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JAK inhibitors and autoimmune rheumatic diseases

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ABSTRACT

The four Janus kinase (JAK) proteins and the seven Signal Transducers of Activated Transcription (STAT) mediate intracellular signal transduction downstream of cytokine receptors, which are involved in the pathology of allergic, autoimmune, and inflammatory diseases. The development of targeted small-molecule treatments with diverse selective inhibitory profiles, such as JAK inhibitors (JAKi), has supported an important change in the treatment of multiple disorders. Indeed, JAKi inhibit intracellular signalling controlled by numerous cytokines implicated in the disease process of rheumatoid arthritis and several other inflammatory and immune diseases. Therefore, JAKi have the capacity to target multiple pathways of those diseases. Other autoimmune diseases treated with JAKi include systemic sclerosis, systemic lupus erythematosus, dermatomyositis, primary Sjogren's syndrome, and vasculitis. In all of these cases, innate immunity stimulation activates adaptive immunity, resulting in the production of autoreactive T cells as well as the stimulation and differentiation of B cells. Mechanism-based treatments that target JAK-STAT pathways have the possibility of improving outcomes by reducing the consumption of glucocorticoids and/or non-specific immunosuppressive drugs in the management of systemic immune-mediated inflammatory diseases.

1. Introduction

The four Janus kinase proteins and the Signal Transducers and Activators of Transcription (STAT) signalling pathway regulate the cellular response to cytokines, interferons, and growth factors by influencing intracellular signals to the nucleus and activating gene expression. JAKs are members of the intracellular, nonreceptor protein tyrosine kinase family, which includes four JAKs (JAK1–3 and TYK2) [1]. They share a common functional domain that regulates their activity. This domain consists of an amino terminus that contains a band 4.1, ezrin, radixin, moesin (FERM) domain that binds to cytokine receptors and regulates kinase activity. Moreover, there is also an SH2-like domain, a pseudokinase domain (also known as JAK homology 2, JH2), and a C-terminal kinase cat (JH1) (Fig. 1).

The FERM and SH2-like domains are required for JAKs to bind to their docking receptors. [2,3]. Moreover, an analysis of the structure of the FERM and SH2 domains confirms a preserved system of interaction between JAKs and their cognate receptors [4]. In addition, the JH2 region has been identified as the negative regulator of the JH1 kinase domain [5]. Indeed, the JH2 domain functions as a regulatory domain, functionally inhibiting JH1 kinase activity, and deletion of the JH2 domain enhances (d) JAK2- and JAK3-mediated signalling [6,7]. A dysregulation of JH2-JH1 interaction, resulting from mutations in JH2 domain, is proposed to be associated with immune disorders and tumour progression [8–10]. Upon binding of the ligand to the surface receptor, the dimerization of JAK associating receptor induces the activation of JAK kinase, which in turn recruits and phosphorylates cytosolic STAT proteins and leads to the nuclear translocation of STAT, acting as a transcription factor [11]. On the other hand, the STAT protein family comprises seven members, including STAT 1–6, STA5a and STA5b [12]. JAK-mediated phosphorylation of STAT results in the formation of homo- or heterodimers, and activated STAT is then translocated into the

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nucleus to regulate genes containing response sequences [12] (Fig. 2). Numerous pro-inflammatory cytokines found in both the tumour and autoimmune microenvironments contribute to JAK/STAT pathway activation. The binding of different types I and II cytokines to JAK-associated receptor subunits, such as type 1 interferons (IFNs), interleukin-6 (IL-6), IL-23, and IL-12 [13], results in the stimulation of specific downstream intracellular signals that play critical roles in the pathogenesis of immune diseases. Notably, IL-6 activated JAKs interact with other activated cytokine-mediated signalling pathways, including the mitogen-activated protein kinase (MAPK) pathway and the phosphoinositide 3-kinase (PI3K)/protein kinase B (or Akt)/mechanistic target of rapamycin (mTOR) signalling pathways, suggesting that blocking the JAK/STAT pathway facilitates the inhibition of several aberrant immune responses.

Given the pathogenetic role of JAK/STAT, regulatory agencies for drug administration have already approved a few JAKi in the setting of either immune-mediated diseases or hematological malignancies, the so-called JAK inhibitors (JAKi), in order to counteract JAK/STAT signal hyperactivation [14].

JAKi represent a new class of orally administered molecules, targeting multiple pathways of the immune system. So far, the approved drugs for the treatment of rheumatoid arthritis (RA) include baricitinib, filgotinib, tofacitinib and upadacitinib. These drugs, although belonging to the same class seem to present different profiles of efficacy and safety that could reflect the differential selectivity of the inhibited JAK isoform [15]. By investigating the in vitro inhibition of STAT phosphorylation, these drugs indeed possess a preferential inhibition of JAK1-dependent pathways and in particular of interferon (IFN)α/pSTAT5 and interleukin (IL)-6/pSTAT1 [16]. JAK1 selectivity appears to be the main driver of the therapeutic efficacy in RA. However, the inhibition of the JAK2-dependent and JAK3-dependent pathways may also contribute to clinical response in RA and in other immune-mediated conditions. In this perspective, the inhibition of JAK2 may contribute to the efficacy of non-selective JAKi via the modulation of platelets that play a supporting role to synovitis [17]. Similarly, the inhibition of JAK3 is critical for lymphocyte proliferation by affecting the production of IL-7 and IL-15, which are involved in RA, systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and primary Sjögren's syndrome (pSS) pathogenesis, thus possibly improving the efficacy of non-selective JAKi [18–20].

No head-to-head clinical trials are available to evaluate the efficacy and safety profiles of JAKi in patients with autoimmune rheumatic diseases yet. A deeper knowledge on the timing of the use of these drugs in the disease course and a detailed characterization of the patients in the perspective of a personalized medicine will guide the drug choice in the next future [21,22].

2. Methods

The literature on existing evidence on JAKi treatment has been reviewed. The manuscript is formatted as a narrative review. English language articles including #JAKi, #tofacitinib, #baricitinib, #upadacitinib, #filgotinib, #rheumatoid arthritis, #systemic lupus erythematosus, #vasculitis, #dermatomyositis, #primary Sjogren's syndrome, #systemic sclerosis were identified through Embase, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Google Scholar and the Clinical trial registries of Europe and the USA published until October 2022. Additional references were identified by a manual search among the cited references. Abstracts that did not include the main text were not considered for review.

3. Results

3.1. Rheumatoid arthritis

Given methotrexate (MTX) modulation of JAK-STAT and the success of the IL-6 receptor inhibitor tocilizumab, drugs targeting JAK1, JAK2, and TYK have emerged as new alternatives for the treatment of RA [23]. Indeed, recent evidence suggested that the combination of JAKi with glucocorticoids yielded better outcomes in early RA than conventional treatment [24].

Diverse clinical trials involving tofacitinib in RA patients have been performed globally [25–27]. Tofacitinib was the first JAKi approved by the FDA and EMA for patients with moderate to severe RA who had failed initial treatment with MTX or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and had poor

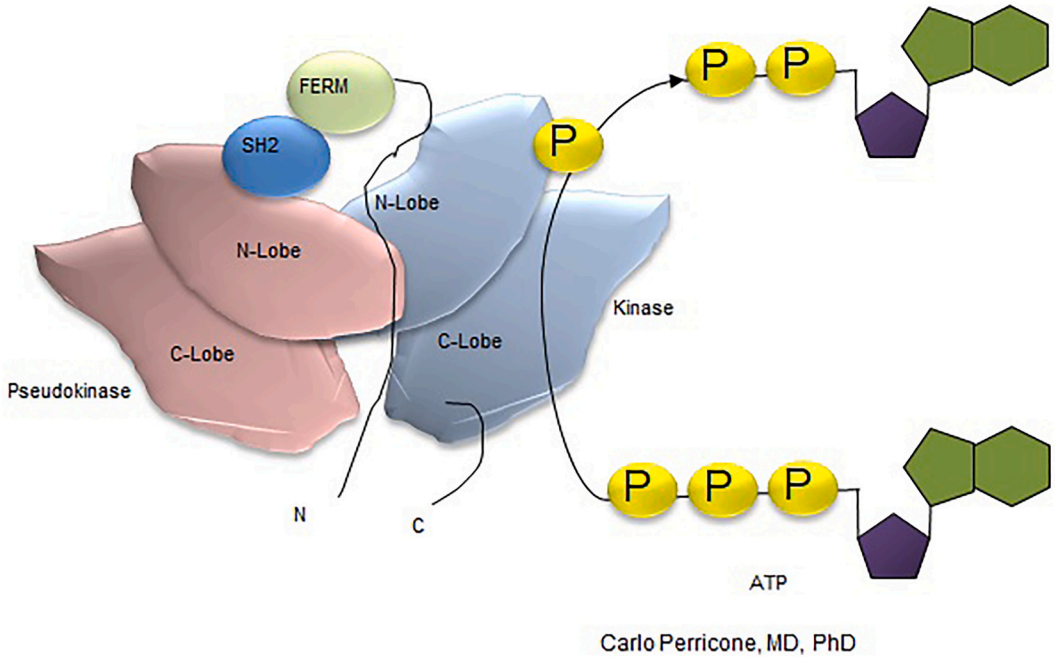

Fig. 1. Janus kinases (JAKs) structure. These are a unique class of tyrosine kinases that contain both a catalytic domain and a second kinase-like domain that serves an autoregulatory function.

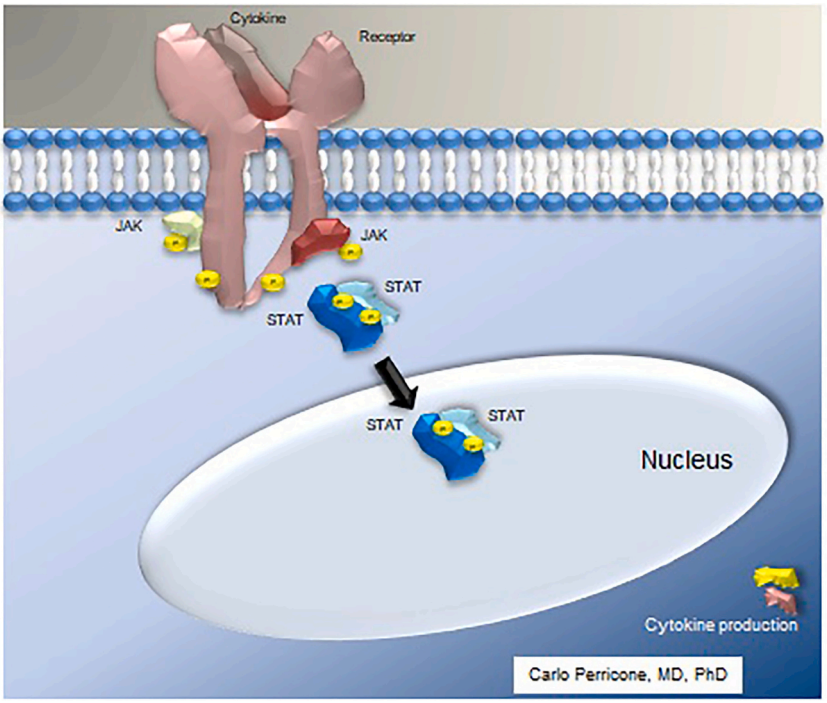

Fig. 2. Phosphorylation Steps Required for JAK/STAT Signaling. After STATS dock on the phosphorylated receptor, the JAKs phosphorylate them, then STATS dissociate from receptor and dimerize via their SH2 domain. STATS translocate to nucleus, bind to DNA and other gene regulatory proteins, and activate transcription of genes involved in the inflammatory response.

prognostic factors. In addition, tofacitinib, either alone or in combination with MTX, has been shown to be efficacious, with clinical responses comparable to or better than TNF-antagonists [25–27]. Tofacitinib has a rapid onset of action, with an ACR20 response in 2–4 weeks when used in combination with MTX. After 6 months, three-quarters of tofacitinib monotherapy patients had ACR20 response and 55% had ACR50 response. Tofacitinib appears to have a long-lasting effect of at least 72 months. There are currently no studies that compare tofacitinib monotherapy to a combination therapy of tofacitinib + csDMARDs.

Following this, the EMA and FDA approved baricitinib, a JAK1/JAK2 inhibitor, for the treatment of RA. In patients with an inappropriate response to MTX, baricitinib has been shown to be more effective than placebo and the TNF antagonist adalimumab [28,29]. After one week, baricitinib outperformed placebo and adalimumab. In the RA-BEGIN study, baricitinib monotherapy did not appear to be inferior to baricitinib + MTX in combination therapy [30]. These effects were maintained or improved at week 52.

Upadacitinib is an oral JAKi with a higher selectivity for JAK1 than for other JAKs. In two phase 2 studies and one phase 3 study, upadacitinib has shown to improve RA signs and symptoms in patients who did not respond to MTX or a TNF-antagonist [31–33]. Upadacitinib was tested against placebo in the latter (SELECT-BEYOND) study in patients with active RA, a previous inadequate response or intolerance to biologic DMARDs, and receiving concomitant background csDMARDs [34]. Over 12 weeks, upadacitinib resulted in a rapid and significant improvement compared to placebo (56–65% ACR20 response vs. 28%, respectively; $p < 0.0001$).

Filgotinib, a selective JAK1 inhibitor, has shown efficacy in several phase 2 studies [35,36]. At week 12 of the DARWIN 2 study, which included 283 patients with moderate to severe active RA, filgotinib at any dose was significantly more effective than placebo (65% vs. 29%, respectively; $p < 0.001$). Most efficacy end-points showed a rapid onset of action, and responses were maintained or improved through week 24 [37]. Filgotinib was shown to be effective in phase III clinical trials. Combe et al. reported that the proportion of patients ($n = 1755$ randomised and treated) achieving ACR20 at week 12 was significantly higher for filgotinib 200 mg/daily (76.6%) and filgotinib 100 mg/daily (69.8%) versus placebo (49.9%; both $p < 0.001$) [37].

All JAKi have proved therapeutically effective in patients with difficult-to-treat RA, and they work even in patients who have previously received at least two bDMARDs [34–39]. No direct comparative research has been conducted between JAKi in RA, only data from a propensity score-based study suggested that baricitinib could more effective than tofacitinib [40].

3.2. *Systemic lupus erythematosus*

The study with MRL/lpr lupus-prone mice was the first direct test of the JAKi role in SLE. Tofacitinib treatment reduced disease activity in this study (nephritis, mucocutaneous presentation, and autoantibody synthesis). Furthermore, tofacitinib treatment reduced the expression of interferons and proinflammatory cytokines. Tofacitinib may also be able to repair endothelial damage and dysfunction [41]. Multiple case reports and small observational studies have also suggested that tofacitinib has the potential to reduce disease activity [42]. These promising results were recently substantiated in patients with SLE treated with tofacitinib. As it has been shown in an ex vivo model with CD4+ T cells from patients with SLE, pre-treatment with tofacitinib resulted in the restoration (inhibition) of distorted Th cells' function via enhancing the expression of TGFβRI. It is plausible that the inhibition of IL-6-signalling realized by the inhibition of a Jak kinase attached to an IL-6 receptor may play a role in this process. Tofacitinib (5 mg twice a day) demonstrated a satisfactory safety profile, decreased IFN type I signature, improved lipid profile disturbances, and restored endothelial function in a recently published randomised, double-blind, placebo-controlled trial in patients with SLE JAKi. However, the authors failed to demonstrate any statistically significant changes in disease activity reduction, despite the fact that it was explicitly stated that the study was not designed to test the drug's efficacy (ClinicalTrials.gov NCT02535689) [43]. By inhibiting the JAK/STAT pathway, baricitinib inhibited B cell differentiation and restored podocytes' disrupted cytoskeletal structures in response to inflammatory stimulation [44]. Those encouraging findings

were confirmed in a double-blind placebo-controlled study of 314 lupus patients who were randomly assigned to receive baricitinib at 2 mg, 4 mg, or a placebo. At the end of the study, at week 24, 70% of patients receiving baricitinib 4 mg had their SLEDAI 2 k arthritis or rash resolved [45]. JAKi use may be associated with a reduction in all or nearly all cytokine signalling via the JAK/STAT pathway. Dörner et al. conducted a trial to examine the expression of key cytokines associated with lupus. Baricitinib 4 mg significantly reduced C—C motif chemokine ligand (CCL) 19, C-X-C motif chemokine ligand (CXCL) 10, tumour necrosis factor-alpha (TNF-), TNF receptor superfamily member (TNFRSF)9/CD137, PD-L1, IL-6, and IL-12 levels at week 12 [46]. Furthermore, the authors observed inhibition of cytokines related to IFN I activities, which translated to a decrease in anti-dsDNA antibody concentrations, an improvement in the SLEDAI 2000 scale, and a decrease in swollen and tender joints [46]. Data from a recently completed trial with filgotinib in patients with cutaneous lupus erythematosus are disappointing. The study did not meet the primary endpoint because filgotinib did not significantly improve CLASI scores [47]. The study's findings, however, are not surprising. Filgotinib is a JAK1 inhibitor that targets almost all SLE-cytokine-related receptors, but it does not inhibit the signalling of IL-12/IL-23, IL3 or IL-5. Given the success of ustekinumab in the treatment of SLE, blocking IL-12/IL-23 signalling may be considered essential in cutaneous lupus. Filgotinib is also being studied in the treatment of lupus membranous nephropathy (NCT03285711) [48]. Data on the efficacy of upadacitinib in SLE are scarce and, so far, only a case report showing resolution of accelerated nodulosis and arthritis has been published [49]. A phase II trial is undergoing to investigate the safety and efficacy of the JAK1 selective inhibitor in SLE in monotherapy or in combination with Bruton's tyrosine kinase (BTK) inhibitor-elsubrutinib (NCT03978520) [50].

3.3. Systemic sclerosis

Given the emerging role of cytokines and interferons in SSc inflammation and fibrosis, it would seem reasonable to investigate whether JAKi have any therapeutic potential for this disease. This may be especially important for IFNs, as type 1 IFN upregulation is central to disease pathogenesis. Therapies that neutralise IFN-α, reduce its production, or block its downstream effects are expected to benefit SSc patients [51]. This could be accomplished by inhibiting JAK kinases (JAK1 and Tyk2) linked to IFNR. The hypothesis of JAKi's utility is currently being tested in three clinical trials from China (baricitinib-NCT05300932), France (ruxolitinib-NCT04206644), and the United States (tofacitinib-NCT03274076). The completed study from the United States did not show that tofacitinib was superior to a placebo in terms of skin improvement (measured as a change in mRSS) or CRISS improvement (Combined Response Index Systemic sclerosis). This is in contrast to previously published data in which tofacitinib contributed to a reduction in skin thickness in SSc patients measured both clinically [52] and with ultrasounds [53]. Undoubtedly, drawing final conclusions is premature. Given that non-selective JAKi may inhibit both proinflammatory and profibrotic cytokines while also having a negative impact on those with anti-inflammatory and antifibrotic potential, it would be reasonable to test the activity of other inhibitors against this condition. A systematic review of the literature was performed in a recent study, and 59 patients (mean age 47 ± 15 years) were included. The average treatment time was 12 (range 6–12) months. In 35 patients (59%), JAKi (tofacitinib in 47 patients and baricitinib in 12 patients) were prescribed as first-line therapy. In 52 patients (88%), there was a significant cutaneous response (a decrease in the mRSS - modified Rodnan skin score - of >5 points and 25% from baseline). Among 31 patients with interstitial lung disease (ILD), 28/29 had no ILD progression during the follow-up period (missing data in 2 patients). Only two patients experienced disease progression during therapies (including one patient with progressive skin fibrosis). The cutaneous response was more common in treatment-naïve SSc patients. The reduction in mRSS after treatment initiation was greater in treatment naïve SSc patients. Without interrupting treatment, eighteen non-serious side effects were observed in 12 patients (20%): six infections, six gastrointestinal disorders, four hepatitis, and three dyslipidemias [54].

3.4. Primary Sjogren's syndrome

The pathogenesis of pSS is unknown, but a number of gene loci, including polymorphisms in IRF5, STAT4, and IL-12A, have been linked to the disease [55,56]. These polymorphisms may confer a susceptibility to increased IFN responses in pSS. The expression of type-I IFN-inducible genes in pSS correlates with anti-SSA/Ro and anti-SSB/La autoantibody titers [57]. Furthermore, the IFN signature was linked to higher disease activity index scores. Activated pDCs are detected in minor salivary gland biopsies from patients with pSS [58]. pDCs are the primary source of type-I IFN production. Peripheral blood cells from pSS patients showed altered STAT3 and STAT5 phosphorylation, but increased phosphorylation of STAT1 Y701 in response to IFN-, IFN-, and IL-6 stimulation [59]. Additional investigation revealed that the TLR7/9-STAT3 pathway was involved in the type-I IFN signature [60]. Mice models (with IB- or its transcriptional regulator STAT3 deletion in epithelial tissues) have partially confirmed the role of IFN-JAK-STAT in the pathophysiology of pSS [60]. Topical tofacitinib has been studied in phase 2 randomised controlled trials for dry eye disease [61,62]. The treatment reduced conjunctival cell surface expression of HLA-DR, corneal infiltration of CD11+ cells, and corneal expression of proinflammatory cytokines (TNF-, IL-23, and IL-17A). In a recent study of 11 patients using the ESSDAI index, baricitinib was found to be effective and well-tolerated in active SS patients with arthritis, rash, and ILD [63].

3.5. Dermatomyositis

Biomarkers related to type I IFN signalling, such as inducible transcripts and proteins, are elevated in dermatomyositis (DM) patients' muscle and skin [64]. Thus, it has been proposed that lichenoid skin reactions and perifascicular atrophy in muscles are directly related to type 1 IFN signalling. The increased expression of IFN-inducible genes in the muscle of juvenile DM patients, as well as their association with histologic and clinical features, adds to the evidence that both type I and type II IFNs play a pathogenic role in juvenile DM [65]. Pinal-Fernandez et al. observed that the IFN1 and IFN2 pathways are activated differently in each myositis subtype [66]. Inhibiting the JAK-STAT pathway was also found to reduce IFN signalling. Tofacitinib has also been shown to inhibit the pro-inflammatory and pro-fibrotic effects of amyopathic dermatomyositis (ADM)-interstitial lung disease (ILD)-derived T cells in vitro [67]. Tofacitinib improved cutaneous and extra-cutaneous manifestations in several subjects with refractory diabetes [68–74]. Kurasawa et al. [68] investigated the efficacy of tofacitinib (5 mg twice daily) combination therapy in a case series of refractory rapidly progressive ILD associated with anti-melanoma differentiation-associated 5 (MDA5) antibody-positive DM. Patients who received tofacitinib had a significantly higher chance of survival despite experiencing relatively high rates of adverse events, particularly viral infections. Tofacitinib efficacy in patients with early-stage anti-MDA5-positive AMD-ILD was recently evaluated in a single-center, open-label clinical study [69]. Treatment with tofacitinib (5 mg twice daily) significantly improved survival at 6 months after the onset of ILD, as well as ferritin levels, the percent of predicted value (FVC), single-breath carbon monoxide diffusing capacity, and high-resolution computed tomography findings. Tofacitinib-related adverse events were also of a low severity. Papadopoulouet al. [75] reported a case of severe refractory Juvenile DM treated with several lines of conventional immunosuppressants, biological agents, and intravenous immunoglobulins in which baricitinib treatment significantly improved the case (skin and muscular symptoms).

3.6. Vasculitis

Vasculitides are a group of autoimmune diseases that affect blood vessels, with giant cell arteritis (GCA) being the most common type [76,77]. The majority of cytokines implicated in GCA pathogenesis, including IL-6, IL-12, IFN-, IL-17, and IL-23, signal via the JAK-STAT pathway [76]. Th1 and Th17 responses have been identified as important regulators in GCA vasculitis lesions [77]. Furthermore, Treg lymphocytes appear to play an important role in GCA pathogenesis; these are reduced in GCA patients' blood and arterial lesions. Hartmann et al. discovered high levels of STAT1 expression in arteritis tissue lesions using an experimentally induced vasculitis model of human temporal arteries grafted in immunodeficient mice [78].

Despite limited clinical data supporting the efficacy of JAKi in the management of vasculitis, there is a strong rationale for the use of these molecules in this context [79].

IFN-γ, the main inducer of STAT1, was found to be ten times higher in GCA patients than in controls. Tofacitinib prevented Th1 cell accumulation in vessel walls and decreased IFN- γ, IL-17, and IL-21 production [80]. Tofacitinib inhibited adventitial microvascular angiogenesis, reduced hyperplastic intima outgrowth, and reduced tissue-resident memory T-cells [81]. In patients with relapsing GCA, one phase 2 trial of baricitinib and one phase 3 trial of upadacitinib are currently underway, with promising preliminary results. Because of the close relationship between GCA and polymyalgia rheumatica, JAKi may become part of the therapeutic strategy for this disease in the future. Despite the fact that available data is still very limited, the potential benefit of JAKi for the treatment of vasculitis may have a significant impact on the management of certain patients, particularly in cases of treatment resistance. Baricitinib is undergoing phase 2 studies to assess its safety and tolerability in polymyalgia rheumatic patients [NCT04027101] and giant cell arteritis [NCT03026504]. Another multicenter, randomised controlled phase 3 study [NCT03725202] is currently underway to assess the safety and efficacy of upadacitinib in patients with giant cell arteritis.

4. Conclusions

The development of selective and non-selective JAKi has revealed a new approach to the treatment of autoimmunity and provides rheumatologists with a new therapeutic strategy. The rapid onset of biological agents in an oral formulation will be appealing for diseases such as RA and other connective tissue diseases. The anti-inflammatory effects of these agents on skin, joint, and muscle lesions, as well as their potential antifibrotic effects, shed light on JAKi's potential efficacy as a promising new alternative for treating inflammatory and autoimmune diseases. JAKi have a similar safety profile to other biological agents; nevertheless, specific cell changes have been defined, as well as an enhanced risk of particular types of infection, most notably herpes zoster, cardiovascular disease, and cancer [82]. Furthermore, JAKi are less selective than biological inhibitors and block the signalling of multiple cytokine axes at the same time, acting as dimmers of the immune-system response. Further clinical data are needed, particularly for highly selective inhibitors, to assess the efficacy and toxicity of selective JAK inhibition in autoimmune rheumatic diseases.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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