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REVIEW

Janus kinase versus TNF inhibitors: where we stand today in rheumatoid arthritis

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ABSTRACT

Introduction: In recent decades, Rheumatoid arthritis (RA) treatment landscape has evolved with the induction of new biological and targeted therapies that provide significant therapeutic benefits in patients with sustained disease.

Areas covered: Tumor necrosis factor inhibitors (TNFi) were the first biologics used in the treatment of RA. Although they present a significant efficacy, an insufficient response of some patients led to further research and discovery of targeted therapies, such as Janus kinase inhibitors (JAKi), which act at a molecular level, regulating many cytokines. Clinical benefits have been seen with both TNFi and JAKi as monotherapy and combined with conventional synthetic disease-modifying antirheumatic drugs. Still, some significant side effects have been reported with JAKi, and several questions remain about their safety and selectivity in action. This review summarizes the current knowledge on the mechanism of action, the clinical efficacy, and safety of TNFi vs. JAKi.

Expert opinion: TNFi and JAKi are particularly useful in treating inflammatory arthropathies. Both drug categories are recommended by ACR and EULAR institutions in RA patients suffering from moderate to severe disease. Safety data in long-term studies are required to determine the optimal benefit to the risk profile of JAKi use.

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Rheumatoid arthritis; treatment; JAK kinase; TNFa; efficacy; side effects

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that causes chronic inflammation in multiple joints of the body. About 0,5–1% of the population is affected, and the disease generally occurs more commonly in women than men, in a 2:1–3:1 ratio [1,2]. When left untreated, RA leads patients to an increased risk of developing cardiovascular disease [3,4]. Also, progressive joint destruction and presenting extraarticular manifestations may result in disability, poor quality of life, and increased mortality [5,6]. Thus, early treatment is essential for controlling disease activity and preventing joint destruction. Until recently, physicians prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and morning stiffness [7], conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), for newly diagnosed patients with RA [8], and biological agents in those patients with inadequate response to csDMARDs, such as Tumor necrosis factor inhibitors (TNFi) [9]. Despite the above drugs, there were difficult to treat cases of RA and substantial unmet needs that led to further research and development of new targeted therapies, called Janus Kinase inhibitors (JAKi), that inhibit specific molecules of the immune system. TNFi and JAKi demonstrate good clinical response with an acceptable toxicity profile, but some differences exist between those agents. Thus, this review will discuss the differences and similarities between those two drug categories regarding the mode of action, clinical response, and adverse events in RA patients.

2. Treatment of Rheumatoid arthritis

Treatment for RA has evolved over the past 25 years to a more treat-to-target strategy with therapeutic drugs that impact disease activity and slow structural joint damage, achieving fast remission in each different patient [10]. The guidelines of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) follow this motif and target early disease treatment, suggesting the use of csDMARDs as soon as the diagnosis is completed [11,12]. Methotrexate (MTX) is considered the 'anchor' of csDMARDs and effective therapy to initiate combined with glucocorticoids (GCs) for newly diagnosed patients. Bridging with GCs establishes rapid disease control, but tapering to doses ≤7.5 mg/day is critical to limit side effects. Further management is required in patients with inadequate response in 3 to 6 months [13]: positive autoantibodies, high disease activity, early erosions, or failure of two csDMARDs are considered poor predictive factors. In that case, a biologic (b)DMARD or csDMARD could be added to the csDMARD. The current biological therapies for RA include inhibiting tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, co-stimulation blockade, and B cell depletion [14]. Among those, TNFi is usually administered as first choice in RA patients, who do not respond to csDMARDs, do not tolerate them, or have medical contraindications for such therapies. It is strongly recommended to administer TNFi together with a csDMARD, such as MTX, which presents the highest efficacy. If this fails, any other

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Article highlights

- TNFi have demonstrated a clinical benefit and sustained remission with an acceptable toxicity profile in randomized controlled studies, extensional and observational studies.
- TNFi remain the bDMARDs of choice in RA patients with inadequate response to csDMARDs.
- JAK regulate many cytokines involved in RA pathogenesis.
- JAKi showed a good clinical response in MTX naïve, or patients with inadequate response to MTX or TNFi, and no inferiority to TNFi use, with superiority in some cases to other bDMARDs.
- Safety data in long-term studies are required to determine the optimal benefit-risk profile of JAKi.

bDMARD (from another or the same class, with a different mode of action) or targeted synthetic (ts)DMARD is recommended. Thus, current recommendations for the treatment of RA propose the initial use of bDMARDs such as TNFi and then switch to targeted therapies such as JAKi in patients with inadequate response to csDMARDs. TNFi and JAKi have different mechanisms of action and side effects. Still, both of them present essential efficacy in treating the disease.

3. The role of TNFa in RA

3.1. TNFa signaling pathway and functions

TNFa is the most widely studied cytokine member of the TNF superfamily due to its crucial role in the cytokine network in RA [15]. Key interacting cells include CD4 + T cells and macrophages. TNFa is secreted primarily by activated monocytes/macrophages in response to inflammatory stimuli and presents a highly pleiotropic action (Figure 1).

TNFa initially binds to the cell membrane in its precursor transmembrane form (tmTNFa). After cleavage, it can be released as soluble TNF (sTNFa). TmTNFa and sTNFa are active and bind to either TNF receptor 1 (TNFR1) or TNF receptor 2 (TNFR2), which are expressed by almost every mammalian cell. That relates to many TNFa effects, such as cell apoptosis, synthesis of protein inflammatory molecules, and regulation of gene transcription factors [16,17].

3.2. Anti-TNF inhibitors

The introduction of TNFi therapy in 1999 has transformed the treatment of RA. These drugs are also used to treat various other conditions, including psoriatic arthritis, inflammatory

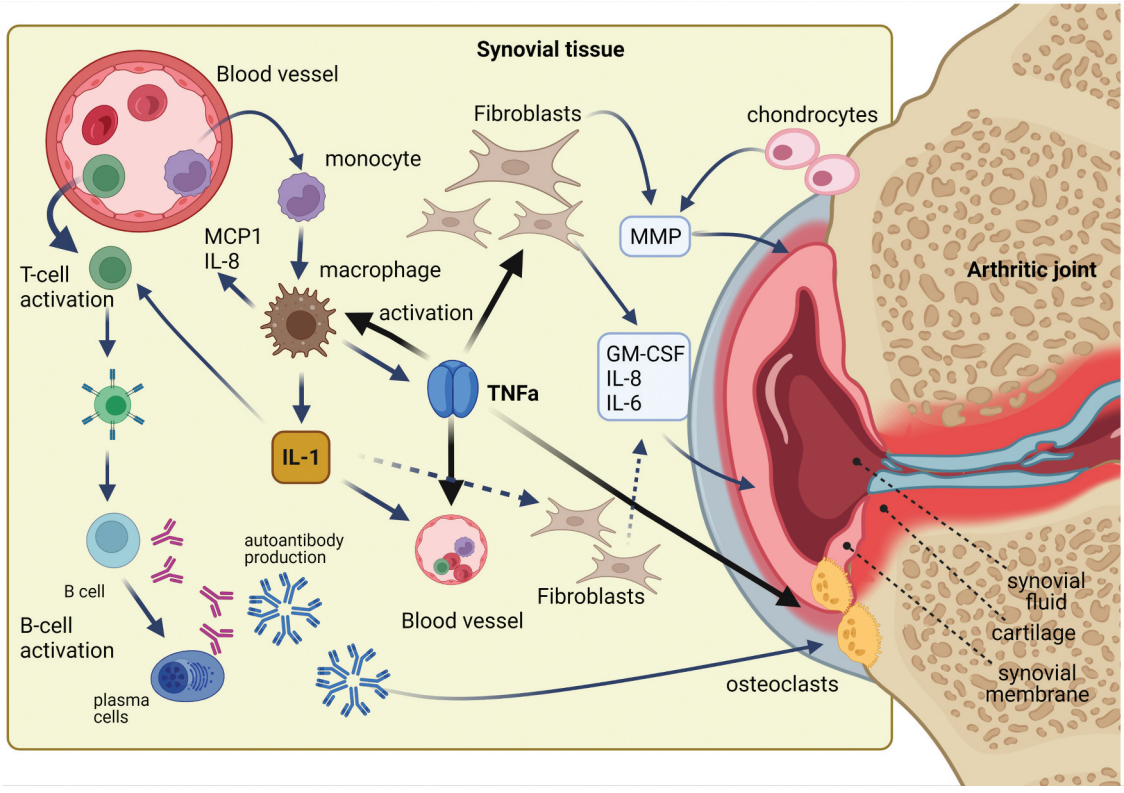

Figure 1. Schematic representation of the main cytokine and cellular interactions in the inflammatory synovium in RA.

TNFa and IL-1 are considered central cytokines of the immune response. TNFa is produced primarily by macrophages and by lymphocytes to a lesser extent. TNFa stimulates monocytes, macrophages, endothelial cells, and fibroblasts and these cells produce more proinflammatory cytokines (IL-6, IL-8, MCP1, and GM-CSF). Cytokines further lead to the production of matrix metalloproteinases (MMP), responsible for tissue destruction and the activation of bone-destroying osteoclasts and joint destruction. GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; MMP, matrix metalloproteinases; MCP1, Monocyte Chemoattractant Protein-1.

Table 1. Overview of TNFi used in the treatment of RA. Sc, Sub-cutaneous injection; IV, intravenous.

Drug	Dose and route of administration	Half-life
Adalimumab	SC injection of 40 mg every 2 weeks (self-administered)	14 days
Certolizumab Pegol	SC (liquid or lyophilized) injections of 400 mg at weeks 0, 2, and 4, followed by 200 mg every other week (or 400 mg every 4 weeks)	14 days
Etanercept	SC injection of 25 mg twice weekly or 50 mg once weekly	4 days
Infliximab	IV infusion of 3 mg/kg over 2 hours at weeks 0, 2, 6, then every 8 weeks, with dose adjustment up to 10 mg/kg if necessary	8–10 days
Golimumab	SC injection of 50 mg once a month or 100 mg in patients over 100 kg body weight with an adequate clinical response	~14 days

bowel disease, and ankylosing spondylitis. Currently, TNFi in use include adalimumab (ADA), certolizumab pegol (CZP), etanercept (ETN), golimumab (GLM), and infliximab (INF). INF was the first TNF therapy for RA authorized and has intravenous administration. All subsequent TNFi have subcutaneous administration [18]. Table 1 shows the available TNFi and their dose and half-life time.

TNFi structure differs (Figure 2) [19] and so does their binding and way of action. Thus, INF binds to both monomer and trimer forms of sTNFa, whereas ETN binds only to the trimer form [20]. INF, ADA, ETN, and CZP bind to tmTNFa, while GLM binds to both sTNFa and tmTNFa. TNFi by blocking TNF suppress the immune system and reduce the inflammation in the joints to prevent joint damage.

3.3. Efficacy of TNFi

Overall, TNFi are effective; besides reducing RA symptoms, they delay disease progression and improve patients' physical function and quality of life. Many clinical trials have demonstrated TNFi high efficacy in patients who have failed in therapy with csDMARDs such as MTX [21–31]. High disease remission at 1 year was seen when treating with ADA plus MTX in the PREMIER trial [43% of patients received combination therapy, 23% of patients ADA alone, and 21% of patients MTX alone ($p < 0.001$ combination therapy vs. both monotherapies)] [32]. Other trials have also shown that in the early stages of the disease, combination therapy with TNFi plus MTX is highly effective [33–37]. Among all TNFi, ADA presents the highest therapy response and disease remission rates, INF has the lowest treatment response and drug adherence, and ETN has the most prolonged drug survival rates [38–40].

Moreover, after the failure of the first, switching to a second TNFi may lead to good clinical results [41,42]. Data from national registries on biological agents have shown that the drug survival differences of the second TNFi reflect those reported by the first TNFi agent [43,44]. Non-obese patients, and those with longer disease duration and higher initial disease activity, are considered the most responsive to TNFi treatment [45].

In RA patients with long-standing clinical remission, tapering of bDMARDs may be considered. Still, elective TNFi withdrawal has been associated with an increased relapse rate and possible radiographic progression [46–48]. Studies are required to identify any distinguishing characteristics of patients or treatments, which may relate to the risk of relapse.

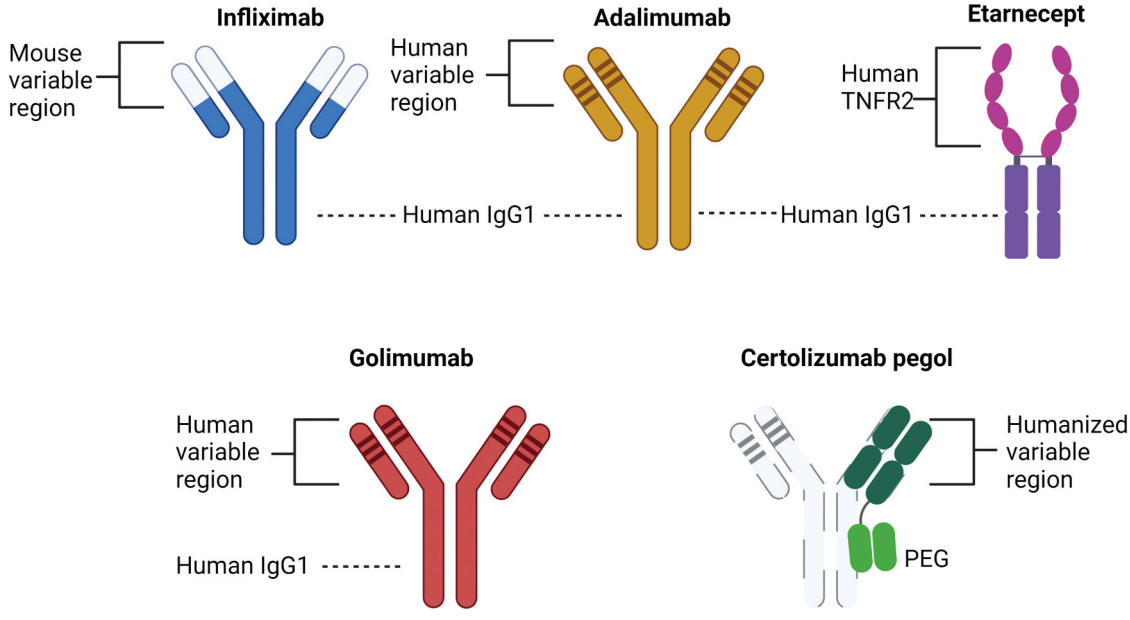

Figure 2. The molecular structure of the five TNF inhibitors.

INF, a chimeric human-murine monoclonal antibody; ADA and GLM, fully human anti-TNF-α monoclonal antibodies (IgG1); ETN, a fusion protein composed of a dimer of the extracellular portions of human TNFR2 (p75) fused to the Fc domain of human IgG1; and CZP, a pegylated, humanized Fab fragment of an anti-TNF-α monoclonal antibody. ADA, adalimumab; CZP, certolizumab pegol; ETN, etanercept; GLM, golimumab; INF, infliximab.

3.4. Safety of TNFi

There is a broad spectrum of possible adverse events associated with TNFi treatment, among which infections are the most common; Upper respiratory tract infections, bronchitis, and urinary tract infections [49,50]. One of the most important infections associated with TNFi is tuberculosis (TB). TNFa plays an essential role in the host defense against TB, and the progression of latent TB infection to active TB is a major concern with the use of TNFi monoclonal antibodies, particularly in endemic countries [51,52]. Other frequently reported side effects include infusion and injection site reactions and hematological and liver abnormalities [53,54]. The relationship between TNFi and demyelinating diseases remains uncertain [55]. Some studies have shown an increased incidence of some malignancies, but the direct effect of the TNFi remains controversial [56]. Overall, TNFi have a good safety profile and benefits that outweigh the possible risk of adverse events. Still, there are concerns about the immunogenicity induced by TNFi [57]. Adverse events can be prevented via baseline screening and periodic patient monitoring.

3.5. Biosimilar TNFi

Biosimilar drugs are highly comparable to the original drug in efficacy and safety but may generally be lower in price [58]. The FDA has developed a four-letter suffix at the end of the drugs' names to help recognize each biosimilar. Currently, biosimilars are starting to be approved and available for RA, including so far 3 INF biosimilars [59,60], 2 ETN [61,62], and 6 ADA biosimilars [63,64]. Their efficacy and safety have been experimentally and clinically proven equivalent to preceding TNFi.

4. The role of JAK – STAT signaling pathway in RA

4.1. JAK/STAT pathway

The JAK/STAT pathway plays a significant role in the pathogenesis of many inflammatory and autoimmune diseases, including RA. JAK is a non-receptor tyrosine kinase that transduces cytokines and growth factor signals. In mammals, there are four JAK proteins: JAK1, JAK2, JAK3, and TYK2 (tyrosine kinase 2) and seven signal transducers and activators of transcription (STATs) [65].

The JAK/STAT system consists of cell receptors, JAKs bound to the receptor, and STATs, which travel into the nucleus. JAKs are inactive prior to cytokine exposure. After cytokines bind to cell receptors, JAKs are activated and phosphorylate receptor-localized STATs. STATs then carry the signal to the nucleus, bind to specific DNA sequences, and further activate gene transcription [66] (Figure 3).

4.2. JAK inhibitors (JAKi)

JAKi antagonize JAK protein function and block the JAK-STAT signaling pathway, which influences the response to many cytokines. JAKi have demonstrated efficacy for RA and are

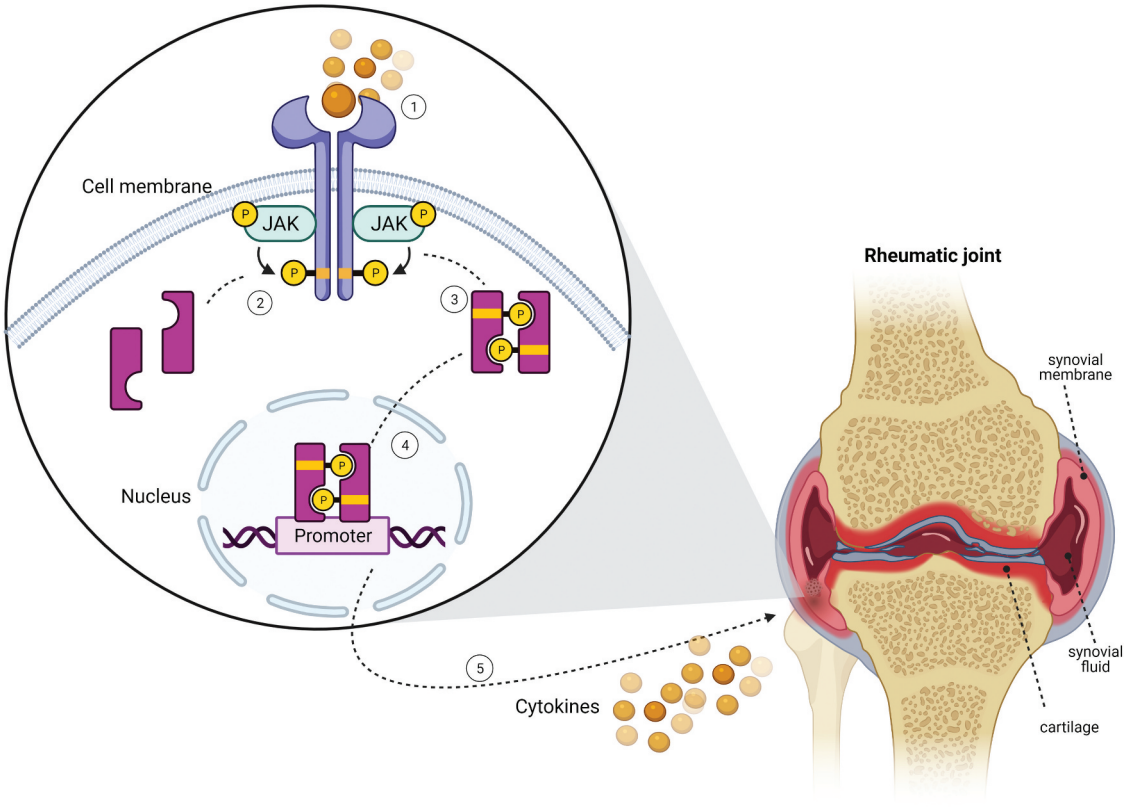

Figure 3. Schematic of the signaling cascade induced by cytokines that signal via the JAK/STAT pathway.

Cytokine binds to a specific receptor leading to the transactivation of JAKs (1). Activated JAKs then phosphorylate tyrosines on the intracellular domains of the receptor (2), which recruit STAT transcription factors (3). STATs are translocated into the nucleus (4) and upregulate the transcription of cytokine-responsive genes.

currently under investigation for other autoimmune diseases, such as psoriasis, spondyloarthropathies, and systemic erythematosus lupus [67]. They act differently from bDMARDs as they inhibit multiple cytokines. Compared to the treatment with TNFi, JAKi have the advantage of oral application, short half-life, and rapid improvement of disease activity driven by pain and inflammation control [68,69]. There are four approved JAKi by the Food and Drug Administration (FDA); Tofacitinib, Baricitinib, Upacitinib, and Filgotinib. So far, all JAKi show benefit in clinical trials for patients with moderate or severe RA. After discontinuation of the first JAKi, either for inefficacy or side effects, switching to a second JAKi seems a safe and efficacious option [70].

Tofacitinib was the first JAKi approved, at a dose of up to 5 mg administered twice daily for moderate to severe RA treatment by the FDA in the US in 2012 and by the European Medicines Agency (EMA) 5 years later. Tofacitinib is regarded as an inhibitor of JAK 1 and 3, with minimal affinity for JAK 2 and TYK2, tyrosine kinase-2 (TYK2). Several phase III clinical trials have shown efficacy in patients who have not received csDMARD as well as in patients with insufficient response to csDMARDs and even bDMARDs [71–73].

Baricitinib was the second JAKi approved, at a dose of 2 mg to treat moderate-to-severe active RA in adults by the FDA, while EMA has been approved at a dose of 2 to 4 mg in patients with moderate to severe RE. It is considered an inhibitor of JAK1 and 2. Compared with placebo and ADA, baricitinib has shown significant clinical improvement in patients with prior impaired response to MTX [74–76]. Compared with MTX monotherapy, Baricitinib combined with MTX has also demonstrated a statistically superior reduction in radiographic progression [77].

Upadacitinib was approved by FDA and EMA in 2019 at a dose of 15 mg once daily. It is a JAKi selective for JAK1 74-fold over JAK2. In RA patients with previous MTX use, Upadacitinib, compared to placebo and ADA, has demonstrated superiority in improving signs, symptoms, and physical function. Moreover, Upadacitinib significantly inhibited radiographic progression compared to placebo [78,79]. Also, in refractory to bDMARDs RA patients, Upadacitinib has shown superiority to abatacept (ABA) regarding reducing the DAS28-CRP and achieving remission at 12 weeks. Still, more severe events were related to the drug [80].

Filgotinib was approved by EMA in September 2020 at a dose of 200 mg once daily. In in-vitro studies, Filgotinib has demonstrated selective inhibition of JAK1. In clinical trials, including patients with active disease, Filgotinib was effective, presenting rapid onset of action and good safety profile, as monotherapy, and when combined with MTX [81,82]. Regarding patients with inadequate response or intolerance to 1 or more bDMARDs, Filgotinib at a dose of 100 mg daily or 200 mg daily, compared with placebo, has shown a significant clinical response at week 12 [83,84]. Table 2 shows the characteristics of JAKi regarding JAK in vitro inhibition, dosage, route of administration, and their half-life time.

Table 2. Overview of JAKi used in the treatment of RA. JAKi, JAK inhibitors; Kg, kilogram; OD, once daily; Bid, 'bis in die' (twice a day); TYK2, tyrosine kinase-2; FDA, food and drug administration; EMA, European medicines agency.

Drug	Jak inhibition	Dose and route of administration	Half-life
Baricitinib	JAK1, JAK2	Oral, 2 mg OD (FDA) Oral, 2–4 mg OD (EMA)	12,5 hours
Filgotinib	JAK1	Oral, 200 mg OD (EMA)	6 hours
Tofacitib	JAK1, JAK3, and to a slightly lesser extent JAK2, TYK2	Oral, 5 mg bid (FDA and EMA)	3 hours
Upadacitinib	JAK1	Oral, 15 mg OD (FDA and EMA)	4 hours

Finally, the data are inconclusive regarding tapering or withdrawal of JAKi in patients with low disease activity or remission. In particular, a study on Baricitinib showed maintenance of remission in 33% and low disease activity in 67% of patients who received a tapered dosage of the drug at 2 mg per day [85]. Moreover, in tofacitinib withdrawal, the absence of any flare was achieved in about one-third out of 64 patients studied with RA, where lower RF titers related to the maintenance of low disease activity after the discontinuation [86]. Nevertheless, it seems preferable to follow a dose-reduction strategy than to immediate withdrawal of JAKi [87].

4.3. Safety of JAKi

JAKi treatment's most frequently reported adverse events in RA patients are pneumonia, upper respiratory tract infections, urinary tract infections, or gastroenteritis [65]. However, the most characteristic infectious complication with JAKi is the reactivation of the varicella-zoster virus [88]. A systematic literature review and meta-analysis of phase II and III randomized controlled trials of tofacitinib, baricitinib, and Upadacitinib found the incidence of Herpes zoster (HZ) higher than expected for the population (3.23 per 100 patient-years) [89]. JAKi such as Filgotinib were excluded from the analysis, although long-term safety analysis across global clinical trials showed that HZ rates were increased for drug dosage at 200 mg vs. 100 mg [90]. Other common adverse events include increased liver enzymes or muscle enzymes in the blood, high levels of blood cholesterol, along with hematopoietic abnormalities (decrease of lymphocytes, neutrophils, and hemoglobin). Nevertheless, and according to each drug's metabolism, physicians should consider adjusting JAKi dosage in cases of moderate-to-severe renal or hepatic dysfunction. Currently, a product warning is in place for JAKi regarding deep venous thrombosis (DVT) risk [91]. Still, a meta-analysis of randomized controlled trials of JAKi at licensed doses did not provide evidence that supports the current warnings of venous thromboembolism risk [92], and further studies are needed [93].

A recent large randomized safety clinical trial showed that risks of major adverse cardiovascular events (MACE) and cancers were higher with tofacitinib and did not meet noninferiority criteria. Older age and smoking (both current and past) were significant risk factors for malignancies [94,95]. Still, real-world data from the (US) Corrona RA registry showed similar MACE, malignancy, death, and VTE rates for tofacitinib and bDMARDs [96]. These data should be interpreted with caution but still emphasize the importance of assessing baseline CV risk and being alert when treating patients with a smoking

history. Moreover, since JAKi share similar mechanisms of action with tofacitinib, extended safety trials are required and expected for the other medicines of this drug class.

4.4. Conclusions

In RA, an early diagnosis and intervention are essential for preventing cartilage destruction and loss of joint function. Nowadays, treating physicians adhere to treat-to-target recommendations by implementing specific protocols to achieve disease remission. bDMARDs, particularly TNFi, present a rapid reduction of inflammation while inhibiting radiographic progression in joints. Analyses of long-term data have underlined several safety issues associated with their use, among which increased risk for tuberculosis and malignancy are the most serious. Still, one-third of RA patients do not respond to anti-TNF leaving space for other treatments.

Interestingly, JAK-STAT pathway receptor families intervene in cytokine signaling and are thought to play a role in the development of RA. Thus, JAKi have developed and are increasingly used for treating inflammatory and autoimmune diseases. Our understanding of JAKi, particularly regarding the risk of infections, especially HZ and hematopoietic abnormalities, is evolving. Finally, future extended observational studies should evaluate the thromboembolic risks related to JAKi and other drugs used in RA treatment and distinguish them from risks associated with the disease's inflammatory nature and potential comorbidities.

5. Expert opinion

Our current understanding of the pathogenesis of RA involves a dysregulation of the cytokine network, where many of the upregulated cytokines play a pivotal role. Proinflammatory cytokines, growth factors, and hormones use the JAK/STAT signaling pathway to regulate, which is essential in inflammatory responses.

This knowledge led to the introduction of bDMARDs, such as cytokine inhibitors, T-cell co-stimulatory blockade, and B-cell depletion by inhibition of CD20 molecules that revolutionized RA's treatment in the last two decades. Notably, patients receiving TNFi showed a good clinical response and achieved sustained remission, with an acceptable toxicity profile in long-term randomized, extensional, and observational studies. Still, in the 'era of biologics,' the use of TNFi places a considerable financial cost on the healthcare system, although the overall costs should take into account the benefit of reducing the consequences of RA disease [97,98].

On the other hand, instead of inhibiting one specific cytokine, such as TNFa, there is now an opportunity to target simultaneously several proinflammatory cytokines by using JAKi. Indeed, many studies using JAKi have shown a very good clinical response in MTX naïve, in inadequate response to MTX or TNFi. In addition, JAKi, compared with ADA or ABA, showed no inferiority and, in some cases, superiority. The oral administration of these drugs is convenient. They also have lower manufacturing production costs.

However, additional safety data in long-term studies are required to determine the optimal benefit to risk profile since there is a higher incidence of infections, HZ, and thromboembolic events. At the same time, a decline of lymphocytes, abnormal liver function test, creatinine kinase, and other hematopoietic abnormalities have been observed in some patients. If and how their way of action, efficacy, and adverse events relates to the attributed different selectivity of each JAKi is of question. New studies have shown that selectivity is dose-dependent, and at higher doses, the compounds lose selectivity [99,100].

Nevertheless, both drug categories are particularly useful in treating inflammatory arthropathies and are recommended by ACR and EULAR institutions in RA patients suffering from moderate to severe disease. The doctor should consider the demonstrated safety profile of TNFi and the safety concerns for JAKi, as there are patients that fit one or another drug class. Thus, the treatment preference is somewhat individualized, and the doctor should also keep in mind the patient's compliance. After consulting with the patient, the best possible treatment option can be applied to achieve maximum results.

In the long run, the safety profile of JAKi in clinical trials and data from registries has been related to increased HZ and venous thromboembolic events and apparently to an augmented cardiovascular and malignancy risk compared to TNFi. Since JAKi are agents used chronically in RA patients, it is mandatory for continuous long-term monitoring as pharmacovigilance. On the other hand, JAKi have demonstrated a good clinical profile in RA patients and non-inferiority from TNFi. JAKi are drugs with a very simple scheme dosage (one or two tablets per day) and are very easy to receive from patients. Consequently, JAKi should be preferred to be administrated in younger RA patients, in patients with less cardiovascular comorbidities, and those with a low dose of steroid usage. On the contrary, TNFi have shown a very good clinical profile in clinical trials, long-term observational studies, and an acceptable toxicity profile compared to JAKi and could also be given with caution in elderly patients.

Abbreviations

ABA, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; CZP, certolizumab pegol; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; bid, 'bis in die' (twice a day); EMA, European Medicines Agency, ETN, etanercept; EULAR, European League Against Rheumatism; HZ, Herpes zoster; GCs, glucocorticoids; GM-CSF, granulocyte–macrophage colony-stimulating factor; GLM, golimumab; IL, interleukin; INF, infliximab; IV, Intravenous; JAK, Janus kinase; MACE, major adverse cardiovascular events; MMP, matrix metalloproteinases; MCP1, Monocyte Chemoattractant Protein-1; MTX, Methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; RA, Rheumatoid arthritis; Sc, Sub-cutaneous injection; sTNFa, soluble TNFa; tmTNF, transmembrane TNF; STAT, signal transducer and activator of transcription; tsDMARD, targeted synthetic disease-modifying antirheumatic drug; TNF, tumor necrosis factor; TNFi, Tumor necrosis factor inhibitors; TNFR, TNF receptor; TYK2, tyrosine kinase-2.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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