofacitinib and baricitinib appear to compare favourably to adalimumab in the ICER report, it does not explain the full story given the variability in WAC country to country. There are multiple adalimumab biosimilars now available as AbbVie's Humira patent expired in Europe in 2017. For example, in the NHS, the acquisition cost is a fraction of that in the US. In 2018, as per the British National Formulary (BNF), the annual cost to the NHS for a year's supply of adalimumab is approximately $10,700 as compared to approximately $60,000 in the US cited in the National Average Drug Acquisition Cost (NADAC), Table 4.[61,62] As per the BNF, the annual cost of tofacitinib 5mg BD in the UK is £9000 or $11,400 in 2020. This compares to $55,480 in the US, again as per data from the NADAC.

Interestingly, the ICER report determined that there was sufficient evidence that upadacitinib plus cDMARD

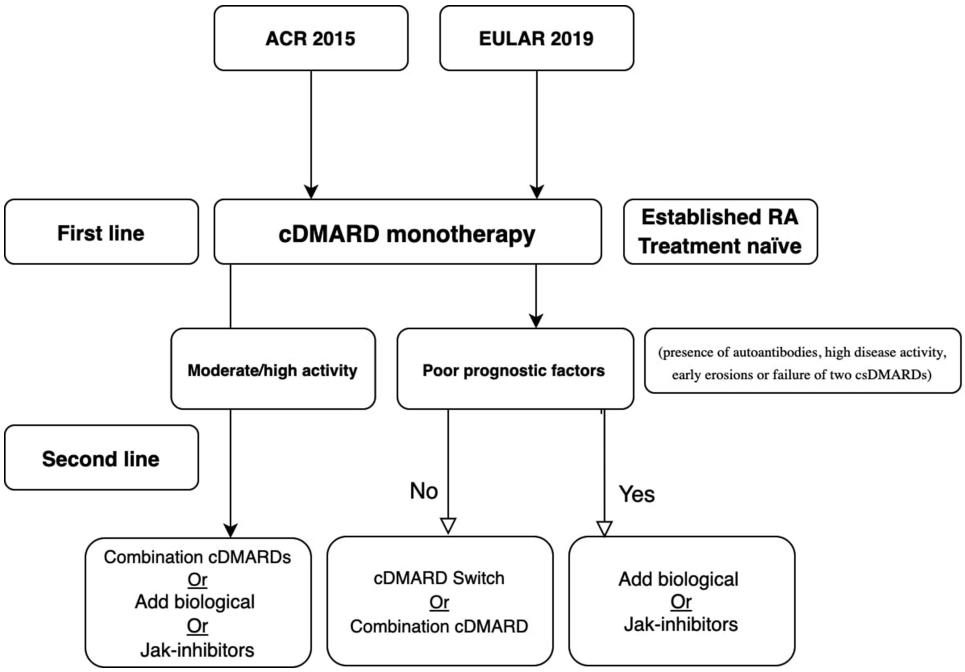


Figure 3 Simplified overview of ACR 2015 and EULAR 2019 guidelines for management of RA.

Table 3 Drug Costs from ICER Report

Drug	WAC per Unit	Discount from WAC	Net Price per Unit	Annual WAC	Annual Net Price
Upadacitinib 15mg Tab	$163.89	26%	$120.56	$59,680	$44,035
Baricitinib 2mg Tab	$71.23	19%	$57.59	$26,017	$21,033
Tofacitinib 5mg Tab	$74.68	34%	$49.50	$54,552	$36,159
Adalimumab 40mg/0.8mL sol	$2587.05	34%	$1696.21	$67,263	$44,102
Methotrexate 2.5mg Tab	$2.55	–	$2.55	$796	$796

Note: Data from reference 95.

Table 4 US vs UK Pharmacoeconomic Comparison June 2020 (US Dollars)

	MTX Annual Acquisition Cost	Adalimumab Annual Acquisition Cost	Tofacitinib Annual Acquisition Cost
US	$796	$60,000	$55,480
UK	$233	$10,700	$11,400

Note: Data from references 93 and 94.

provided net health benefit compared to adalimumab plus cDMARD. However, they did not find sufficient evidence that tofacitinib plus cDMARD provided net health benefit compared to adalimumab plus cDMARD. In Europe, pharmacoeconomic considerations may be very different within public healthcare systems, making the JAK inhibitors attractive options.

Conclusion

The JAK inhibitors are a rapidly developing treatment space in RA. They offer a targeted oral therapy with comparable efficacy to TNF inhibitors while maintaining a similar safety profile. Their oral formulation makes them a particularly appealing treatment option for patients. Early pain relief seems to occur before the return of inflammatory markers to normal, suggesting a possible role in attenuation of central pain processing. In relation to this, there is objective measurable efficacy from as early as 2 weeks with maximum effect beyond 3 months. To date, upadacitinib 15mg + MTX and baricitinib 4mg + MTX demonstrate the highest ACR response rates. With regards to SAEs, HZV risk is increased but multidermatomal or disseminated infection is very rare. The FDA has identified an increased risk of thrombophilia with JAK inhibitors and tofacitinib in RA is only approved at the 5mg BD dose. Careful consideration should be given to VTE when deciding on suitability for 2nd line treatment. JAKi have been incorporated into the ACR and EULAR guidelines for treatment of moderate to severe RA refractory to MTX monotherapy. It is anticipated that JAK inhibitors will be increasingly used as prescribing practices change with long-term safety and efficacy data.

Executive Summary

JAK inhibitors are a rapidly developing treatment space.

JAK inhibitors demonstrate comparable efficacy to TNF inhibitors.

Early pain relief suggests attenuation of central pain processing with JAK inhibitors.

The JAK inhibitor class slow radiographic progression.

There is objective measurable efficacy as early as 2 weeks with maximum effect beyond 3 months.

Upadacitinib + MTX combination demonstrates the highest ACR response rates among available JAK inhibitors.

HZV risk is acceptable and disseminated infection is rare.

There is an excess of VTE risk at higher doses and tofacitinib is only approved at 5mg BD in RA.

To date, there is no excess in cardiovascular risk at approved doses.

Meta-analyses have not revealed an increased risk of malignancy.

ACR and EULAR guidelines have incorporated JAK inhibitors into the RA treatment algorithm.

JAK inhibitors are likely to become increasingly used in RA in the coming decade.

Disclosure

The authors report no conflicts of interest for this work.

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