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Role of Janus Kinase Inhibitors (JAKis) in Autoimmune Disorders

Review

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Abstract – JAK inhibitors (JAKis) comprise a crucial therapeutic tool for managing patients with immune-mediated inflammatory disorders. Although often perceived as a uniform class of medications thought to be largely interchangeable, notable variances exist in their efficacy and safety profiles. This review explores the pharmacokinetic and pharmacodynamic distinctions among JAKis, underscoring their clinical significance based on the most recent evidence available. The article seeks to furnish rheumatologists, gastroenterologists, and dermatologists with pragmatic guidance in selecting the most suitable JAKi for each patient, given the void of evidence-based recommendations in this sphere, to enhance clinical outcomes. Due to its preferential mechanism on JAK1, metabolic processing in the intestine, and demonstrated lack of effect on male fertility, filgotinib may present an improved benefit/risk proportion in contrast to other less targeted JAKis.

Keywords – JAK inhibitors, pharmacokinetic, pharmacodynamic, efficacy, safety.

I. Introduction

Immune-mediated inflammatory disorders (IMIDs) constitute a diverse array of chronic conditions sharing common pathways (1). The most frequently impacted areas of the body include the joints, skin, and gastrointestinal system, resulting in conditions such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JiA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA), atopic dermatitis (AD), alopecia areata (AA), and inflammatory bowel disease (IBD) (1,2). Immunomodulatory drugs (IMIDs) rank among the most prevalent illnesses in Western nations (1) and have a profound effect on patients, not only due to the potential destruction of affected tissues but also because of their detrimental influence on health-related quality of life, everyday activities, and social functioning (3)While IMIDs display significant heterogeneity from a pathophysiological perspective, they all share a persistent overproduction of proinflammatory cytokines stemming from immune system dysregulation (4).Current evidence suggests a shift in IMIDs classification from an organ-based approach to a molecular-based framework, where each condition can be characterized by a distinct cytokine signature (5). For instance, in RA, interleukin (IL)-6 serves as a critical pathogenic node, while IL-23 and IL-17A are pivotal in driving intestinal and spinal inflammation in IBD and axSpA, respectively. In this paradigm, TNF-α likely represents a common pathway operating downstream in the inflammatory progression of all IMIDs. Cytokines and other mediators involved in the inflammatory response have emerged as vital therapeutic targets for treating IMIDs, with the advent

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of neutralizing monoclonal antibodies and recombinant proteins against these targets revolutionizing treatment approaches (2). Recently, Janus kinase inhibitors (JAKis) have been introduced to inhibit the action of proinflammatory cytokines in IMIDs. These small-molecule agents do not directly bind to specific cytokines but instead interfere downstream in the inflammation cascade by blocking the JAK/STAT pathway, essential for intracellular signal transduction initiated by cytokine-receptor interactions on cell membranes (6). Tofacitinib was the first available JAKi, approved by the Food and Drug Administration (FDA) in 2012 and by the European Medicines Agency (EMA) in 2017 for rheumatoid arthritis (RA) treatment; presently, four JAKis are authorized in the European Community (EC) for RA therapy, specifically baricitinib, filgotinib, upadacitinib, and tofacitinib (7,8). Filgotinib, the latest contender in the JAKi category, received approval on 20 September 2020 in the European Union and Japan; it was designed as a reversible ATP-competitive inhibitor with a preference for JAK1, targeting inflammatory ailments such as: RA and ulcerative colitis (UC) (9). After a decade-plus of clinical application, JAKis are now acknowledged as a pivotal treatment modality for individuals affected by IMIDs, owing to their efficacy and the ease of oral administration (7). Nevertheless, despite the common ability of all JAK inhibitors (JAKis) to hinder the function of JAK proteins, there are notable variations in selective JAK family members (namely JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]), which carry significant consequences for efficacy and safety profiles. Even with these variations, these medications are still deemed interchangeable, and there are no evidence supported guidelines to assist clinicians in selecting the most suitable Jaki tailored to each patient's unique characteristics. This article seeks to distinctly outline the variations among the four JAKis available in the EU for treating rheumatoid arthritis (RA) based on their pharmacodynamics and pharmacokinetic properties, followed by a discussion on how these distinctions might influence the clinical application of these drugs. Additionally, it offers general recommendations for selecting patients eligible for treatment with specific molecules.

1. Pharmacodynamic considerations

1.1 Cytokine signaling via the JAK/STAT pathway and its inhibition

Cytokines comprise a diverse array of proteins that play vital biological roles, particularly in modulating both acute and chronic inflammatory responses (10). It is widely recognized that the dysregulation of these substances is pivotal in the pathogenesis of immune mediated inflammatory diseases (IMIDs), with excessive production of proinflammatory cytokines being a characteristic feature of such conditions (2). Cytokine activity occurs through their interaction with various receptor types (2), which from a biochemical perspective, are transmembrane glycoproteins consisting of multiple subunits (11).Cytokine receptors fall into several families, which include tumor necrosis factor (TNF) family receptors, the transforming growth factor receptor superfamily, the tyrosine kinase receptor superfamily, G protein coupled receptors superfamily, and Type 1 and Type 2 receptor superfamily (2,10). Research indicates that the pathogenesis of IMID predominantly involves proinflammatory cytokines acting upon Type 1 and Type 2receptors (12). Importantly, all Type 1 and Type 2 receptors utilize the Janus kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway for signal transduction (12), establishing it as a target for disrupting proinflammatory cytokine signaling in IMIDs. JAKs serve as a crucial element of the JAK/STAT system: these kinases are linked to the intracellular domain of Type 1 and 2 receptors and come in four different isoforms: JAK1,JAK2,JAK3,and TYK2 (2). For effective cytokine signal transduction, at least two JAKs must be present in the receptor, which can be of the same type or of two different types (13). The transduction of cytokine signals commences when a cytokine attaches to its receptor; this binding induces conformational shifts in the receptor that lead to the phosphorylation of specific tyrosine residues on JAKs by ATP molecules (Figure 1) (13).The phosphorylation of JAK results in the phosphorylation and dimerization of STAT proteins in the cytoplasm; when dimerized, STATs move into the nucleus, where they initiate the transcription of genes responsible for cytokine production. This process ultimately dictates the production and release into the extracellular environment, thereby determining the biological activity of cytokines (2,12).

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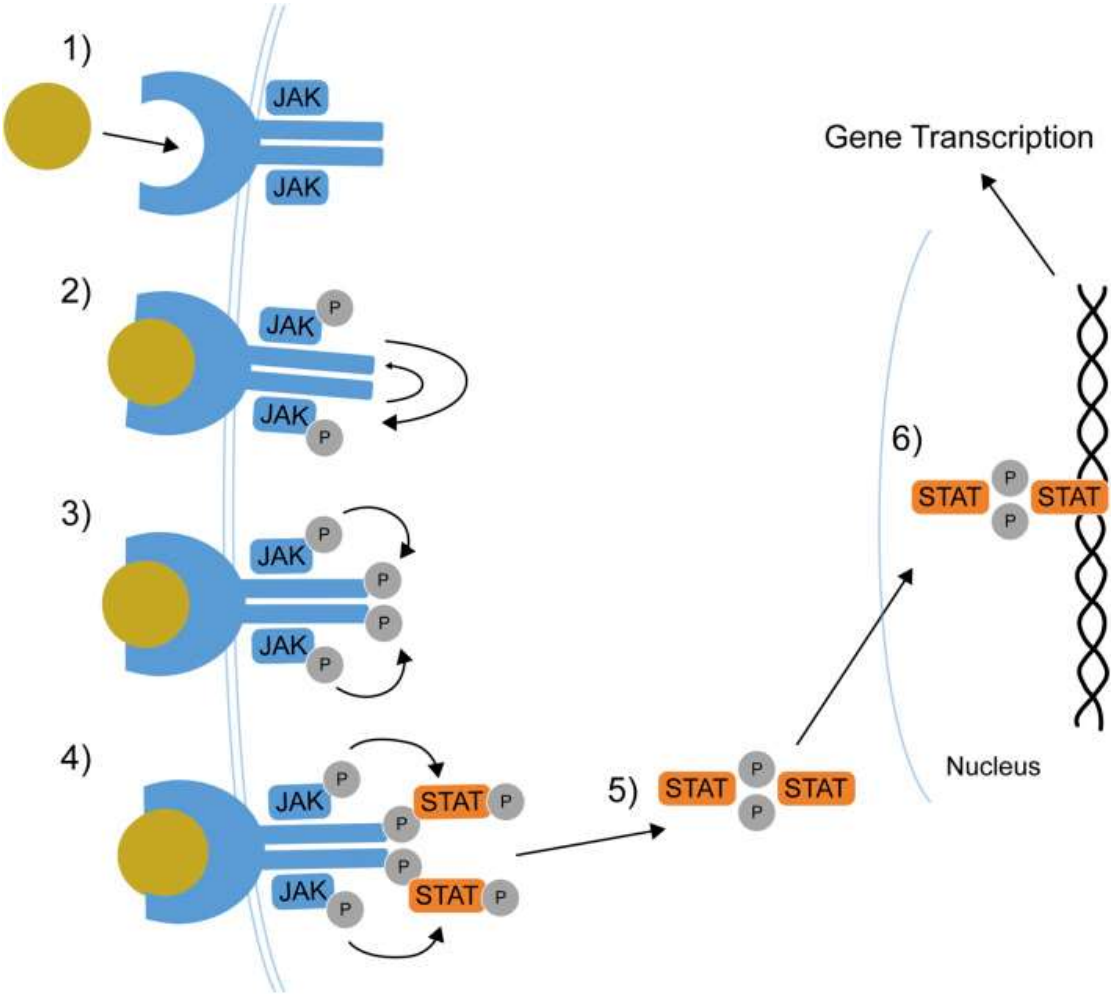
FIGURE 1.



The JAK-STAT signaling pathway. 1) A cytokine attaches to its receptor. 2) JAKs associated with the receptor phosphorylate and activate one another. 3) The JAKs add phosphate groups to the receptor's tail. 4) STATs bind to the receptor tail and undergo phosphorylation. 5) STATs detach from the receptor and form dimers. 6) The STAT dimers move into the nucleus, where they control gene transcription. (JAK): Janus kinase, P: phosphate group, STAT: Signal Transducer and Activator of Transcription. Adapted from (15). JAK inhibitors obstruct ATP binding on JAKs, hindering the phosphorylation of these proteins and the ensuing cascade of events that facilitate cytokine signal transduction (15).

1.2 Various JAKs yield diverse biological outcomes

Different cytokine receptors utilize unique combinations of JAK isoforms for signal transduction (16). This is a crucial aspect to consider when developing or selecting a JAK inhibitor, as varying selectivity for JAK isoforms can lead to different biological outcomes, affecting the drug's efficacy and safety profile (14,15,16). Based on current available evidence, only JAK1 and TYK2 among the various JAK isoforms appear to play a predominant role in inflammatory signal transduction and may serve as optimal targets for managing disease activity in IMIDs (16). Several investigations indicate that the effectiveness of JAK inhibitors in rheumatoid arthritis primarily depends on the inhibition of JAK1 (17,18). Similarly, the most significant proinflammatory cytokines implicated in IBD pathogenesis seem to exert their effects through JAK1 and TYK2 (19).In contrast, JAK2 and JAK3 also regulate other essential physiological processes (16).

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For instance, a pre-clinical study, in which a conditional knockout approach was used to inactivate JAK2 at any stage of prenatal or postnatal development, showed that JAK2 plays a key and non-redundant role in hematopoiesis. Adult mice in which JAK2 had been inactivated showed a reduction in blood cell counts, abnormal erythrocyte morphology, reduction of bone marrow hematopoietic potential, and splenic atrophy (20).This evidence is not surprising, considering that JAK2 is present in the form of a homodimer on the erythropoietin and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) receptor, playing a crucial role in erythropoiesis, myelopoiesis and platelet production. (16).JAK2 is also associated with the myeloproliferative leukaemia (MPL) receptor, which is stimulated by thrombopoietin (TPO) and is crucial for platelet production. An *in vitro* study has shown that, in the presence of TPO, exposure to suboptimal doses of a JAK2 inhibitor leads to a paradoxical increase in platelet production both *in vitro* (in $CD34^+$ cells) and *in vivo* (in C57BL/6 mice) (21).

In addition, the JAK2 homodimer is associated with leptin receptors and transduces the leptin signal of this adipokine by phosphorylating STAT3. Leptin is an adipokine that regulates energy homeostasis and glucose and lipid metabolism. It has been shown that hyperphagia and obesity occur in cases of congenital leptin deficiency or loss-of-function mutations of this adipokine receptor (22).Finally, JAK3 is associated with JAK1 in the IL-15 receptor, representing the dominant JAK for signal transduction. IL-15 receptor has been shown to be critical for the development and functioning of natural killer (NK) cells. These immune cells play a crucial role in defending the body against viruses and cancer (2).It should be emphasized, however, that the whole picture of the biological effects associated with each JAK isoform and the role of this kinase's different variants in IMIDs pathophysiology are not yet fully clarified; and should be considered only as a selection of the most accepted available evidence.

1.3 Assessment of the preferential selectivity of JAKis

JAK family members are structurally homologous and share a highly conserved ATP binding pockets. JAKis compete with ATP for binding these pockets and differences in affinity for the pockets of each single JAK result in the distinct affinity profiles of these drugs for JAK members (15).All JAKis block the IFN-alpha and IL-6 signaling pathways, both of which are dependent on JAK1, with no significant differences between drugs. On the contrary, there were significant differences in the effect of JAKis on the other pathways. Importantly, filgotinib showed the lowest inhibitory potency on the IFN-gamma (JAK1/JAK2), IL-2/IL-15/IL-16 (JAK1/JAK3), G-CSF/IL-12/IL-23 (JAK2/TYK2) and GM-CSF (JAK2/JAK2) pathways compared with all other drugs in the class .In general, the *in vitro* studies carried out so far show that tofacitinib can be considered a pan-inhibitor, since it inhibits all JAK isoforms indiscriminately; baricitinib, on the other hand, has prevalent selectivity for JAK1 and JAK2; upadacitinib and especially filgotinib are JAK1 preferential inhibitors, with limited effects on other isoforms (23).

1.4 From pharmacodynamics to clinical safety

Adverse events such as infections, venous thromboembolism (VTE) events, cancer, and blood cell cytopenia are considered class effects of JAKis by regulatory agencies. However, differences observed in the pharmacodynamic profiles of JAKis along with the results from pivotal trials weaken the strength of this assumption. Currently is well established that JAKis' efficacy is associated with their preferential selectivity for JAK1, while safety concerns emerge as inhibition of JAK2- and JAK3-dependent pathways increases (16).Therefore, the reduced inhibition of JAK2 and JAK3-dependent cytokine signaling pathways by filgotinib may theoretically explain its improved tolerability profile.

2. Pharmacokinetic Insights

2.1 Influence of JAK inhibitor metabolic pathways in poly-treated individuals

Recent literature reviews (28,29) have compiled possible pharmacokinetic interactions between JAK inhibitors and other pharmaceuticals.The initial review focused on tofacitinib, baricitinib, and upadacitinib. The administration of baricitinib resulted in a 30% decrease in simvastatin Cmax, while upadacitinib's use led to a roughly 20% reduction in the Cmax of rosuvastatin and atorvastatin. Consequently, in patients receiving these JAK inhibitors, the effectiveness of statins may be diminished (28). Unsurprisingly, administration of fluconazole or ketoconazole (known to inhibit the metabolism of various drugs) elevates the Cmax of all JAK inhibitors, which may heighten the risk for adverse effects. Conversely, the use of rifampicin (a known inducer of liver enzymes and transporters) significantly decreases the AUCs of tofacitinib, baricitinib, and upadacitinib (28).The second review concentrate

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d on filgotinib (29). Due to its gastrointestinal metabolism, filgotinib does not present a clinically meaningful inhibitory or induci ng effect on hepatic cytochromes, the enzymes most frequently implicated in drug interactions. Thus, filgotinib is characterized by a lower likelihood of interactions with other medications, making it particularly suitable for polytreated patients using pred ominantly hepatically metabolized drugs (30). Rifampicin was the sole drug identified that interacts with the active metabolite of f ilgotinib, resulting in a reduction of its AUC.Moreover,filgotinib exhibited a nonsignificant trend towards increasing rosuvastat in's Cmax and AUC, given that these drugs share the same transport mechanisms (29).

2.2Influence of JAK inhibitors on lipid profiles

A welldocumented class effect of JAK inhibitors is the augmentation of lipid levesin the bloodstream. In this regard, it's beneficial to examine the evidence surrounding tofacitinib, as it was the first approved JAK inhibitor, and thus has the longest available safe ty follow-up.

Among the vast array of data regarding tofacitinib's impact on lipid levels, notable findings arose from the OCTAVE study progra m, which encompassed over 1,100 patienswith ulcerative colitis (29).The OCTAVE study program consisted of two 8-weekinduction trials, succeeded by a 52weeks maintenance study (OCTAVE Sustain) and an Open Label Extension (OLE), result ing in an accumulated drug exposure of around 7 years (29,31).Tofacitinib modified the lipid profile of ulcerative colitis patients asearly as the induction phase of the OCTAVE study,where a mild rise in both LDLc and HDLc compared to placebo was noted (32).This effect was dose
dependent and reversible upon discontinuation of the drug. During the maintenance phase, while LDLc and HDLc levels remaine d consistently elevated in ongoingtofacitinib treatment,those who switched to placebo saw their lipid levels rapidly
return to baseline. Notably, the LDLc/HDLc ratio remained stable throughout the maintenance phase of the OCTAVEstudy (31). HDLc and LDLc changes remained relatively unchanged in OLE patients given the 10 mg BID dose of tofacitinib, while t hey decreased over time in those administered the 5 mg BID dose (32).

In the OCTAVE study program, the most significant increases in cholesterol levels attributed to tofacitinib were observed in pa tients with elevated baseline lipid levels (32).Filgotinib and baricitinib showed similar effects on cholesterol levels to tofacitinib. Filgotinib impact on lipid profile has been evaluated in the SELECTION study (31). In this trial filgotinib resulted in minor increases in total cholesterol, LDL-c and HDL-c during the induction phase (10 weeks). These changes are not clinically relevant since in filgotinib highest dose group (200 mg), the cholesterol increases were similar to those observed in the placebo group (total cholesterol +29.3 mg/dL vs. +29.1 mg/dL respectively; LDL-c +24.2 mg/dL vs. +23.2 mg/dL; HDL-c +16.0 mg/dL vs. 11.9 mg/dL). Moreover, during the SELECTION study 52-week maintenance phase, cholesterol levels in both filgotinib arms remained stable.

Despite the increase in cholesterol being a class effect, significant differences between JAKis can be observed. A recent meta-analysis of patients with rheumatoid arthritis showed that filgotinib increased LDL-c and HDL-c levels to a similar extent while maintaining their ratio approximately constant (33). In contrast, with tofacitinib and upadacitinib, LDL-c increases more than HDL-c. These differences between JAKis have also been confirmed in a recent Italian real-world study in patients with RA, where filgotinib proved to be the only JAKi with a neutral effect on the LDL/HDL-c ratio (34).These results may be clinically relevant because LDL-c is an established atherogenic component of the lipid profile, and the main guidelines on cardiovascular risk prevention recommend reaching specific LDL-c targets, considering other lipid parameters less critical (35).However, even in the long-term safety follow-up of tofacitinib, cholesterol increase has not been clinically meaningful since the Reynolds cardiovascular risk score (which assesses the risk of cardiovascular events at 10 years) did not increase after 8 weeks of treatment, and only 4.8% of patients had to start a lipid-lowering therapy during the study (32).It should be mentioned that in IBD blood lipid levels are typically lower than in the general population and inversely related to disease activity; therefore, a treatment capable of reducing disease activity is expected to increase blood cholesterol levels (36,37) ls is not direct but due to drug-related improvement of inflammation. This has been confirmed by a study on tofacitinib, where in treated patients showed a reduction in the activity of the cholesterol-esterase enzyme was observed, which correlated with the inflammation burden reduction (36).

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2.4 Feasibility of co-treatment with JAKis and statins

Although rarely needed both in clinical trials (<5% of patients) and clinical practice, statin therapy initiation may be required to reduce the JAKis-related LDL-c elevation (31).In patients treated with JAKis, statin therapy can effectively restore normal LDL-c levels (8,24,25,26). However, the Summaries of Product Characteristics (SmPCs) of different JAKis not always include comprehensive information about JAKi-statins interactions . For example, tofacitinib SmPC do not mention possible interactions with statins, while baricitinib SmPC only excludes the risk of interactions with simvastatin.SmPC: summaries of product characteristics, NM: not specified in SmPC, PK: pharmacokinetics, AUC: area under the curve, JAKi: Janus kinase inhibitors. Sourced from the European Medicine Agency (8,24,25,26).Filgotinib and upadacitinib are the solitary JAKis examined for pharmacokinetic interactions with statins in healthy subjects (37,38).

The filgotinib investigation aimed to determine whether the in vitro inhibitory action of this JAKi on OATP-1B1 and OATP-1B3 (the transporters for statins) could result in pharmacokinetic implications in humans. Importantly, the 2020 iteration of the filgotinib SmPC imposed a contraindication for the co-use of this JAKi and statins. Findings revealed that filgotinib did not produce clinically significant effects on atorvastatin, pravastatin, or rosuvastatin levels, leading to the removal of the co-administration contraindication from the SmPC (24).The upadacitinib investigation yielded similar outcomes, indicating that the JAKi had no clinically significant impact on the pharmacokinetics of rosuvastatin and atorvastatin; thus, the current upadacitinib SmPC states that no dose modifications are required when taken alongside these statins (26,38).

3. JAKi and male fertility

All JAKis, with the exception of upadacitinib, have indicated a potential effect on fertility in animal studies . While tofacitinib and baricitinib suggested a possible decline in female fertility in animal models, filgotinib highlighted a decrease in male fertility. Indeed, the initial version of this JAKi's SmPC included a caution regarding the potential treatment-related impairment of spermatogenesis and adverse histopathological impacts on male reproductive organs.Moreover, filgotinib could be a suitable option for male individuals with UC who intend to begin a family. This demographic is particularly significant as UC is more commonly found in males, usually emerging between the ages of 30 and 40 (39). The safety profile of filgotinib in these patients is reinforced by two investigations (MANTA and MANTA-Ray), which have shown its neutral impact on sperm metrics (40).Ultimately, lacking direct comparative research, an indirect evaluation of filgotinib alongside other JAK inhibitors (especially tofacitinib) implies that this medication may offer a more advantageous benefit/risk ratio. This stems from filgotinib’s selective action on JAK1, the inhibition of which is linked to the anti-inflammatory effects of JAK inhibitors. Conversely, filgotinib’s inhibitory action on JAK2 and JAK3 is minimal; this accounts for its reduced likelihood to elicit the adverse responses typically associated with JAK inhibitors.

In summary, while JAK inhibitors represent a significant treatment option for immune-mediated inflammatory diseases (IMIDs), they do not constitute a uniform category of medications. There are considerable variances in the pharmacokinetic and pharmacodynamic characteristics of these agents. Recognizing these distinctions is crucial to determine the most suitable JAK inhibitor for each patient. This article has evaluated the most pertinent data regarding JAK inhibitors to aid in distinguishing the unique attributes of each compound. We have encapsulated our findings in seven key considerations to assist rheumatologists, gastroenterologists, and dermatologists in selecting a JAK inhibitor for their patients .

4. Key considerations for selecting a JAK inhibitor for IMID patients.

1. JAK inhibitors manifest diverse mechanisms of action regarding their binding selectivity for JAK isoforms. JAK1 and TYK2 chiefly affect the transduction of inflammatory signals. Besides their role in inflammatory signaling, JAK2 and JAK3 are involved in regulating hematopoiesis. Filgotinib primarily inhibits JAK1.

2. JAK inhibitors vary in their biotransformation mechanisms: baricitinib, tofacitinib, and upadacitinib undergo hepatic metabolism via the P450 cytochrome system, whereas filgotinib is fully metabolized in the intestines through distinct enzymatic pathways (CES2). This trait may be beneficial for patients on multiple medications that predominantly undergo hepatic metabolism.

3. In human subjects, filgotinib and upadacitinib have not shown pharmacokinetic interactions with atorvastatin, pravastatin, and rosuvastatin, suggesting that co-administration of these JAK inhibitors with these statins may not lead to significant clinical effects.

4. According to its labeling, the administration of filgotinib at 200 mg/day does not affect sperm parameters in patients with IMIDs.

5. From a safety standpoint, the employment of JAK inhibitors in individuals with rheumatoid arthritis (RA) and underlying risk factors has been linked to adverse cardiovascular events; however, there is a lack of data on the risk for ulcerative colitis (UC) patients or comparisons among individual agents.

6. There are no established markers to guide the selection of particular JAK inhibitors for specific patient types or disease stages.

Janus kinases (JAKs) are protein tyrosine kinases (TYKs) capable of binding to transmembrane type I and type II cytokine receptors, mediating cellular reactions to various cytokines and growth factors. These mediators play crucial roles in immune defense and in immune-mediated conditions. Several pharmacologic JAK inhibitors (JAKi) are available for clinical application as oral and topical treatments for immune-mediated and inflammatory disorders, though the availability of different JAKi varies across regions and countries. The range of applications for these small molecules continues to expand. JAKi have received approval for numerous autoimmune diseases and are being considered for additional inflammatory and autoimmune conditions. Despite considerable progress, there remains a significant demand for innovative therapeutic strategies for these illnesses. When targeting specific cytokines outside the cell does not reliably attain full remission, an appealing alternative is to target the actions of various cytokines intracellularly, which is the core characteristic of JAKi.In this review, we will concentrate on the JAK-STAT pathway, instrumental in the inflammation and autoimmune response processes. Targeting this pathway is essential in the management of autoimmune diseases to inhibit the inflammatory response. We will subsequently outline the currently approved indications for JAK inhibitors, and finally, we will discuss the existing evidence and future prospects of JAK inhibitors in other autoimmune disorders.

5. JAK inhibitors

The initial therapeutics introduced in rheumatology were intravenous antibody drugs targeting cytokines or their receptors, such as anti-IL6 receptor and anti-TNF alpha. However, their limited specificity resulted in several unwanted side effects. JAK inhibitors arose from the necessity for more targeted therapeutic approaches for specific signaling pathways and the increased patient demand for oral medications. JAK inhibitors are small synthetic compounds that predominantly induce phosphorylation of JAK on the intracellular domain of the transmembrane receptor. These inhibitors function in a reversible manner. Signal disruption can be accomplished either competitively by (i) binding to the ATP-binding site within the catalytic domain or (ii) allosterically by attaching to an alternate site to inhibit receptor activation [11,41,42]. There are two generations of JAK inhibitors [43]:

• The first generation comprises non-selective molecules that inhibit multiple JAKs (pan-JAKi), such as tofacitinib or baricitinib;

• The second generation comprises molecules that are more specific to one isoform of JAK, like filgotinib. Available JAK inhibitors (JAKi) for clinical application vary in their selectivity for specific JAK isoforms.

Nonetheless, it remains unclear how this evident JAK selectivity observed in laboratory environments and experimental animal studies corresponds to significant variations in clinical efficacy among these agents across a range of chronic inflammatory conditions. At concentrations similar to those that are clinically effective, the overall selectivity of JAK inhibitors for specific JAK isoforms appears to be less than what is observed in cellular and biochemical evaluations. Tofacitinib, baricitinib, ruxolitinib, and peficitinib are characterized as pan-JAK inhibitors, whereas upadacitinib stands out as a highly selective JAK1 inhibitor. Filgotinib also serves as a highly selective JAK1 inhibitor. However, perfect selectivity or specificity is lacking. For instance, even though upadacitinib strongly inhibits JAK1, it also exhibits minimal inhibition of JAK2 and TYK2.

6. Confirmed indications in systemic and autoimmune disorders

6.1. Rheumatoid arthritis

From a pathophysiological standpoint, rheumatoid arthritis (RA) is marked by a significant infiltration of the synovium by immune cells, which secrete numerous soluble mediators and pro-inflammatory cytokines, including IL-6, a cytokine dependent on the JAK-

STAT pathway. Thus, employing JAK inhibitors could restore the balance of cytokines. Currently, four agents (tofacitinib, baricitinib, upadacitinib, and filgotinib [limited to women]) are approved for moderate to severe RA in patients who have failed or poorly tolerated one or more conventional synthetic disease-modifying antirheumatic drugs (DMARDs) or biological therapies, used either alone or in conjunction with methotrexate. Tofacitinib showed quicker effectiveness than methotrexate, achieving a satisfactory response as early as 2 to 4 weeks based on the American College of Rheumatology (ACR) 20 criteria [44,45,46,47]. Baricitinib, when combined with a synthetic DMARD, exhibited superior efficacy compared to adalimumab [48]. The RA BEGIN study [49] also established the superiority of baricitinib monotherapy over methotrexate in active RA. 3 phase III trials [50,51,52] demonstrated the effectiveness of upadacitinib in individuals with moderate to severe RA after failing synthetic DMARDs or biological therapies [53]. A phase III study (DARWIN 1) assessing the combination of filgotinib with methotrexate against placebo and DARWIN 2 evaluating filgotinib alone showcased the efficacy of filgotinib compared to placebo [54]. Due to reports of fertility issues in men taking filgotinib, it has only been approved for women with moderate to severe RA who have not succeeded or are intolerant to first-line treatments. Peficitinib is restricted to Japan, not available in the US or Europe, and is under investigation or development in several other nations. Nonetheless, safety concerns from a Phase 3b/4 clinical trial [55]. A dose-dependent increase in the risk of major adverse cardiovascular events, malignancy, opportunistic infections, venous thromboembolism, and overall mortality with tofacitinib compared to TNF inhibitors in RA patients with cardiovascular risk factors. Consequently, the US Food and Drug Administration (FDA) has advised the use of JAK inhibitors only after the failure of TNF inhibitors, rendering it no longer a viable option for many patients.

6.2 Psoriatic arthritis and spondyloarthropathy

The cytokine release pattern in spondyloarthropathy (SpA) underlines the production of pro-inflammatory cytokines such as IL12/IL23, which relies on the JAK/STAT pathway. Tofacitinib, administered at 5 mg twice daily, has been authorized for active psoriatic arthritis with insufficient response (or intolerance to DMARDs). Its effectiveness has been validated in two clinical trials [56]. In the SELECT MONOTHERAPY trial [57], upadacitinib demonstrated effectiveness against methotrexate, and an extension application has been submitted. The EQUATOR trial [58] examined the effectiveness of filgotinib compared to placebo in moderate to severe psoriatic arthritis after intolerance, contraindication, or failure of at least one synthetic DMARD, with notable responses 16 weeks post-first dose favouring filgotinib (80% vs. 33%).For axial and peripheral SpA, a randomized phase III trial [59] evaluated the efficacy of tofacitinib against placebo in cases of failure following at least two non-steroidal anti-inflammatory drugs, demonstrating the superiority of tofacitinib relative to placebo. A phase II/III trial [60] showed the enhanced effectiveness of upadacitinib over placebo. The TORTUGA trial [61] confirmed the efficacy of filgotinib against placebo. An extension of the marketing authorization for SpA following the failure of two non-steroidal anti-inflammatory drugs has been requested, although its position remains uncodified.

6.3 Inflammatory bowel disease

Tofacitinib has gained marketing clearance (and upadacitinib has received FDA endorsement) for moderate to severe active ulcerative colitis (UC) after inadequate response or poor tolerance to conventional therapy or a biological product. In the OCTAVE 1 and 2 trials [62], tofacitinib has been demonstrated to outperform placebo. An open-label extension investigation, OCTAVE Open (NCT01470612) will furnish long-term efficacy and safety information regarding the application of tofacitinib in ulcerative colitis (UC). In Crohn's disease, two phase 2b investigations have examined the utility of tofacitinib for this indication, but contrary to UC, the outcomes did not reveal a notable distinction between tofacitinib and placebo [63]. Selective inhibitors such as upadacitinib [64] and filgotinib [65] have indicated promising clinical outcomes, with Phase II and III trials currently in progress.

6.4 JAK inhibitors in dermatology

JAK inhibitors present a hopeful category of medications in dermatology, offering fresh therapeutic avenues for chronic and challenging skin disorders. Their focused mechanism permits customized treatments, potentially enhancing patient results where conventional therapies have been ineffective. The body of literature regarding the effectiveness of JAK inhibitors in treating alopecia areata, vitiligo, atopic dermatitis, psoriasis, and several other inflammatory and autoimmune diseases is expanding. With the endorsement of the JAK inhibitors baricitinib, upadacitinib, and abrocitinib, new systemic therapeutic agents are now accessible

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for moderate to severe atopic dermatitis (AD). Other conditions where the efficacy of these small molecules has been demonstrated include psoriasis, vitiligo, and alopecia areata.

6.4.1 Atopic dermatitis

In the realm of atopic dermatitis, key cytokines involved in pathogenesis signaling through the JAK-STAT signaling pathway include IL-4, IL-13, and IL-31. Utilizing baricitinib (JAK1/2 inhibitor), upadacitinib (JAK1 inhibitor), and abrocitinib (JAK1 inhibitor) as systemic therapies, moderate to severe atopic dermatitis is currently at the forefront of dermatological approvals of JAK inhibitors. In a concluded phase 3 study (BREEZE-AD7), baricitinib combined with topical corticosteroids demonstrated significant effects compared to placebo at a dose of 4 mg for the primary endpoint [66]. Upadacitinib, a selective JAK1 inhibitor, achieved its coprimary and secondary endpoints and showed improvement in pruritus [67]. Furthermore, abrocitinib (JAK1 inhibitor) exhibited significant efficacy relative to placebo. Following 24 weeks of topical application, delgocitinib (pan JAK inhibitor) and ruxolitinib (JAK1/2 inhibitor) notably improved pruritus and EASI in patients with moderate to severe atopic dermatitis [68,69].

6.4.2 Psoriasis

In Germany, tofacitinib (JAK1/3/2 inhibitor) is the sole JAK inhibitor presently sanctioned for treating psoriatic arthritis. In various phase 3 studies, this agent has also proven effective in cases involving skin and nail manifestations [70,71]. Another exciting therapeutic strategy in psoriasis is the targeting of TYK2 with deucravacitinib, which was shown to be efficacious compared to placebo in a phase 2 study [40]. Manufacturer data indicates that a PASI75 response of 58.7% was achieved with deucravacitinib against 9.4% with placebo and 35.1% with apremilast in the phase 3 study POETYK PSO-1 [73]. Other JAK inhibitors (like baricitinib) have been investigated in psoriatic arthritis, but no added benefit compared to tofacitinib has been established thus far [74].

6.4.3 Alopecia and vitiligo

A recently published meta-analysis of JAK inhibitors in alopecia areata revealed that 72.4% of the subjects experienced a therapeutic response [75]; with 45.7% showing good regrowth (50–100% of hair) and 21.4% experiencing partial response (5–50% regrowth of hair). However, during administration, a fourfold superior response of oral JAK inhibitors (baricitinib, tofacitinib, ruxolitinib) relative to topical application was observed. In non-segmental vitiligo, two recent phase 3 studies (TRUE-V1) and (TRUE-V2) conducted concurrently in the USA and Europe displayed a greater enhancement in the primary endpoint, which involved an increase in F-VASI75 (a reduction of at least 75% in the Facial-Vitiligo Area Scoring Index) at week 24 with the application of topical ruxolitinib 1.5% administered twice daily compared to the control group: TRUE-V1 29.8% vs. 7.4%, $P < 0.001$, and TRUE-V2 30.9% vs. 11.4%, $P < 0.001$. These findings were mirrored in the secondary endpoints, which particularly targeted extra-facial regimentation.

7. Perspectives in systemic and autoimmune diseases

7.1 Systemic lupus erythematosus (SLE)

7.1.1. In animal models

A study by Furumoto et al. [76] explored the therapeutic potential of tofacitinib in a murine model of SLE. The research revealed that tofacitinib administration enhanced survival rates and reduced proteinuria in SLE-afflicted mice. Additionally, tofacitinib treatment diminished the population of activated T and B cells in the spleen while lowering the production of pro-inflammatory cytokines. MRL/lpr mice (Fas mutation mice) exhibiting active lupus nephritis demonstrate elevated levels of STAT1 and phospho-STAT1 within their glomerular cells [77]. Moreover, stimulating mesangial cells with type 1 IFNs in vivo results in the phosphorylation of STAT1. Treatment of MRL/lpr mice using a selective JAK2 inhibitor (AG490) led to a notable decrease in native anti-DNA antibody levels, proteinuria, and immune deposits within the glomerulus. In NZB/NZWF1 mice (a model of lupus featuring nephropathy and predominantly female disease expression), identical findings were noted with tofacitinib [78], [79]. Chan

et al. [80] Investigated the impact of ruxolitinib on the progression of cutaneous lupus in a murine model, resulting in an enhancement of the dermal T cell infiltrate in the treated subjects.

7.1.2 In individuals with SLE

The stimulation of plasmacytoid dendritic cells due to the inadequate clearance of apoptotic debris triggers the release of cytokines including type 1 IFNs. The family of type 1 IFN receptors consists of cytokine receptors linked to JAK inhibitors. Additionally, STAT4 genetic variations have been linked to more severe manifestations of lupus. The deployment of JAK inhibitors is emerging as a hopeful therapeutic avenue currently being assessed for this condition. Observational studies and/or controlled trials have been conducted for the following compounds.

7.1.2.1 Tofacitinib

A recently released, randomized, double-blind, placebo-controlled trial of tofacitinib (5 mg administered twice daily) in SLE patients demonstrated an acceptable safety profile, improvements in lipid profile abnormalities, a reduction in the type I IFN signature, and a restoration of endothelial function. However, the authors did not report any statistically significant differences in disease activity reduction, clarifying that the study was not geared towards evaluating the drug's effectiveness. The outcomes of an open-label phase 2 pilot study assessing oral tofacitinib in adults with discoid lupus erythematosus are forthcoming, with five participants enrolled. The main outcome measure is the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) at the 24-week mark. Results are still pending. Another phase 2, open-label assessment of tofacitinib for managing moderate to severe skin manifestations in young adults with SLE is underway. You et al. reported improvements in rash and arthritis as evaluated by SLEDAI-2K at their center. Among 10 patients in this series, 6 exhibited enhancements in skin involvement and 4 in joint symptoms. Awaited findings from a phase I assessment (tofacitinib versus placebo), initiated in 2015 and concluded in 2018, are still pending. All of these investigations were conducted in the United States.

7.1.2.2 Baricitinib

Baricitinib has displayed effectiveness in managing lupus disease in a double-blind Phase II trial (conducted in the United States), where remission was evaluated using SLEDAI-2K at a dosage of 4 mg/day (74 of 104 [67%] showed a response at 24 weeks in comparison to 53% in the placebo group concerning skin and/or joint involvement). In this investigation, the 2 mg/day dosage did not yield any clinical enhancements. Serious adverse events occurred in 9.6% of patients in the 4 mg baricitinib group, compared to 4.8% in the placebo cohort. Reports by Yuan et al. indicated that the 4 mg baricitinib dose lacked FDA approval for RA due to potential escalated risks of infectious and thromboembolic complications. Dörner et al. performed a randomized, double-blind, placebo-controlled phase II trial (conducted in the United States) to evaluate the safety and efficacy of baricitinib in diminishing anti-DNA antibody levels in SLE patients, who were randomized in a 1:1:1 ratio to receive either 2 mg or 4 mg of baricitinib, or placebo once daily for 12 and 24 weeks. The primary endpoint targeted the percentage of patients achieving a reduction in anti-DNA antibody levels of 25% or more at weeks 12 and 24. Results indicated that a significantly higher percentage of individuals in the baricitinib group reached the primary endpoint compared to placebo. No effects on complement activation were demonstrated. This study provides evidence that baricitinib may decrease anti dsDNA antibody levels in SLE patients, suggesting its potential as a therapeutic option for this group.

In a multicenter, double-blind, randomized, placebo-controlled, parallel-group, phase 3 study, SLE-BRAVE-I (conducted in the United States), patients (aged ≥ 18 years) with active SLE receiving stable background therapy were randomly assigned in a 1:1:1 ratio to receive baricitinib 4 mg, 2 mg, or placebo once daily for 52 weeks alongside standard care. The primary endpoint was the proportion of patients attaining an SLE Responder Index (SRI)-4 response at week 52 in the baricitinib 4 mg treatment group versus placebo. Ultimately, 760 participants were randomized and received at least one dose of either baricitinib 4 mg (n = 252), 2 mg (n = 255), or placebo (n = 253). A markedly greater proportion of those receiving baricitinib 4 mg (P = 0.016), but not baricitinib 2 mg (P = 0.47), achieved the SRI-4 response compared with placebo. There were no significant differences noted between the proportions of participants in either baricitinib group regarding major secondary endpoints when compared to placebo, including glucocorticoid tapering and time to first significant flare. Serious adverse events occurred in 26 (10%) patients receiving baricitinib 4 mg, as

compared to 24 (9%) in the 2 mg group, and 18 (7%) in the placebo group. The safety profile of baricitinib in individuals with SLE remained in line with the established safety profile of baricitinib. In summary, the main endpoint of this investigation was achieved for the 4 mg baricitinib cohort. Nonetheless, vital secondary endpoints were not fulfilled. No new safety concerns were identified.

In a separate phase 3 double-blind, randomized, placebo-controlled investigation, SLE-BRAVE-II (conducted in the United States) [81], patients with active SLE on stable background therapy were randomly allocated in a 1:1:1 ratio to baricitinib 4 mg, baricitinib 2 mg, or placebo once daily for a duration of 52 weeks. The primary endpoint examined was the percentage of patients demonstrating an SRI-4 response at week 52 in the baricitinib 4 mg treatment group compared to placebo. A total of 775 patients were randomly assigned, with at least one dose of baricitinib 4 mg (n = 258), baricitinib 2 mg (n = 261), or placebo (n = 256) administered. There was no significant difference in the primary efficacy outcome concerning the percentage of SRI-4 responders at week 52 among participants receiving baricitinib 4 mg, 2 mg, or placebo. None of the major secondary endpoints, including glucocorticoid tapering and the timing of the first severe flare, were satisfied. Serious adverse events were noted in 29 (11%) participants in the baricitinib 4 mg group, 35 (13%) in the baricitinib 2 mg group, and 22 (9%) in the placebo cohort. The safety profile of baricitinib in SLE patients mirrored the known safety profile of baricitinib. While phase 2 evidence indicated baricitinib as a potential treatment for SLE patients, as corroborated in SLE-BRAVE-I, these findings were not replicated in SLE-BRAVE-II, prompting a cessation of baricitinib usage in SLE.

7.1.2.3 Ruxolitinib

Ruxolitinib, a JAK1 and JAK2 inhibitor approved by the FDA for myelofibrosis treatment, displayed promise in mitigating severe skin alterations in a mouse model of SLE [82]. Following these encouraging results, a team from Rochester University began recruiting patients for a 12-week study using Ruxolitinib cream applied topically to areas with active lupus skin lesions. Results from this study will be available imminently. In 2016, Wenzel et al. [83] documented improvement in a lupus engorgement case with ruxolitinib prescribed in the context of myelofibrosis.

7.1.2.4 Filgotinib

A randomized phase II trial (conducted in the United States) assessed the efficacy of filgotinib in lupus extra-membranous glomerulonephritis involving 9 patients. A greater than 50% reduction in 24-hour proteinuria at week 16 was noted with filgotinib [84]. However, disappointing outcomes emerged from a recently completed trial with filgotinib in cutaneous lupus erythematosus patients. The study failed to meet the primary endpoint as those treated with filgotinib did not significantly enhance their CLASI [85].

7.1.2.5 Upadacitinib

A Phase 2 Investigation (conducted in the United States) explored the safety and efficacy of elsubrutinib (BTK inhibitor) and upadacitinib either Alone or in Combination (ABBV-599 Combination) in subjects with moderately to severely active SLE. At week 24, upadacitinib 30 mg given alone or as a combination therapy (ABBV-599 high dose [elsubrutinib 60 mg and upadacitinib 30 mg]) achieved the primary endpoint of SRI-4 response and steroid dose less than or equal to 10 mg prednisone equivalent daily in patients with moderately to severely active SLE receiving standard lupus therapies. Upadacitinib demonstrated more pronounced improvements in SLE disease activity at week 48, evaluated using the British Isles Lupus Assessment Group-Based Composite Lupus Assessment (BICLA), SRI-4, Lupus Low Disease Activity State (LLDAS), and lupus flare counts in comparison to placebo. No new safety signals were evident beyond the recognized safety profile of upadacitinib. Adverse effects reported with the ABBV-599 high dose were akin to those noted for patients treated solely with upadacitinib. Study findings were presented as an oral presentation at the European Congress of Rheumatology, EULAR 2023.

7.1.2.6 Deucravacitinib

Deucravacitinib is an oral selective, allosteric inhibitor of TYK2 that binds to the regulatory domain and locks the enzyme in an inactive state, setting it apart from inhibitors of JAK1, JAK2, and/or JAK3 that attach to the highly conserved active domains [86]. Morand et al. [87]A randomized, double-blind, placebo-controlled phase 2 study (conducted in the United States) was carried out

to assess the safety and effectiveness of deucravacitinib in individuals with moderate-to-severe SLE. The research involved 363 participants who were randomly assigned in a 1:1:1:1 ratio to receive deucravacitinib at either 3 mg twice daily, 6 mg twice daily, or 12 mg once daily, or a placebo. The primary goal was SRI-4 response at week 32. Secondary evaluations conducted at week 48 included SRI-4, British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response, CLASI-50, Lupus Low Disease Activity State (LLDAS), and enhancements in active (swollen plus tender), swollen, and tender joint counts. The findings indicated that deucravacitinib 3 mg and 6 mg twice daily were linked with a significantly greater number of patients reaching the primary endpoint compared to placebo and deucravacitinib 12 mg (58% [$P < 0.001$]; 50% [$P = 0.02$]; 34% and 45% [$P = 0.08$], respectively). The medication also showed improvements in several secondary measures. Adverse event rates were comparable among the groups, apart from elevated rates of infections and skin-related issues, such as rash and acne, associated with deucravacitinib treatment. The rates of serious adverse events were similar, with no instances of death, opportunistic infections, tuberculosis infections, significant adverse cardiovascular events, or thrombotic complications reported. In summary, the investigation revealed that deucravacitinib effectively reduced disease activity in patients suffering from moderate to severe SLE. These results imply that deucravacitinib could be a promising therapeutic option for SLE patients in the future.

7.1.2.7 Other JAKi

Subsequently, numerous randomized studies have been undertaken to investigate the inhibition of JAK STAT pathway in this context. A selective JAK2 inhibitor (CEP-33779) is presently undergoing phase I trials. GSK2586184, a JAK1 inhibitor, was analyzed in a phase II study that was prematurely halted due to inadequate reduction of the IFN signature in the initial patients involved. A topical JAK SYK inhibitor (R333) was tested in a phase II trial and failed to demonstrate regression of skin lesions in discoid lupus (NCT01597050). Pf-06700841, an oral JAK1 TYK2 inhibitor, is currently being examined in patients with moderate to severe systemic lupus (NCT03845517).

Overall, the effectiveness and application of JAKi in SLE remain insufficient for making definitive conclusions. Although several case series and phase I/II trials have illustrated their efficacy in skin and joint involvement, outcomes from some randomized studies lack consistency. For instance, the SLE-BRAVE-I trial validated baricitinib as a potential treatment for SLE patients, but this finding was not echoed in SLE-BRAVE-II, resulting in a suspension of its use for SLE. Nevertheless, other JAKi, like Deucravacitinib, have shown promise; a randomized phase 2 trial demonstrated its effectiveness in diminishing disease activity in individuals with moderate to severe SLE. Upadacitinib, used alone or in combination with a BTK inhibitor, also appears encouraging. Currently, there is insufficient evidence for JAKi effectiveness in addressing neurological or renal damage caused by lupus. The challenge in evaluating the efficacy of lupus treatments may arise from the disease's variability and the differing classification criteria utilized across trials. There is a need to augment these findings with randomized phase 3 studies, some of which are already in progress.

7.2 Dermatomyositis

No preclinical research exists. An IFN type 1 signature is recognized in patients with inflammatory myositis [88]. Paudyal et al. [89], in a recently published literature review, identified over 50 patients with resistant DM treated with JAKi (tofacitinib or ruxolitinib). Improvements in skin, muscle, and overall condition were noted with JAKi. A case of favourable progression of diffuse interstitial lung disease (ILD) associated with anti-MDA5 positive DM refractory to rituximab, cyclophosphamide, cyclosporine A, and high-dose corticosteroids has been documented. An important aspect to highlight is the potential significance of certain JAKi in treating subcutaneous calcinosis present in some refractory DM, as reported in case studies [90], [91]. One theory is that the STAT3 pathway mediates calcium storage and release.Observational studies and/or controlled trials exist for the following compounds.

7.2.1 Tofacitinib

Several case reports have indicated that JAKi may prove effective in managing DM [92], [93], [94], [95], [96], [97]. Specifically, two studies focused on the role of tofacitinib in treating rapidly progressive ILD in anti-MDA5-positive DM patients. Kurasawa et al. [93] presented a case series of 5 patients who were administered tofacitinib at a dosage of 10 mg/day after not responding to a triple therapy involving high-dose glucocorticoids, cyclosporine, and cyclophosphamide. The authors compared the outcomes of

these 5 patients with 6 historical patients who received triple therapy without tofacitinib. Both patient groups were comparable regarding key factors indicating poor prognosis, including elevated serum ferritin levels, worsening pulmonary infiltrates, and generalized ground-glass opacities. Notably, three individuals in the tofacitinib group exhibited a positive response, while the remaining patients, including all from the historical cohort, did not. On the other hand, reactivation of cytomegalovirus remained consistent among individuals undergoing triple therapy alongside tofacitinib. Chen et al. [95] from China carried out an open-label clinical trial at a single-center to assess the effectiveness of tofacitinib in the early phases of anti-MDA5 positive DM-related ILD. From July 2017 to September 2018, a total of 18 consecutive patients were included and primarily treated with glucocorticoids and tofacitinib (5 mg/12 h), occasionally supplemented with other immunosuppressants (2 individuals received cyclosporine and 1 mycophenolate mofetil). When compared to a historical control group of 25 patients who underwent a progressive immunosuppressive strategy involving cyclosporine, mycophenolate mofetil, and/or cyclophosphamide, the survival rate at 6 months was markedly higher in the tofacitinib-treated group than in the historical group. Notably, patients achieved positive outcomes without severe immunosuppression, thus minimizing the risk of infectious complications such as cytomegalovirus reactivation and other opportunistic infections. In severe DM cases, Marchiset et al. [98] reported a case involving a patient newly diagnosed with rapidly progressive ILD associated with anti-MDA-5, for whom no therapies proved effective, including glucocorticoids, cyclophosphamide, plasma exchanges, tofacitinib, and tacrolimus. She was placed on mechanical ventilation and Veno venous extracorporeal membrane oxygenation two weeks after her diagnosis as part of a bridge-to-transplant process. She underwent a successful transplant 20 days later after being registered with high priority on the French National Lung Transplant Waiting List. One year post-surgery, her pulmonary function tests were satisfactory, and no indications of relapse of anti-MDA-5 DM were evident. The article underscores the necessity of a swift and comprehensive assessment of patients with anti-MDA-5 DM exhibiting respiratory symptoms, as lung transplantation may be a critical option for severely ill patients. However, this procedure comes with risks and should be approached cautiously. Shirai et al. [99] described a case involving a patient with severe anti-MDA5 antibody-positive DM who underwent an intensive induction regimen that combined tofacitinib, rituximab, and plasma exchange. Following the treatment, the patient showed considerable improvement in both skin and muscle symptoms, which persisted for at least 6 months following the completion of therapy. The authors advocate that this aggressive induction therapy approach may represent a promising treatment for severe instances of anti-MDA5 antibody-positive DM. Overall, the article illustrates the potential of integrating various treatments to tackle severe DM cases, especially those linked to specific autoantibodies such as anti-MDA5. Paik et al. [100] conducted an open-label pilot study involving 10 patients to examine the effectiveness and safety of tofacitinib in active, treatment-resistant DM (STIR trial). Tofacitinib was administered at a daily dose of 11 mg to all 10 participants who had a complete washout from all steroid-sparing agents. The primary outcome was defined by the International Myositis Assessment and Clinical Studies (IMACS). The response rate was assessed using the 2016 ACR/EULAR Myositis Response Criteria based on the total improvement score (TIS). Secondary outcomes included the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), chemokine levels, skin STAT 1 expression via immunohistochemistry, RNA sequencing analysis, and safety. All 10 subjects achieved the primary outcome at the 12-week mark, with 50% showing moderate improvement while the other half had minimal improvement on the TIS scale. A statistically significant mean change was recorded in the CDASI activity score from baseline to 12 weeks (28 ± 15.4 vs. 9.5 ± 8.5, $P = 0.0005$). This study marks the first prospective, open-label clinical trial of tofacitinib in DM demonstrating substantial clinical efficacy for a pan JAK inhibitor.

7.2.2 Baricitinib

Zhao et al. [101] introduced a prospective open-label study evaluating the effectiveness and safety of baricitinib in treating cutaneous DM. Twelve patients with cutaneous DM received baricitinib (2 mg twice daily) over a span of 12 weeks. Concurrent treatments, including prednisone ($\leq$ 30 mg/day) and/or hydroxychloroquine, were either continued or reduced at the discretion of the attending clinicians. The primary outcome measure was the CDASI score. All 12 patients (mean age: 40.8 ± 10.4 years, 66.7% female) presented with active skin disease, as established by a CDASI score of at least 14 upon enrolment. Notable improvement was observed as early as week 4. Significant enhancements in the CDASI score ($P < 0.001$) and the Dermatology Life Quality Index score ($P < 0.001$) were noted from baseline to week 12. While this study is small and uncontrolled, it supports baricitinib as an encouraging therapeutic option for cutaneous DM. Further research is needed to validate these results and to identify patients who would benefit the most from JAK inhibitors. Delvino et al. [102]

A patient suffering from resistant cutaneous DM was effectively managed with baricitinib. This individual had undergone several unsuccessful treatments, including glucocorticoids, hydroxychloroquine, mycophenolate mofetil, methotrexate, and intravenous immunoglobulin. Following the initiation of baricitinib, the patient saw notable improvement in skin symptoms within 4 weeks. With ongoing treatment, the skin lesions showed continued enhancement, and no considerable adverse reactions were reported. This case report indicates that baricitinib may present a hopeful therapeutic alternative for patients with resistant cutaneous DM who have not responded to prior therapies. A prospective investigation by Allenbach's group (conducted in Paris, France) is currently assessing the efficacy of baricitinib in patients with relapsing or naïve DM (BIRD) (NCT04972760). This multicenter phase III double-blind randomized placebo-controlled study consists of two parallel arms (1:1 ratio). It serves as an adjunct to standard care with a swift tapering of corticosteroids. Participants in both the experimental and control cohorts will receive corticosteroids alongside a conventional immunosuppressant (either azathioprine or methotrexate). They will be randomly assigned in a 1:1 ratio to receive either baricitinib plus a prednisone taper along with one immunosuppressive agent (either methotrexate or azathioprine) (experimental group) or placebo combined with a prednisone taper and one immunosuppressive drug (either methotrexate or azathioprine) (control group) for a span of 24 weeks. Corticosteroid tapering will follow a defined protocol in both arms. Their hypothesis proposes that baricitinib will facilitate DM enhancement with a steroid-sparing benefit compared to standard treatment. Their main objective is to assess the efficacy of baricitinib in achieving moderate improvement free from prednisone (ACR/EULAR ≥ 40) in DM relative to placebo, in conjunction with standard care, over 24 weeks. The outcomes of this trial are forthcoming.

7.2.3 Ruxolitinib

Some isolated case reports have indicated that JAK inhibitors (JAKi) may offer effectiveness in severe juvenile DM[103,104,105]. However, there is limited evidence regarding ruxolitinib's efficacy in adult DM. Hornung et al. [106]documented a case involving a patient with stubborn DM who attained remission after ruxolitinib treatment, having previously not responded to various therapies including glucocorticoids, methotrexate, mycophenolate mofetil, and intravenous immunoglobulin. On starting ruxolitinib, the patient showed significant enhancement in both skin and muscle symptoms within 4 weeks. Continued treatment led to further symptom alleviation without notable adverse effects. This report implies that ruxolitinib may serve as a viable treatment for refractory DM, especially in instances where prior therapies have been ineffective. Moreover, Paik et al [107]. performed a systematic literature review concerning JAKi application in DM. They identified 48 publications that included 145 unique patients (adult DM, n = 84; Juvenile DM [JDM], n = 61). Among adult DM cases, 61 out of 84 (73%) demonstrated resistant skin disease at the outset, all reporting improvement in cutaneous symptoms. From the adult DM patient group, 16 out of 84 (19%) had persistent muscle disease at the beginning, with all (16 out of 16) indicating muscle symptom enhancement. In cases of adult DM merged with ILD (n = 33), a substantial 31 (94%) patients noted improvement following JAKi. Of the JDM patients exhibiting resistant skin disease initially (60 out of 61), the majority (57 out of 60; 95%) experienced betterment in skin symptoms post-JAKi treatment. Among JDM patients with persistent muscle issues at the outset (36 out of 61), most (30 out of 36; 83%) noted muscle symptom enhancement. Four JDM patients with ILD showed improvement in pulmonary disease activity following JAKi treatment. In both DM and JDM cases, all participants (17 with DM and 16 with JDM) exhibiting heightened serum IFN and/or IFN-stimulated gene activity initially showed a reduction in IFN or IFN gene expression. Although the interpretations from this analysis are limited due to variances in assessments across studies, the overall treatment with JAKi for DM and JDM patients was linked with substantial improvements across a variety of DM manifestations, including skin lesions, muscle weakness, and ILD. This systematic review suggests the potential viability of JAKi as a treatment avenue for DM/JDM, warranting randomized controlled trials to substantiate these discoveries. In conclusion, the prospect of JAKi in the management of dermatomyositis appears encouraging, with preliminary results from randomized trials supporting treatment outcomes for cutaneous, articular, and pulmonary involvement in swiftly progressing, refractory cases. The specific role and choice of agent remain to be established, as we await the findings from ongoing randomized trials.

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7.3 Myocarditis Triggered by Immune-Checkpoint Inhibitors

7.3.1 Ruxolitinib

The myotoxicity associated with immune-checkpoint inhibitors (ICIs) affects both the heart (myocarditis) and skeletal muscles (myositis), often occurring simultaneously with a high mortality rate. Salem et al. [108] presented findings from a strategy that involved identifying patients with severe ICI myocarditis by screening for and managing concurrent respiratory muscle involvement via mechanical ventilation, in addition to administering the CTLA4 fusion protein abatacept and the JAK inhibitor ruxolitinib. A total of forty confirmed cases of ICI myocarditis were included, with the majority showing pathological evidence of accompanying myositis. In the first group of ten patients, adherence to standard protocols resulted in a myotoxicity-related fatality rate of 60%, aligning with historical benchmarks. In contrast, the fatality rate linked to myotoxicity was only 3.4% (1/30) among the subsequent 30 patients, significantly lower than the first quartile ($P < 0.0001$). These clinical observations are thought-provoking and warrant additional investigation.

7.4 Systemic Sclerosis

Systemic sclerosis (SSc) is a multifaceted autoimmune condition characterized by fibrosis, vascular irregularities, and immune system dysregulation. Several considerations support the potential use of JAK inhibitors in the treatment of SSc.

7.4.1 In Animal Studies

Bellamri et al. [109] explored the therapeutic effectiveness of the JAK1/2 inhibitor ruxolitinib in preclinical SSc models. The research employed two murine models of SSc, one induced by bleomycin and the other via the Tsk/+ mutation, assessing the impact of ruxolitinib on skin fibrosis, lung fibrosis, and immune cell infiltration. The findings indicated that treatment with ruxolitinib led to a significant reduction in skin fibrosis and enhancement of skin structure in both SSc mouse models. Furthermore, ruxolitinib also mitigated lung fibrosis in the bleomycin-induced model, though not in the Tsk/+ strain. The study additionally revealed that ruxolitinib therapy reduced the presence of infiltrating immune cells, including T cells, B cells, and macrophages, in the skin and lungs of SSc-affected mice. Aung et al. [110] examined the effects of tofacitinib on immune dysfunction in a bleomycin-induced SSc mouse model finding that tofacitinib therapy improved skin thickness and collagen levels. Moreover, tofacitinib decreased the immune cell infiltration in the skin and lowered the production of pro-inflammatory cytokines. The study also showed that tofacitinib increased the levels of regulatory T cells (Tregs) within the skin of SSc mice, highlighting their vital role in immune regulation and suppression of other immune cells' activity.

7.4.2 In Systemic Scleroderma (SSc) Patients

Transforming growth factor (TGFb) serves as a crucial cytokine in the profibrotic processes. TGFb transmits signals through both SMAD and non-SMAD pathways to elicit diverse biological effects. Tang et al. [111] demonstrated that the interplay between the JAK1 STAT3 and SMAD pathways is vital for TGFb's role in liver fibrosis. Additionally, similar to systemic lupus erythematosus and various connective tissue disorders, patients with SSc showed elevated levels of IFNα, indicating a direct pathogenic implication in disease progression [112]. Notably, the IFN signature can be identified very early in the disease course, even years prior to a definitive diagnosis, suggesting that IFN upregulation is an early event significantly contributing to the disease's pathogenesis [113]. Therefore, inhibiting IFNs via JAK-STAT pathway blockade could be of considerable interest. Another crucial component in SSc pathogenesis is IL-6, along with the IL-6 cytokine family, both of which can be targeted by JAK inhibitors. IL-6 plays a role in vasculopathy and is involved in the fibrotic processes within SSc. The levels of IL-6 in plasma correlate with disease severity and skin thickening extent [114]. This pathophysiological context supports clinical trials focused on inhibiting IL-6 activity [114,115]. While these efforts are promising, previous studies have not met their primary objectives [116]; however, tocilizumab has received FDA approval for use in SSc patients with interstitial lung disease. Wang et al. [117] examined the activation of the JAK-STAT signaling pathway in SSc. The authors conducted experiments using skin and blood samples from SSc patients to assess the expression and activation of numerous components of the JAK-STAT pathway. The findings indicated significant activation of the JAK-STAT pathway in SSc patients compared to healthy controls, with this activation linked to increased fibrosis and inflammation. They also demonstrated that tofacitinib effectively inhibits the JAK-STAT pathway in samples from SSc patients, leading to reduced

expression of pro-fibrotic and pro-inflammatory markers. Given these results, the authors propose that tofacitinib might be a viable treatment for SSc due to its ability to inhibit the JAK-STAT pathway and diminish fibrosis and inflammation. However, they emphasize that further research is essential to confirm the safety and efficacy of tofacitinib in SSc patients and to determine optimal dosing and administration strategies. Observational studies and/or controlled trials are available for the following compounds.

7.4.2.1 Tofacitinib

Moriana et al. [118] offer a thorough review of existing literature regarding the application of JAK inhibitors (JAKi) in treating systemic sclerosis (SSc). The authors executed an extensive search across various databases to locate pertinent studies, incorporating both preclinical and clinical investigations in their review. This analysis indicates that JAKi could serve as a viable treatment option for SSc, given their capacity to modulate immune responses, alleviate inflammation, and inhibit fibrosis. Nonetheless, the authors emphasize that the current evidence primarily derives from preclinical research and a limited selection of clinical trials, necessitating additional studies to confirm the safety and effectiveness of JAKi in patients with SSc. Nallapati et al. [119] detailed a case study involving a patient with diffuse cutaneous systemic sclerosis (dcSSc) who saw notable improvements in skin conditions following treatment with tofacitinib. This patient had been experiencing progressively severe skin changes, including thickening, tightening, and hyperpigmentation, despite previous therapies. Upon initiating treatment with tofacitinib, the patient reported significant improvements, marked by a reduction in both thickening and hyperpigmentation. Deverapalli et al. [120] explored the potential role of JAKi as a treatment path for progressive SSc. In their review, they scrutinized the current scholarship surrounding the use of JAKi in SSc while assessing the potential benefits and drawbacks of this treatment strategy. The authors pointed out the involvement of the JAK-STAT pathway in SSc's pathogenesis and proposed that JAKi may effectively target the fibrotic and inflammatory processes characteristic of the disease. Additionally, they examined outcomes from various clinical trials assessing the safety and efficacy of JAKi, including tofacitinib and baricitinib, in SSc patients.

Their review concluded that JAKi might hold promise as a treatment avenue for progressive SSc, although further investigation is critical to determine the ideal dosage, treatment duration, and safety profile for these medications in this demographic. They underscored the necessity of vigilant patient monitoring for possible adverse effects, such as infections and thrombosis, during JAKi therapy. Overall, the findings suggest that JAKi could offer a hopeful treatment prospect for progressive SSc, yet more comprehensive research is essential to thoroughly appraise their safety and efficacy within this patient group. You et al. [121] examined the potential application of tofacitinib as a remedy for skin thickening in dcSSc. They conducted a small pilot study involving five dcSSc patients who received tofacitinib for six months and were assessed for variations in skin thickness and other clinical attributes. The study's outcomes presented a significant decrease in skin thickness across all participants, along with enhancements in additional clinical characteristics, including hand functionality and quality of life. The authors proposed that the mechanism through which tofacitinib operates—targeting the JAK-STAT pathway implicated in fibrosis and inflammation—could explain these improvements. However, they acknowledged the study's small size and absence of a control group, indicating that more extensive research is required to validate the safety and effectiveness of tofacitinib for dcSSc patients. They also stressed the importance of larger clinical trials to ascertain the optimal dosing and administration of tofacitinib for this patient population. Overall, the research indicates that tofacitinib may have significant potential as a treatment for skin thickening in dcSSc, though further investigations are necessary to substantiate these findings. The authors proposed that JAKi could exert therapeutic effects on the underlying mechanisms responsible for SSc-related skin transformations, including inflammation and fibrosis. A Phase I/II TOFA SSc trial (NCT03274076, 2020) assessed the safety, tolerability, and efficacy of tofacitinib (5 mg twice daily) compared to placebo in patients with diffuse, early modified Rodnan Skin Score (mRSS) ranging from > 10 to < 45 for 24 weeks. The study included fifteen participants. Results indicated that tofacitinib was well tolerated, exhibiting manageable adverse effects with no grade 3 or higher complications, coupled with trends suggesting improvements in clinical outcome measures. The completed study conducted in the USA did not demonstrate the superiority of tofacitinib over placebo concerning skin improvement mRSS or an enhancement in the Combined Response Index Systemic Sclerosis (CRISS). This contrasts with earlier published data, which indicated that in smaller observational studies, tofacitinib contributed to a reduction in skin thickness among SSc patients as measured through clinical assessments [122] and ultrasound [122]. A prospective observational study revealed improvements in skin involvement with tofacitinib comparable to standard immunosuppressants [119].

7.4.2.2 Baricitinib

Numerous instances were documented. Hou et al. [123] investigated a study examining the effectiveness of baricitinib in addressing skin fibrosis and finger ulcers in individuals with SSc. The research was performed on mice and human dermal samples, alongside a small group of SSc patients. Findings indicated that baricitinib treatment enhanced skin fibrosis and minimized the intensity of digital ulcers in both animal models and human tissues. Furthermore, SSc patients receiving baricitinib displayed improvements in skin fibrosis and a decrease in the occurrence of digital ulcers. Fiorentini et al. [124] explored the potential role of JAK inhibition in treating SSc-related interstitial lung disease (SSc-ILD), a serious complication of SSc that may lead to pulmonary fibrosis and respiratory failure. The authors present a narrative review on the underlying mechanisms of SSc-ILD and current therapeutic options, outlining the shortcomings of existing treatments. They then investigate the prospective advantages of JAK inhibition in managing SSc-ILD, referencing both preclinical and clinical evidence indicating that JAK suppression can alleviate inflammation and fibrosis in lung tissues. Additionally, the authors address the safety and tolerability of JAK inhibitors in SSc-ILD patients, relying on real-world data from everyday clinical settings.

A study assessing the effectiveness and safety of baricitinib in SSc is underway (NCT05300932) (phase 3/4). This is a 48-week, prospective, double-blind, controlled trial. Sixty participants were enrolled. The specific aims are to ascertain if baricitinib is effective and safe for treating individuals with dcSSc compared to those treated with cyclophosphamide, and to determine whether baricitinib outperforms cyclophosphamide, as gauged by changes in CRISS. It integrates changes in the mRSS, Forced Vital Capacity (FVC) percent predicted, clinician and patient global evaluations, and Health Assessment Questionnaire Disability Index (HAQ-DI). Moreover, hemoglobin-adjusted diffusion capacity (DLCO), Medsger Severity Scale (MSS), along with other physician and patient-derived outcome metrics will be utilized. The primary objective is the alteration in mRSS at week 24. Results are currently pending.

7.4.2.3 Ruxolitinib

The SCLERO-JAK study aims to assess the influence of ruxolitinib on monocyte-derived macrophage (MDM) activation profiles in SSc patients (NCT04206644). The main outcome will be the level of CCL18 measured using ELISA in the conditioned media of MDM from SSc patients, pretreated or not with ruxolitinib in vitro.

7.4.2.4 Itacitinib

A Phase II study is ongoing to assess the efficacy and safety of itacitinib in SSc (NCT04789850) (phase 2 trial). Seventy-four patients diagnosed with dcSSc, as defined by the American College of Rheumatology (ACR), with disease duration of fewer than 36 months were involved. The safety and effectiveness of Itacitinib in adults with SSc versus placebo are being examined. The primary endpoint is the shift in mRSS at 360 days. The SCLEROJAKI study is a multi-center retrospective study conducted in France, aiming to delineate the application of JAK inhibitors in real-world SSc-ILD. The secondary objectives include evaluating the effectiveness and safety of JAK inhibitors in SSc-associated ILD. The main measure is the relative change in FVC following 12 months of JAK inhibitor treatment. Results are underway. In summary, the current evidence regarding JAK inhibitors in SSc is mainly based on case series or phase I/II trials with findings that can occasionally be contradictory, notably in regards to efficacy concerning skin involvement. While some study outcomes are encouraging, it remains essential to complement these findings with randomized trials, several of which are presently in progress.

7.5. Other systemic diseases

7.5.1 Primary Sjögren's syndrome

Limited foundational research exists pertaining to JAK inhibitors in primary Sjögren's syndrome (pSS). No preclinical investigations have been conducted. The pathophysiology of pSS is still not thoroughly comprehended. However, similar to lupus, it appears that type I IFNs, and consequently the JAK STAT signaling pathway, play a significant role in the development and persistence of the autoimmune condition [125]. Genomic analyses have uncovered polymorphisms in genes associated with IFN signaling via JAK STAT (IRF5 and STAT4) [126]. The IL-12/23-Th17 pathway also seems to be implicated, with polymorphisms

in the IL-12A gene having been noted [127].Case reports and observational studies or controlled trials are available for the following compounds.

7.5.1.1 Tofacitinib

One case report illustrates the effectiveness of topical tofacitinib in treating dry eye syndrome [128]. A Phase I/II study investigating the safety and tolerability of oral tofacitinib in pSS is currently in progress (NCT04496960).

7.5.1.2 Baricitinib

A recent investigation highlighted that baricitinib inhibited the degeneration of acinar cells within the salivary glands of pSS patients by eliminating IFN-γ induced CXCL10 expression and CXCL10 dependent immune cell infiltration in human salivary gland ductal cells. CXCL10 is a chemokine induced by IFN-γ through the JAK STAT pathway during Th1 immune responses, secreted by peripheral blood mononuclear cells, fibroblasts, and endothelial cells. Aota et al. [129] established that baricitinib considerably decreased IFN-γ-triggered CXCL10 production in an immortalized human salivary gland ductal-cell clone, and western blot analysis further demonstrated its strong inhibition of STAT1 phosphorylation, with a lesser effect on STAT3. These findings indicate a potential therapeutic role for Baricitinib in pSS management. A downward trend in IgG and ESR (Erythrocyte sedimentation rate) levels was likewise recorded. Main clinical features demonstrating improvement compared to baseline included skin rash and arthritis, aligning with findings from baricitinib treatment in active SLE patients [130],

Very recently, the effectiveness and safety of Baricitinib in treating active pSS patients have been assessed in a pilot non-controlled trial [106]. This investigation enrolled 11 pSS patients, all meeting the 2016 ACR/EULAR classification criteria for pSS, exhibiting an ESSDAI of no less than 5. An improvement of at least 3 points in ESSDAI has been deemed the minimal expected clinical improvement. Additional metrics, including European pSS Patient Reported Index (ESSPRI), Physician Global Assessment Score (PGA), Immunoglobulin G (IgG), and remission/improvement of individual organ manifestations have also been gathered and scrutinized. Participants were administered Baricitinib at a dosage of 2 mg per day and were monitored at 3 and 6 months following the initiation of therapy. Baricitinib treatment resulted in a significant reduction in ESSDAI, as well as improvements regarding ESSPRI and PGA. At 6 months, 88.9% of patients observed minimal clinical improvement in their ESSDAI [131]. Alongside weight loss, anemia, and cytopenia. Two pSS patients suffering from ILD and symptoms like cough, shortness of breath, and dyspnea post-exertion reported relief, coinciding with enhanced lung involvement as indicated by follow-up High-resolution computed tomography (HRCT) scans. A flare of hepatitis B virus was the sole adverse event documented [131]. Despite significant limitations of the study, chiefly the lack of a control group, baricitinib treatment appears to hold promise for pSS, necessitating high-quality randomized controlled clinical trials to validate these preliminary findings.

7.5.1.3 Filgotinib

Recent results from a multicenter, double-blind, placebo-controlled randomized phase II clinical trial, which included an arm featuring filgotinib alongside other agents (i.e., lanraplenib and tirabrutinib), aimed to evaluate both safety and effectiveness in patients with active pSS (ESSDAI ≥ 5) have been published recently [107]. Patients assigned to the filgotinib arm received a dose of 200 mg daily for 48 weeks. The primary endpoint was identified as the proportion of patients achieving both protocol-defined improvement and no worsening criteria at week 12, based on C-reactive protein (CRP) and pSS-related symptoms, measured by visual analogue scale (VAS) assessing global disease, pain, oral dryness, ocular dryness, and fatigue. Change in ESSPRI and ESSDAI were included as secondary endpoints and evaluated at weeks 12 and 24. Exploratory efficacy endpoints encompassed objective assessments such as Schirmer's test and salivary flow (both unstimulated and stimulated), treatment response on specific ESSDAI domains, and alterations in the ESSDAI score from baseline in patient subgroups. Additionally, exploratory biomarker endpoints were focused on the change from baseline for selected peripheral biomarkers, such as IgA, IgG, IgM, rheumatoid factor (RF) and CRP, as well as B cell and plasma cell subsets, and IFN signature, for each patient at weeks 4, 12, and 24 [132].

At week 12, 43.3% of the filgotinib cohort met the primary endpoint, although no statistically significant differences were observed compared to the placebo cohort [132]. None of the secondary endpoints were achieved. Nevertheless, some compelling evidence emerged from the trial. Changes in ESSDAI appeared more marked following filgotinib treatment in the pSS subgroup of patients

with baseline ESSDAI ≥ 14 or those not on disease-modifying antirheumatic drugs/corticosteroids. Moreover, by week 24, more substantial reductions in RF, IgM, IgG, and IgA were observed in the filgotinib group relative to placebo, and intriguingly, IFN activity showed a significant decrease from baseline at weeks 4 and 12. The therapeutic effects of filgotinib also led to a reduction in cytosolic DNA sensing and chemokine signaling pathways. In exploratory analyses, salivary production and tear generation stabilized at levels comparable to baseline during filgotinib treatment [132].

Ultimately, the majority of adverse events were not severe, and the overall safety and tolerability remained aligned with the previously established safety profile. Given this context, even though the primary and secondary objectives were not achieved, these findings advocate for post-hoc analyses within specific subsets of pSS patients, potentially informed by unique biomarkers. This, coupled with a comprehensive reassessment of pSS outcome metrics for clinical trials—currently in progress—could enable more precise targeting of pSS patients and possibly demonstrate the effectiveness of promising new therapeutic agents, such as filgotinib, for clinical application [132].In summary, the available data regarding JAK inhibitors in pSS is presently inadequate. It is essential to enhance this data with randomized phase 3 trials.

7.5.2 Sarcoidosis

In individuals with sarcoidosis, the comprehension of the underlying pathophysiology has been altered by the identification of T lymphocytes producing both IFN- and IL-17 within a so-called “Th17.1” environment. Moreover, a transcriptomic assessment disclosed an overabundance of RNA from genes associated with JAK STAT signaling in a cohort of 17 patients [133].No preclinical studies exist. Observational studies and/or controlled trials are available for the following compounds.

7.5.2.2 Baricitinib

The review of existing literature indicated seven patients with uveitis and five with sarcoidosis who received JAK inhibitors, showing improvement in their symptoms. An open-label, non-randomized, non-controlled, multicenter, interregional study (JAKUVEITE) is currently in progress to assess the efficacy of Baricitinib in refractory, non-infectious uveitis.

7.5.2.3 Ruxolitinib

A case report by Valeyre et al. [135] documented a sarcoidosis case associated with Vaquez disease featuring a JAK2 V617F mutation, revealing improvement, especially in pulmonary interstitial involvement post-ruxolitinib treatment. Another case report illustrated enhancement of cutaneous sarcoidosis during ruxolitinib therapy in conjunction with Vaquez disease [136]. A recent case report from Levraut et al. [137] detailed a systemic granulomatosis that showed improvement due to ruxolitinib. Overall, the existing data concerning JAK inhibitors in sarcoidosis largely relies on case series. Randomized trials are needed to supplement this data.

7.5.3 Relapsing polychondritis

The cause of relapsing polychondritis (RP) remains unidentified. In patients with RP, genetic vulnerability is suggested by the correlation between RPC and human leukocyte antigen (HLA) DR4 or other HLA class II alleles. Evidence of autoimmunity, both antibody-mediated and cell-mediated, directed against extracellular matrix components of cartilage—including types II, IX and XI collagen; matrilin-1; and proteoglycan components—has been documented. The immune response and the consequent release of cytokines may drive cartilage destruction in RP. Immune complexes, formed either in situ or localized by affinity to polyanionic proteoglycans, attach to the surface of cartilage. Their attempted clearance by scavenger cells fosters the release of matrix-degrading metalloproteinases, reactive oxygen species, and/or cytokines. Cytokines such as IL-1 and tumor necrosis factor (TNF) stimulate chondrocytes to produce matrix-degrading metalloproteinases, plasminogen activator, and prostanoids [138], [139]. A frequent association exists between RP and a wide range of immune-mediated connective tissue disorders, endocrine issues, and inflammatory bowel diseases, including systemic necrotizing vasculitis, Graves’ disease, and ulcerative colitis. A significant number of patients with vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome also receive a clinical diagnosis of RP. No preclinical studies are available. Case reports, observational studies, and/or controlled trials exist for the following compounds.

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7.5.3.1 Tofacitinib

The application of JAK inhibitors remains largely anecdotal [140]. Meshkov et al. [141] documented a case study involving a 39-year-old female patient suffering from a 6-year-long history of relapsing polychondritis (RP) characterized by gradually worsening nasal chondritis leading to a saddle nose deformity, recurrent arthritis, scleritis, involvement of laryngeal and tracheal cartilages, persistent low-grade fever, and indicators of inflammation evident in laboratory results (including elevated erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factor). Initially, a moderate-dose regimen of prednisone (30 mg/day) was beneficial. In an effort to taper off steroids, methotrexate, azathioprine, mycophenolate mofetil, and dapsone were sequentially administered. However, all immunomodulatory treatments were eventually halted after a brief duration due to adverse reactions or ongoing clinical and laboratory activity. Despite administering medium to high doses of corticosteroids (up to 40 mg/day), the disease progressed, marked by recurring acute respiratory distress episodes and sustained laboratory activity. The patient declined any treatment with parenteral biologics. Nevertheless, she consented to off-label oral administration of tofacitinib. This medication was selected due to its influence on the intracellular mechanisms responsible for instigating inflammatory responses. The introduction of tofacitinib at a dose of 10 mg daily quickly led to a noticeable reduction in disease activity alongside steroid tapering. After 12 months of therapy, she maintained stable clinical remission without corticosteroids, and CT imaging revealed improved thickening of the laryngeal wall.In summary, existing evidence on JAK inhibitors in RP primarily derives from case series. There is a pressing need for randomized, prospective trials to thoroughly assess the effectiveness of JAK inhibitors for this condition.

7.5.4 Giant cell arteritis

Among patients diagnosed with giant cell arteritis (GCA), recent advancements in treatment, emphasizing a broader application of tocilizumab, stem from a deeper comprehension of the underlying mechanisms of this vasculitis. The activation of dendritic cells located within the vascular walls, triggered by an unknown event, leads to the recruitment of CD4+ cells with a Th1 response profile. This Th1 environment promotes the influx of macrophages that secrete pro-inflammatory cytokines like IL-6 and IL-1. Additionally, it has become evident that a Th17 signature also exists during GCA [142].No preclinical studies currently exist. However, case reports, observational studies, and/or controlled trials are available for the following agents.

7.5.4.1 Upadacitinib

The demonstrated effectiveness of tocilizumab in large vessel vasculitis suggests that JAK inhibitors could also be advantageous for this condition. A trial was conducted to evaluate the safety and efficacy of upadacitinib in individuals with GCA (SELECT-GCA) (phase III) (NCT03725202). This investigation comprises two phases. The aim of Period 1 is to assess the efficacy of upadacitinib in conjunction with a 26-week corticosteroid taper protocol, compared to a placebo paired with a 52-week corticosteroid taper regimen, measured by the rate of participants achieving sustained remission at Week 52, as well as to evaluate the safety and tolerability of upadacitinib in individuals with GCA. The second period aims to explore the safety and efficacy of continuing versus discontinuing upadacitinib in maintaining remission for those who achieved it in Period 1. A total of 420 patients were recruited. The primary endpoint was the percentage of subjects attaining sustained remission (at week 52). Results indicated that by week 52, 46% of patients receiving upadacitinib achieved sustained remission, in contrast with 29% in the placebo group, reflecting a statistically significant benefit ($P = 0.0019$). Sustained complete remission (absence of symptoms alongside normalized inflammatory markers including ESR and CRP) was observed in 37% of those in the upadacitinib group compared to 16% in the placebo cohort ($P < 0.0001$). Additionally, flare-ups were significantly reduced: only 34% of patients in the upadacitinib group experienced disease flares, as opposed to 56% in the placebo group ($P = 0.0014$). Serious infections were reported at slightly lower rates in the upadacitinib group (6% vs. 11% in placebo).

7.5.4.2 Baricitinib

A trial is set to evaluate the safety and efficacy of baricitinib in relapsing GCA (phase II) (NCT03026504). All participants will commence the study on prednisone. The dosage of prednisone will be tapered according to a standardized regimen while participants continue taking one daily tablet of baricitinib for 52 weeks. This study will be an open-label pilot examining the safety and tolerability of baricitinib (4 mg daily, oral, for 52 weeks) in conjunction with a standardized glucocorticoid taper. It is expected that

adjunctive baricitinib will be safe and well tolerated in GCA patients, and demonstrate preliminary efficacy through reductions in inflammatory markers, decreased steroid needs, and improved relapse-free survival. Fifteen patients were enrolled. Prigent et al. [143]A case has been documented involving a 76-year-old female patient suffering from recurring GCA and large vessel vasculitis, illustrated through 18F-FDG-PET/CT imaging. Despite attempts at remission using methotrexate and tocilizumab, the patient ultimately showed a positive clinical and imaging response to baricitinib. This instance indicates that baricitinib could be an encouraging therapeutic option for giant-cell arteritis-associated large-vessel vasculitis, and highlights the potential of 18F-FDG-PET/CT in assessing treatment response, although further prospective and randomized trials are essential to measure the effectiveness of JAK inhibitors in GCA. Presently, the available information regarding JAK inhibitors in GCA primarily stems from case series, while a phase II trial is currently in progress. There is a need for increased caution in treating elderly patients who may also possess cardiovascular risk factors.

7.5.5 Takayasu's disease

The mechanisms behind Takayasu arteritis remain largely unclear. It is believed that cell-mediated processes play a crucial role, potentially resembling those seen in giant cell arteritis (GCA) [144]. Immunohistopathological studies have indicated that the infiltrate in aortic tissue is predominantly composed of cytotoxic lymphocytes, particularly gamma-delta T lymphocytes [145].No preclinical trials are currently available. For the following substances, there are case reports, observational studies, and/or controlled trials.

7.5.5.1 Tofacitinib

Kong et al. [146] executed a prospective observational investigation to compare the effectiveness and safety of tofacitinib with methotrexate (MTX) in Takayasu arteritis. A total of fifty-three patients exhibiting active disease from an ongoing prospective cohort in China were included. Of these, twenty-seven patients received glucocorticoids (GCs) alongside tofacitinib, whereas twenty-six were treated with GCs and MTX. The study spanned a duration of 12 months. Metrics such as complete remission (CR), changes in inflammatory parameters, tapering of GCs, and safety profiles were evaluated at the 6th, 9th, and 12th months. Vascular anomalies were assessed at the 6th and 12th months, and relapse rates were analyzed over the 12-month period. The CR rate was higher in the Tofacitinib cohort compared to the MTX group (6 months: 85.19% vs. 61.54%, $P = 0.07$; 12 months: 88.46% vs. 56.52%, $P = 0.02$). Throughout the 12-month treatment, the Tofacitinib group exhibited a comparatively lower relapse rate (11.54% vs. 34.78%, $P = 0.052$) and a longer median duration without relapse (11.65 ± 0.98 vs. 10.48 ± 2.31 months, $P = 0.03$). Notably, the average glucocorticoid dosage at the 3rd, 6th, and 12th months was lower in the Tofacitinib group than in the MTX group ($P < 0.05$). No significant differences in disease improvement or progression on imaging were observed between the groups ($P > 0.05$). The incidence of adverse effects remained low for both cohorts (3.70% vs. 15.38%, $P = 0.19$).

4.5.5.2. Upadacitinib

The SELECT-TAK trial is a Phase III, multi-center, randomized, placebo-controlled study aimed at assessing the efficacy and safety of upadacitinib in patients with Takayasu arteritis. The primary endpoint is to determine whether upadacitinib, in conjunction with a corticosteroid tapering regimen, can more effectively prevent relapses of Takayasu arteritis compared to a placebo. This study focuses on individuals who have encountered recent disease relapses despite being on corticosteroid therapy. Results are currently awaited. Overall, data concerning JAK inhibitors in Takayasu's disease is largely derived from case series. Randomized, prospective trials are needed to assess the effectiveness of JAK inhibitors for this condition. We are anticipating the findings from the SELECT-TAK study.

7.5.6 Behçet's disease

Behçet's disease is an inflammatory condition of undetermined origin characterized by the occurrence of bipolar aphthosis along with other systemic inflammatory manifestations. Genomic research has identified various polymorphisms related to Behçet's disease, some of which are associated with the JAK STAT signaling pathway, including STAT1 and 2, IL-6R, IL-10, SOCS1 and 3, which function as endogenous inhibitors of JAK. The inflammatory characteristics of this condition stem from a complex interplay of specific genetic profiles and an aberrant innate and adaptive immune response to external stimuli. Key cytokines involved in this

pathology mainly derive from Th1 and Th17 pathways, including IL12/23, TNF, IFN, IL-6, and IL-1 [147].No preclinical investigations are available. There are case reports, observational studies, and/or controlled trials regarding the following agents.

There are no available preclinical studies. The following compounds have case reports, observational studies, and/or controlled trials documented.

7.5.6.1 Tofacitinib

As of now, a retrospective examination involving 13 patients has assessed the effectiveness of tofacitinib, showcasing enhancements in vascular and joint health after 7 months [148]. Every patient experienced favourable outcomes from tofacitinib treatment. Following a median observation period of 8 (IQR: 5.5–19) months, a notable improvement was recorded in the overall BDCAF score (5 [IQR: 4–5] vs. 0 [IQR: 0–1.5], $P < 0.001$). Notably, patients with vascular/cardiac and joint issues attained both clinical and radiological remission, with significant declines in erythrocyte sedimentation rate (21 [IQR: 7–101] mm/h vs. 5 [IQR: 1–11] mm/h, $P = 0.0028$) and C-reactive protein levels (21 [IQR: 1.24–67] mg/L vs. 0.5 [IQR: 0.32–1.3] mg/L, $P = 0.019$). Among patients with gastrointestinal complications, one individual saw resolution of intestinal ulceration, whereas it persisted in the other five. The median prednisone-equivalent glucocorticoid dosage was reduced (initial: 10 [IQR: 10–17.5] mg/day vs. final visit: 10 [IQR: 5–12.5] mg/day, $P = 0.028$), suggesting a possible steroid-sparing effect. Five patients had their cyclophosphamide dosages reduced and one discontinued treatment altogether. One patient ceased tofacitinib due to disease progression, and two patients stopped treatment due to herpes zoster (HZ) infections. In summary, existing data on JAK inhibitors in Behçet's disease primarily rely on case series and retrospective analyses. Well-designed, randomized trials are essential to thoroughly assess the effectiveness of JAK inhibitors for this condition.

7.5.7 Other vasculitis

A few pilot investigations and case accounts have illustrated the benefits of JAK inhibitors (tofacitinib) for ANCA-associated vasculitis [149], polyarteritis nodosa [150], and cutaneous leukocytoclastic vasculitis [151]; nonetheless, information related to other vasculitis forms remains scarce, preventing any definitive conclusions from such limited data.

7.5.8 Auto-inflammatory diseases

The cytokine landscape in auto-inflammatory syndromes features various pro-inflammatory cytokines, several of which are reliant on the JAK-STAT pathway.No preclinical studies available. Case reports, observational studies, and/or controlled trials are accessible for the following agents.

7.5.8.1 Tofacitinib

In 2020, the FDA granted approval for tofacitinib for the treatment of juvenile idiopathic polyarticular arthritis resistant to methotrexate or alternative biologic interventions [152].

7.5.8.2 Baricitinib

A randomized, double-blind, Phase III investigation (NCT04088396) is currently assessing the effectiveness of baricitinib in systemic juvenile idiopathic arthritis. Aicardi-Goutières syndrome (AGS) is a hereditary multi-system disorder of innate immunity marked by excessive interferon production. AGS is notably characterized by early-onset encephalopathy consequential in severe intellectual and physical disabilities. The role of interferon is recognized as potentially harmful not just to the brain but also to the skin, liver, lungs, heart, and several other organs. A clinical trial, NCT03921554, is presently exploring the efficacy of baricitinib in AGS patients. The main aim is to ascertain whether baricitinib administration results in improvement or stabilization of the AGS scale from baseline at 52 weeks. The trial is actively Moreover, a Phase 2/3, multi-center, open-label study (NCT04517253) is ongoing, recruiting participants and is anticipated to conclude in 2024.Running for 52 weeks to analyze the efficacy and safety of baricitinib in adult and pediatric Japanese individuals with Nakajo-Nishimura syndrome/chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (NNS/CANDLE), stimulator of interferon genes-associated vasculopathy with infant onset (SAVI), or Aicardi-Goutières syndrome (AGS). Baricitinib may represent a promising therapeutic avenue for patients with NNS/CANDLE, SAVI, and AGS, showing a favourable benefit/risk ratio in a sensitive patient group with multiple comorbidities.

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7.5.8.3 Ruxolitinib

VEXAS syndrome (vacuoles, E1 enzyme, X-linked, auto-inflammatory, somatic) arises from a somatically acquired mutation in the E1-ubiquitin ligase UBA1, resulting in the production of a catalytically impaired isoform within myeloid cells. This syndrome combines severe auto-inflammatory symptoms and is often linked with myeloid neoplasia (MN). The prognosis for VEXAS is grim, and many patients need high doses of corticosteroids for inflammation management [153]. Therapeutic choices outside of steroids are currently scarce for these individuals. In this retrospective multi-center analysis, the authors reported some clinical benefits of JAK inhibitors in VEXAS patients. They assessed 24 UBA1 mutated subjects treated with JAK inhibitors (11 with ruxolitinib, 11 with tofacitinib, 1 with baricitinib, 1 with upadacitinib). Complete clinical response (CCR) and complete biological response (CBR) were defined as complete resolution of clinical symptoms and normalization of inflammatory markers (CRP), respectively. Partial clinical (PCR) and biological response (PBR) were characterized by at least a 50% reduction in clinical or inflammatory markers. Clinical signs observed at VEXAS diagnosis included skin involvement (87.5%), arthritis or arthralgia (83.3%), vasculitis (37.5%), fever (75%), ocular issues (29.2%) and pulmonary infiltrates (41.6%). Before the initiation of JAKi, patients had undergone a median of 2.5 treatments involving immunosuppressants or immunomodulators. One month later, 12 out of 24 patients (50%) had exhibited either clinical or biological response. Clinical Complete Response (CCR) and Clinical Benefit Response (CBR) were seen in 7 out of 11 (64%) and 6 out of 11 (54%) individuals receiving ruxolitinib, while those on other JAKi experienced CCR and CBR rates of 3 out of 13 (23%) and 2 out of 13 (15%) respectively. At the three-month mark, CCR was 100% and CBR was 80% (10 evaluable patients) within the ruxolitinib group, contrasting with 25% for both responses in the other JAKi cohort (8 evaluable patients) ($P = 0.0036$ and 0.0055 respectively). For ruxolitinib patients, median reductions in CRP and steroid dosage were 72.5% and 66.25% respectively at the three-month check-in. With a median follow-up duration of 4 months, only 1 patient treated with ruxolitinib had lost their response, while the median time before the next treatment was recorded at 3.4 months for those on alternative JAKi. These preliminary retrospective findings, given their limited follow-up, necessitate careful interpretation and will be updated at the forthcoming meeting. A prospective study by the Groupe Francophone of Myelodysplasia (GFM) will soon assess the impact of ruxolitinib on VEXAS patients who also have myeloid neoplasia.The application of JAKi in certain auto-inflammatory conditions, particularly VEXAS syndrome, appears relevant yet primarily relies on retrospective data. Among the options, ruxolitinib stands out as the preferred treatment for VEXAS syndrome. Randomized clinical trials are essential to further substantiating these findings.

7.5.9 Refractory Blau syndrome

Blau syndrome (BS) is characterized as an auto-inflammatory condition marked by non-caseating granulomatous dermatitis, arthritis, and uveitis. This rare familial disorder is inherited in an autosomal dominant manner and is typified by arthritis, uveitis, cutaneous rash, and granulomatous inflammation. BS distinguishes itself from sarcoidosis by the absence of lung involvement, lymphadenopathy, the specific arthritis pattern, and its familial inheritance pattern. The gene linked to BS was discovered in 2001 within the nucleotide-binding domain of caspase recruitment domain (CARD15/NOD2), also implicated in the etiology of Crohn's disease. Typically, the condition manifests in early childhood. Treatments for BS are largely empirical, frequently necessitating corticosteroids along with immunosuppressive agents. Reguera et al. [154] presented a challenging case of severe refractory BS treated first with tofacitinib and subsequently with baricitinib. Their aim was to evaluate the clinical and immunological outcomes from JAKi treatment. Blood tests and serum samples were collected during the follow-up phases with Tofacitinib and Baricitinib. The effects on clinical outcomes, acute phase reactants, absolute lymphocyte counts (ALCs), lymphocyte subpopulations, immunoglobulins, and cytokine levels were assessed. A literature review on JAKi use for treating uveitis and sarcoidosis was also performed. Tofacitinib rendered a rapid and sustained control of the disease alongside a steroid-sparing effect, presenting a decrease in ALC, CD3+, CD4+, CD8+, and natural killer (NK) cell counts from baseline. B-cell counts remained stable. Serum levels of interleukin (IL)-4 and tumor necrosis factor alpha (TNF-α) increased, while levels of IL-2, IL-6, IL-10, and IL-17 remained unchanged. Treatment with tofacitinib was halted after 19 months due to notable lymphopenia. Transitioning to Baricitinib resulted in satisfactory disease activity management with an acceptable safety profile. Overall, the existing evidence regarding JAKi for refractory Blau syndrome primarily derives from case series. There is a pressing need for randomized, prospective trials to assess the effectiveness of JAKi for this condition.

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7.5.10 Hemophagocytic lymph histiocytosis (HLH)

Maschalidi et al. [155] administered ruxolitinib to LCMV-infected, perforin- or RAB27A-deficient mice (models representing primary HLH), along with wild-type mice subjected to repeated CpG DNA injections (a model for secondary HLH). These methods revealed that ruxolitinib mitigated several HLH symptoms, such as splenomegaly, cytopenias, hypercytokinemias, inflammation in peripheral organs and the central nervous system, and it notably increased survival rates.Hemophagocytic lymphohistiocytosis (HLH) is a rare hyper-inflammatory syndrome characterized by the excessive activation of T cells and macrophages, which liberate an array of pro-inflammatory cytokines, including interferon (IFN)-gamma, interleukin (IL)-1-beta, IL-2, IL-6, IL-10, IL-18, and tumor necrosis factor (TNF). The emergence of these cytokines contributes to numerous clinical and pathological signs of HLH, which can result in multi-organ failure and death if untreated. The introduction of etoposide-based treatment protocols, such as the Histiocyte Society HLH-94 and HLH-2004, has significantly lowered mortality rates associated with HLH, yet the five-year survival remains at approximately 60%. To enhance these outcomes, investigations are directed towards novel cytokine-targeted therapies to diminish inflammation in HLH. Among the agents under examination is ruxolitinib, a powerful Janus Kinase (JAK) inhibitor that interrupts the signal transducer and activation of transcription (STAT) pathway, known to be downstream of many cytokines involved in HLH.Reports from case studies, observational explorations, and/or control trials are available for the following substances.

7.5.11 Ruxolitinib

HLH is intricate. It signifies an actual cytokine tempest [156]. In murine models, ruxolitinib has demonstrated its capability to mitigate the detrimental effects caused by excessive macrophage activation [157]. A pilot study conducted in a single center, which was open-label, assessed the efficacy of ruxolitinib in five patients with secondary HLH and indicated an enhancement [158]. Wang et al. [159] explored the effectiveness of ruxolitinib in refractory secondary HLH and found a 73% rate of partial or complete response within an observational framework. In a prospective, multicenter, non-randomized clinical trial, the combination of ruxolitinib + doxorubicin + etoposide + methylprednisolone was examined in refractory HLH. They recorded a 78% rate of partial or complete response [160].

7.5.12 Itacitinib

A prospective phase II trial is investigating the treatment of sporadic non-severe HLH with itacitinib (HLH-JAK). It aims to assess the potential of itacitinib to replace corticosteroid therapy in patients with HLH lacking severe manifestations, noting that: corticosteroids are not targeted for HLH and can complicate the diagnosis of certain associated disorders, particularly the histopathological diagnosis of specific hematologic illnesses. They also elevate the risk of infections. The prescriptions (dosage and duration) for corticosteroids are not standardized, which accounts for some prolonged prescriptions and the numerous known side effects. The treatment currently under examination, itacitinib, is given orally on a daily basis as follows: from day 1 to day 15, at a dose of 300 mg, requiring no special premedication. Efficacy is evaluated on D15. If by D15 there's no clinical improvement and the treatment is tolerated well, the dosage of itacitinib may be increased to 400 mg daily. Treatment may continue for up to 30 days, depending on the disease's progression and the physician's judgment. The outcomes are yet to be determined.The application of JAK inhibitors in HLH appears pertinent but largely relies on retrospective analyses. The preferred molecule seems to be ruxolitinib. Randomized studies are necessary to further elucidate these findings.

II. Conclusion

In this review, we have elaborated on the advancements in understanding and the current applications and various prospects of JAK inhibitors in autoimmune and systemic diseases. Additional randomized controlled trials are required to clarify the precise role of JAK inhibitors in the therapeutic arsenal for these conditions, while their range of applications continues to expand. However, their utilization is not without risk and necessitates careful precautions and oversight.

Conflict of Interest

All authors declare no conflicts of interest.

Author Contribution

Authors have equally participated and shared every item of the work.

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