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Review

Janus Kinase Inhibitors (JAK) As Potential Candidate Targets to Rheumatoid Arthritis

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A B S T R A C T

The development of Janus kinase (JAK) inhibitors has revolutionized the treatment of rheumatoid arthritis (RA), facilitating the attainment of clinical remission for patients. On the other hand, there have been reports of opportunistic infections (OIs) emerging in relation to JAK inhibitor treatment. In order to compile reports of OIs connected to JAK inhibitor therapy for RA in clinical trials, methodical literature research was carried out. Janus kinases (JAKs) are crucial for growth factor receptors, cytokines, haematopoiesis and immune system processes, playing a vital role in intracellular signalling cascades. A family of drugs known as Janus kinase (JAK) inhibitors has drastically changed the way rheumatoid arthritis (RA) is treated. Cytokine receptors play a crucial role in the pathophysiology of inflammatory, allergy and autoimmune illnesses, mediated by the four Janus kinase proteins and seven STAT transcription factors. Janus kinase (JAK) family comprises four members: JAK1, JAK2, JAK3 and TYK2, which regulate gene transcription in inflammatory, immunological and cancerous diseases through the JAK-STAT pathway. This review covers eleven approved clinically-used JAK inhibitors, including fedratinib, filgotinib, oclacitinib, pacritinib, peficitinib, ruxolitinib, baricitinib, fedratinib, tofacitinib and upadacitinib. Mechanism-based therapies targeting the JAK-STAT pathways may be beneficial in treating systemic immune-mediated inflammatory disorders by reducing the use of glucocorticoids and immunosuppressant. These medications' putative metabolic routes and metabolites were also depicted. In conclusion, the information presented in this study may be useful in the development of novel JAK inhibitors that may be used to treat autoimmune and inflammatory disorders.

Keywords: Janus kinase, Fedratinib, Ruxolitinib, Tofacitinib, Upadacitinib and Rheumatoid Arthritis

Highlights

1. JAK inhibitors potentially target to Rheumatoid arthritis.
2. JAK inhibitors target the Janus kinase signalling pathway, which plays a crucial role in immune cell activation and inflammatory responses by blocking specific JAK enzymes (JAK1, JAK2, JAK3 and TYK2).
3. Tofacitinib, Baricitinib, Upadacitinib, etc. as efficacious and potential approved drugs for the treatment of Rheumatoid arthritis.

1. Introduction

As we know, over 70% are female and 55% are above the age of 55 who are mostly affected by an auto immune disease called rheumatoid arthritis, which causes inflammation, discomfort and eventually joint destruction as a result of the immune system attacking the joints[1]. Although it can affect other parts of the body as well, it usually affects the tiny joints of the hands and feet. The ancient labels arthritis deformans and rheumatic gout were replaced by rheumatoid arthritis by A. B. Garrod in 1858[2]. Thus, c Bannatyne (1896) was the first to describe the appearance of joints damaged by rheumatoid arthritis. The International Committee on Rheumatism was established in 1932. Later on, it changed its name to American College of Rheumatology and subsequently American Rheumatism Association[3]. Rheumatoid arthritis affected 18 million persons globally in 2019. Rehab may be beneficial for the 13 million individuals who suffer from mild to severe rheumatoid arthritis. The JAK-STAT pathway is used by the Janus kinase (JAK) family of intracellular, non-receptor tyrosine kinases to transduce cytokine-mediated signals[4]. Since they were only two of many findings from a PCR-based screen of kinases, they were originally dubbed "just another kinase" 1 and 2, but they were eventually published as "Janus kinase"[5]. While one domain displays kinase activity, the other adversely controls the first domain's kinase activity. There are four members of the JAK family: Janus kinase 1 (JAK1), Janus Kinase 2(JAK2), Janus Kinase 3 (JAK3) and Tyrosine kinase 2 (TYK2)[6]. JAK1-deficient transgenic mice have impaired cytokine responses, including interferon-gamma. Type II (interferon-gamma) interferon signalling involves JAK1 and JAK2, while type I interferon signalling involves JAK1 and TYK2[7]. Mice lacking TYK2 have impaired function of natural killer cells. A kind of immune modifying drug called a Janus kinase inhibitor (JAK1, JAK2, JAK3, TYK2) reduces the activity of one or more of the Janus kinase family of enzymes, interfering with the JAK-STAT signalling pathway in lymphocytes. It is also referred to as a JAK inhibitor or jakinib[8].

2. Janus Kinase (JAK)

The intracellular, non-receptor tyrosine kinases known as Janus kinases (JAKs) are essential for the signalling cascades of several growth factor receptors and cytokines. They are essential for haematopoiesis or the production of new blood cells and for the control of certain immune system processes[9]. As a nod to their dual function as signal transducers and regulators, "Janus" kinase" is named after the Roman deity of two faces. Instead of being receptors by themselves, Janus kinases (JAKs) are intracellular signalling proteins that bind to the receptors of different growth factors and cytokines[10].

2.1. Types

JAK 1: Participates in the signalling of several cytokine receptors, such as interleukins and interferons[11].

JAK 2: Vital for erythropoietin, thrombopoietin and various another hematopoietic cytokine signalling via receptors[12].

JAK 3: Particularly engaged in communication via standard γ-chain cytokine receptors, as those for interleukins IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21[13].

TYK2(Tyrosine kinase 2): Involved in interferon and interleukin (IL-10 and IL-12) signalling via receptors[14].

2.2. Structure

The seven domains that make up the structure of JAKs are JH1-JH7. The domains of the four JAKs are identical, with a 48% total similarity.JH1, which is located at the C-terminal, is the first domain[15]. This domain is also referred to as the kinase domain as it is in charge of the kinase's enzymatic action[16]. JH2, the second domain, is a pseudo-kinase domain that is devoid of tyrosine kinase activity[17]. Nonetheless, JH2 is crucial for controlling kinase activity. JAKs also include two domains **(Figure 1)**, JH3–JH4, which is homologous to the Src-homology-2 (SH2) domain[18]. The FERM domain, located at the N-terminal of JAKs, is the fourth area of JAKs and is involved in the binding of JAKs to cytokine receptors[19].

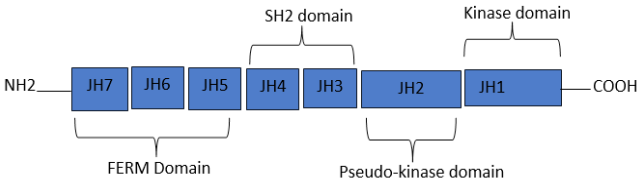

Figure 1: Domain structure of JAKs.

The activation follows JAK-STAT Pathway which includes steps like Receptor Binding, Auto phosphorylation, Phosphorylation of STATs and Gene Expression. Receptor Binding involves the intracellular domains of different cytokine receptors which are linked to JAKs[20]. A cytokine's binding to its receptor results in a conformational shift that activates the JAKs that are connected to it[21]. Then it brings about Autophosphorylation which involves JAKs that have been activated by phosphorylating themselves or auto-phosphorylation, which increases the kinase activity of the protein[22]. Which then leads to Phosphorylation of STATs includes signal transducer and activator of transcription proteins (STATs) which are phosphorylated by JAKs **(Figure 2)**. Following phosphorylation, STATs translocate to the nucleus and dimerize[23]. After Phosphorylation of STATs, Gene Expression gets proceeded in the nucleus, STAT dimers bind to certain DNA sequences to control target gene transcription, which in turn triggers the cytokine signalling-driven biological reactions[24].

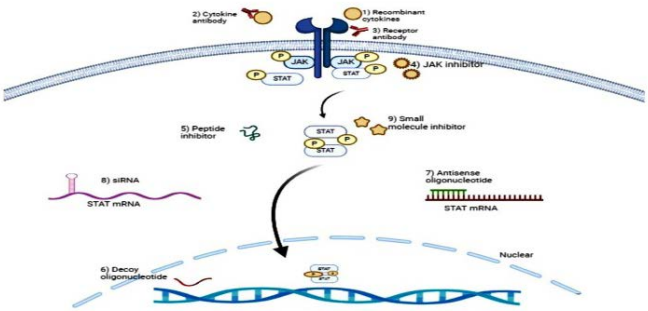

Figure 2: Molecular level signalling of JAK-STAT Pathway.

2.3. Biological functions

Numerous cytokines and growth factors have an impact on immune cells and JAKs are implicated in mediating those effects. For instance, interleukin receptor signalling, which controls immune cell activation and differentiation, depends on JAK1 and JAK3[25]. A number of hematopoietic growth factors, such as erythropoietin and thrombopoietin, which are necessary for the generation of red blood cells and platelets, respectively, rely on JAK2 for their signalling pathways[26]. JAKs have a role in controlling inflammatory reactions as well. Numerous

inflammatory and autoimmune disorders can result from the dysregulation or over activation of JAK pathways[27].

2.4. Clinical relevance

These medications belong to a class that blocks JAK activity and are used to treat diseases linked to excessive or improper JAK signalling[27]. As an examples, we can consider rheumatoid arthritis that involves JAKs which are inhibited by medications like tofacitinib and baricitinib to lower immune system activation and inflammation and Myelo proliferative disorders that involves a JAK2 inhibitor called rufolitinib is used to treat conditions including essential thrombocythemia and polycythaemia vera[28]. Numerous disorders can result from mutations in the JAK gene. For example, mutations in JAK2 are frequently linked to tumours that are myeloproliferative[29].

3. Janus Kinase Inhibitors and Their Mechanism of Action

A class of medications known as Janus kinase inhibitors or JAK inhibitors, target the Janus kinase (JAK) family of enzymes, which are essential for the signalling pathways of several cytokines and growth factors[30]. These medications are used to treat a number of inflammatory and autoimmune diseases in addition to specific cancers[31]. JAKs are intracellular enzymes that influence gene expression by sending signals from cell surface cytokine receptors to the nucleus[32]. They participate in the signalling pathways of many different cytokines, including those linked to inflammation and immunological responses **(Figure 3)**. JAK inhibitors function by preventing one or more of the JAK enzymes (JAK1, JAK2, JAK3 and Tyk2) from being active[33]. JAK inhibitors can aid in the management of illnesses marked by hyperactive immune responses by blocking these pathways[34].

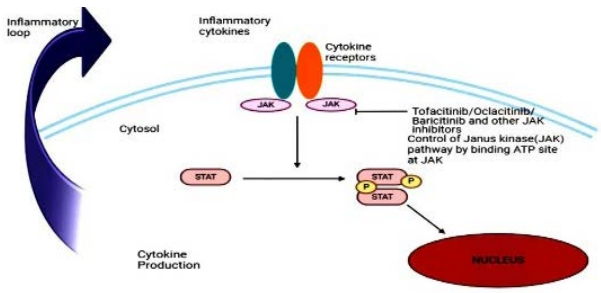

Figure 3: Graphical representation of mechanism of action of JAK inhibitors.

3.1. Classification of JAK inhibitors

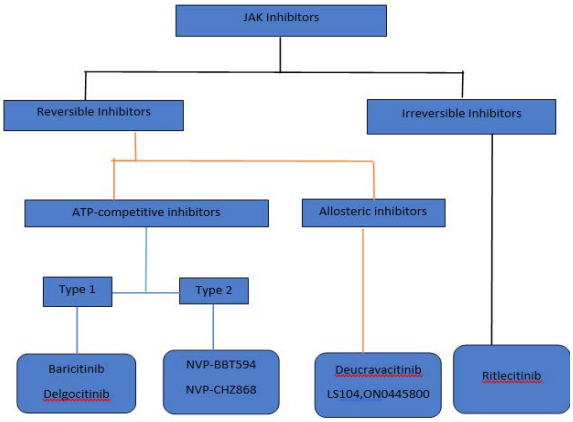

Figure 4: Classification of JAK inhibitors with representative example.

3.2. Reversible and Irreversible JAK Inhibitor

Competitive inhibitors of JAKs bind to the amino acids of the four JAKs in a reversible, non-covalent manner. This class of JAK inhibitors forms hydrophobic and hydrogen bonding interactions during binding. There are two subclasses within the class of reversible JAK inhibitors. These inhibitors work by competing with ATP for the catalytic ATP-binding site in JAKs, which is how their mechanism of action works. The kinase domain conformation that these inhibitors bind to can also be used to categorize them[35]. Type 1 JAK Inhibitors attach to the JAKs' ATP-binding site while the kinase domain is in its active state. Clinically authorized medications like filgotinib, which functions as a selective JAK1 inhibitor and fedratinib, which shows selective inhibition of JAK2, fall under this category[36]. Tofacitinib and peficitinib, on the other hand, work by blocking several JAKs. The much-conserved structure of the ATP-binding site in the four JAKs may be the reason why type I JAK inhibitors can bind to different kinases and function as non-selective inhibitors[37]. Type 2 JAK Inhibitors also bind to the ATP-binding region of the kinase domain. Representative examples of type II inhibitors that target JAK2 include NVP-BBT594 and NVP-CHZ868[38]. Allosteric JAK Inhibitor are small molecule inhibitors that bind to a location other than the ATP-binding site in JAKs are among the allosteric JAK inhibitors[39]. Deucravacitinib (BMS-986165) is one of these inhibitors that selectively inhibit TYK2 allostery. Furthermore, JAK2 allosteric inhibitors include LS104 and ON044580[38,40-42]. Irreversible JAK3 Inhibitors was also reported on this family of irreversible JAK inhibitors that target JAK3. These inhibitors' mode of action is dependent on their covalent interaction with JAK3's distinct Cys909 residue[43]. These inhibitors' chemical structures contain groups that can create covalent bonds, like acrylamide and α-cyanoacrylamide, which can link with the Cys909 residue[44].

3.3. Types Of Jak Inhibitors

There are many JAK inhibitors, each with unique indications and selectivity profiles **(Table 1)**:

3.4. Clinical uses

JAK inhibitors are used in a number of situations were reducing inflammation or the immune system is advantageous:

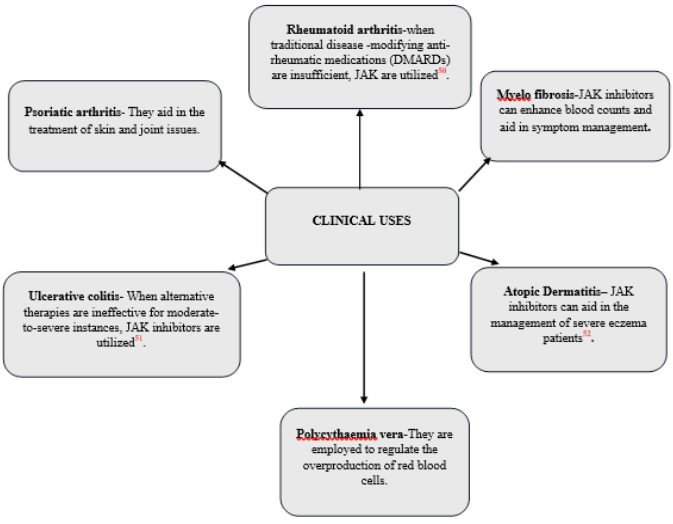

Figure 5: Diagrammatic representation of Clinical uses of JAK inhibitors.

Table 1: Types of JAK inhibitors with mechanism, indications and side effects.

S.no.	Drugs	Mechanism	Indications	Side effects
1.	Tofacitinib (Xeljanz)	Mainly prevents JAK1 and JAK3	Used to treat ulcerative colitis, psoriatic arthritis, rheumatoid arthritis (RA) and other ailments[45].	Include the possibility of an increased risk of developing certain malignancies, elevated cholesterol levels, infection and abnormalities in liver enzymes.
2.	Ruxolitinib (Jakafi)	Supresses JAK1 and JAK2	Mostly used for some forms of graft-versus-host disease, polycythaemia vera and myelofibrosis[46].	May involve abnormal liver enzyme levels, thrombocytopenia, anaemia and infections.
3.	Baricitinib (Olumiant)	Supresses JAK1and JAK2	Used in certain situations for COVID-19 and moderate-to-severe rheumatoid arthritis[47].	Might include abnormal liver enzyme levels, headaches and upper respiratory tract infections.
4.	Fedratinib (Inrebic)	Mostly prevents JAK2	For myelofibrosis use[48].	May include symptoms related to the digestive system, anaemia and thrombocytopenia.
5.	Upadacitinib (Rinvoq)	JAK1 is specifically inhibited	Used to treat atopic dermatitis, psoriatic arthritis and moderate-to-severe rheumatoid arthritis[49].	Might include headaches, increased liver enzymes and upper respiratory tract infections.

3.5. Safety and monitoring

Because of the possibility of adverse effects, patients on JAK inhibitors need to be monitored often. The point those need to be considered as infection risk i.e., compromised immunity as a result of immune system modification[53]. Keeping an eye on cholesterol levels, as certain JAK inhibitors might cause a rise in cholesterol[54]. To keep an eye out for liver problems, have regular liver enzyme testing. Focus on blood cell count variations that might indicate thrombocytopenia or anaemia[55].

4. Janus Kinase in Rheumatoid Arthritis

4.1. JAK Affecting rheumatoid arthritis: mediators and mechanism of action

the intracellular signal transduction system known as the JAK/STAT pathway is activated by a variety of cytokines and can result in the creation of additional pro- and anti-inflammatory cytokines as well as locally damaging enzymes[56]. Pro- and anti-inflammatory cytokines have a well-established role in the pathophysiology of RA. A class of medications known as Janus kinase (JAK) inhibitors is used to treat rheumatoid arthritis (RA) by focusing on particular inflammatory mediators that are part of the disease process[57]. Several inflammatory mediators play a critical role in sustaining joint damage and inflammation in rheumatoid arthritis. JAK inhibitors function by obstructing these mediators' signalling pathways[58]. JAK inhibitor-affected major inflammatory mediators in RA includes Cytokines, Tumour necrosis factor-alpha (TNF-α) etc. Although JAK inhibitors do not directly target TNF-α, it is a part of the inflammatory cascade that they assist regulate[59]. By encouraging inflammation and joint destruction, IL-6 has a profound effect on the pathophysiology of RA. JAK inhibitors have an impact on the signalling cascades triggered by IL-6[60]. In RA, IL-1 has a role in joint degradation and inflammation. Because JAK inhibitors have a more extensive effect on cytokine networks, they can also indirectly affect IL-1 signalling[61]. Similarly, IL-2 is necessary for the proliferation and activation of T cells. JAK inhibitors work by blocking JAK pathways, which in turn lessens IL-2 signalling and the associated activation of immune cells **(Table 2)**. Likewise, IL-4 (interleukin) and IL-13 (interleukin-13); these cytokines play a role in inflammation and T helper cell polarization. The effects of these cytokines on immunological responses can be adjusted by JAK inhibitors[62].

Table 2: Table summarises the roles these cytokines play in mediating pain associated with RA and their relationship to the JAK/STAT pathway, including indirect relationships in the case of TNF and interleukin (IL)-1.

Cytokine (ligand/receptor)	Elements of JAK /STAT pathway affected	Association with pain mechanism
GM-CSF/GM-CSFR	Jak2 STAT3 STAT5	Induced hyperalgesia Up-regulates sodium channel expression (Nav1.7-Nav1.9)[63].
IL-6/IL-6R, sIL-6R	JAK1, JAK2, TYK2, STAT3	Pro-nociceptive factor contributes to development of hyperalgesia/allodynia in rats can have detrimental effect on cognitive function[64].
IL-10/IL-10R	Jak1 STST3	Mitigates pain (anti-nociceptive effect)
IL-27/gp130	TYK2, STAT1, STAT3, STAT5a/b gp130-signaling subunit	Diminished expression of gp130 can attenuate pain[65].
TNF-α/TNFR1, TNFR2	Indirect via IFN-β-JAK/STAT expression and STAT١	Can initiate pain and induce pain-receptor sensitization (both mechanical and thermal hyperalgesia) Is associated with neuropathic pain and has detrimental effect on cognitive function[66].
IL-18/IL-18R	Jak1 and STAT3	Increased expression level is noted in experimental arthritis[67].

4.2. Janus kinase inhibitors -immune response

The therapeutic landscape for rheumatoid arthritis (RA) has been profoundly changed by a class of drugs known as Janus kinase (JAK) inhibitors. They have a complicated and specific effect on the immune response in RA, opening up new treatment options for this inflammatory chronic illness. The impact of JAK inhibitors on immunological responses in RA is examined in detail below:

4.2.1. Mechanism of action

Table 3: Mechanism of action of JAK inhibitors.

BLOCKING JAK FUNCTION	MECHANISM OF ACTION
Targeted Blocking	JAK inhibitors function by preventing one or more JAK enzymes from being active. These enzymes are essential for the signalling of many growth factors and cytokines that are involved in inflammation and immunological responses[68].
b) Specificity	The specificity with which different JAK inhibitors target members of the JAK family, including JAK1, JAK2, JAK3 and TYK2, varies. Their effectiveness and adverse effect profiles maybe impacted by this specificity[69].
DIMINISHED SIGNALLING OF CYTOKINES	
Cytokine Receptors	These medications stop the activation of downstream signalling pathways—which are necessary for the synthesis of pro-inflammatory cytokines like TNF-α, IL-6, IL-1 and IL-17—by inhibiting JAKs[70].
STAT Pathway	Reduced activation of STAT proteins, which are essential mediators in converting cytokine signals into cellular responses such as inflammation and immune cell activation, results from the inhibition of JAKs[25].

4.2.2. Impact on Immune response in arthritis: The JAK inhibitors show promising impact in arthritis by reducing inflammation by lowering cytokine levels which worsen the inflammatory process and encourage inflammation. This reduction alleviates the joint pain and stiffness. JAK inhibitors effectively target multiple inflammatory pathways, making them beneficial for patients who struggle with biologics or DMARDs. With reduction in inflammation, JAK inhibitors also affect T and B cell activation, proliferation and function. This may regulate the overactive immune responses characteristic of RA, impacting myeloid cells like macrophage and dendritic cells, thus reducing their capacity to induce chronic inflammation.

4.3. Signalling molecule in Janus kinase inhibitors

Janus kinase (JAK) inhibitors prevent certain JAK pathways that are essential for cytokine signalling, which an effect on the signalling molecules has connected to rheumatoid arthritis (RA).

4.3.1. Key signalling molecules and pathways targeted by JAK inhibitors

- Cytokines and Their Receptors: TNF-α, also known as tumour necrosis factor, is TNF-α signalling is impacted indirectly but not directly. By blocking the upstream cytokine pathways, JAK inhibitors can lower the amount of TNF-α produced73. One of the main pro-inflammatory cytokines in RA is IL-6. JAK inhibitors lessen the impact of IL-6 on inflammation and joint injury by blocking its signalling pathways74. Another key inflammatory cytokine whose signalling can be modulated by JAK inhibition. Involved in the RA inflammatory process. By changing upstream signalling, JAK inhibitors can affect IL-17 pathways75.
- **Signal Transducers and Activators of Transcription (STATs):** STAT3 is an important participant in inflammation; STAT3 is frequently triggered by IL-6 and other cytokines. JAK inhibitors lessen tissue damage and inflammation by inhibiting STAT3 activity[51]. JAK activity affects these STAT proteins, which are engaged in several immunological reactions. JAK inhibition decreases STAT1 and STAT5 activation, which affects the function of immune cells and inflammatory responses[76].
- **Downstream Signalling Pathways:** By stopping JAKs from phosphorylating STAT proteins, JAK inhibitors directly block this pathway. By stopping the transcription of genes that promote inflammation, this inhibition lowers inflammation and RA disease activity[77]. JAK inhibitors can indirectly affect MAPK (Mitogen-Activated Protein Kinase) pathways even if they are not the main target. These pathways play a role in inflammation and cell proliferation and variations in JAK-STAT signalling may alter how active these pathways are[78].

4.3.2. T and B cell activation: By inhibiting cytokine receptors necessary for T cell activation, such as IL-2 and IL-6 receptors, JAK inhibitors lessen the activation and proliferation of T cells. By interfering with signalling pathways crucial for B cell function and antibody production, they also have an impact on B cell activation and differentiation79.

4.3.3. Role of signalling molecules in RA: These medications lessen the production and action of pro-inflammatory cytokines such IL-6, IL-1 and TNF-α by blocking JAKs. This aids in lowering inflammation in the RA-affected joints and other tissues. JAK inhibitors aid in controlling T cell activity, which is one of the main causes of inflammation in RA[80]. They lessen the production of inflammatory cytokines by T helper cells, particularly Th1 and Th17 cells[81]. They have the ability to control B cell activity and lower autoantibody synthesis, both of which are important in the RA pathogenesis. Joint pain, oedema and stiffness are among the symptoms that JAK inhibitors relieve by focusing on several inflammatory pathways. They can slow the progression of joint damage and improve physical function in RA patients[60].

4.3.4. Clinical implication: JAK inhibitors frequently relieve RA symptoms quickly, which is helpful for individuals who require prompt inflammatory control[82]. JAK inhibitors often provide rapid RA symptom relief, which is advantageous for people who need immediate inflammatory control. JAK inhibitors can raise the risk of infections because of their effect on immune function[51]. It's crucial to regularly check for infections and other negative effects. To completely comprehend the long-term safety profile of JAK inhibitors, more research is required[83].

4.4. Interrelationship between adipokines, rheumatoid arthritis and Janus kinase inhibitors

Adipokine levels may be impacted by chronic inflammation, which is linked to RA. Pro-inflammatory adipokines such as

IL-6 and TNF-alpha, for instance, can be raised in RA and have a role in the pathophysiology of the disease[84]. By focusing on the cytokine signalling pathways that control the generation of these inflammatory adipokines, JAK inhibitors can aid in lowering their levels. Insulin resistance in RA can be caused by chronic inflammation, in part because of the actions of certain adipokines[85]. JAK inhibitors may help normalize the levels of adipokines implicated in glucose metabolism, such as resist in and adiponectin and enhance insulin sensitivity by lowering systemic inflammation[86].

- **Impact on leptin levels:** Inflammatory circumstances can affect leptin, an adipokine involved in energy balance regulation. By decreasing inflammation, JAK inhibitors may help return leptin levels to normal, albeit the precise results may differ and rely on a patient's unique circumstances[87].
- **General effect on adipokines profile:** All things considered, JAK inhibitors' anti-inflammatory properties may result in a more balanced adipokine profile, which may help with the treatment of RA symptoms and related metabolic disorders[83].

5. JAK Inhibition in Rheumatoid Arthritis

HLA-DRB1 showed the strongest connection among disease-susceptibility genes including PTPN22, CTLA4 and STAT4 in genome-wide association studies (GWAS) of SNPs in RA patients. Anti-citrullinated protein antibodies are produced in response to HLA-DRB1 alleles, which encode protein chains containing the common epitope motif88. The identification of specific auto antigens remains elusive; however, the combination of genetic, environmental and extracellular matrix citrullination factors, along with altered conformational changes and epigenetic modification, can induce autoimmunity in RA by impairing the immune system's tolerance to antigens89. Consequently, auto reactive T and B lymphocytes build up in the synovial tissue, causing angiogenesis, vasodilation and synovial cell proliferation. Furthermore, naive T cell differentiation into TH1 cells, TH17 cells, TFH cells and TPH cells, along with B cell activation, result in the development of germinal centre- and lymphoid-follicle-like structures that trigger the generation of autoantibodies90. Pro-inflammatory cytokines are produced excessively as a result of close cell–cell contact, which causes RA. In the presence of macrophage colony-stimulating factor (M-CSF) and RANKL, monocytes can develop into osteoclasts produced from immature dendritic cells. This process is dependent on IL-4 and GM-CSF91. Additionally, rheumatoid synovial fibroblasts overproduce pro-inflammatory cytokines, primarily IL-6. These and other pathogenic processes in RA suggest that JAK inhibitors directly target a number of cytokines, such as IL-6, interferons and GM-CSF, while indirectly affecting the production of other cytokines, such TNF30.

6. JAK Inhibitors Used the Treatment of Rheumatoid Arthritis

6.1. Tofacitinib

The main indication for Tofacitinib is the management of autoimmune diseases, including ulcerative colitis, psoriatic arthritis and rheumatoid arthritis[92]. The U.S. FDA authorized it in 2012 for the treatment of rheumatoid arthritis after Pfizer produced it[93]. The medicine is a member of the class of drugs called Janus kinase (JAK) inhibitors. A prevalent theme in medications that target kinases is the pyridopyrimidine backbone seen in tofacitinib. This structure makes it possible for the medication to attach to Janus kinases' ATP-binding site and so limit their activity. The compound has many aromatics and nitrogen-containing heterocyclic rings, a hydroxy group (-OH) and a cyano group (-CN) that improve its selectivity for JAK inhibition. JAK1 and JAK3 are preferentially inhibited by tofacitinib, with a lower degree of JAK2 inhibition[94]. These kinases are a component of the JAK-STAT signalling system, which influences the transcription of genes involved in immune responses by sending signals from different cytokines to the cell nucleus[95]. Tofacitinib inhibits JAK1 and JAK3, which in turn decreases the activity of cytokines including interleukin-2 (IL-2), IL-6 and interferons that are important in the pathophysiology of autoimmune disorders[77]. Inhibition of these cytokine pathways leads to decreased inflammation and activation of immune cells. Following oral treatment, tofacitinib is quickly absorbed; peak plasma concentrations happen in 0.5 to 1 hour[96]. The liver predominantly uses the cytochrome P450 enzymes (CYP3A4 and CYP2C19) to metabolize the medication. Due to the medication's brief half-life of three to four hours, it must often be taken twice daily[97].

6.2. Ruxolitinib

As a selective inhibitor of JAK1 and JAK2, ruxolitinib is a fundamental part of the JAK-STAT signalling cascade, which is important for controlling immunological responses, cell division and haematopoiesis. It is a member of the group of medications called Janus kinase (JAK) inhibitors[98]. Ruxolitinib preferentially inhibits JAK1 and JAK2 due to its core structure, which is based on a pyrazole ring connected to a pyrrolo [2,3-d] pyrimidine scaffold[99]. Nitrogen atoms in the molecule participate in hydrogen bonding, which is essential for interacting with the ATP-binding site of JAK enzymes and causing an inhibitory impact. Because ruxolitinib has chiral centres, it can exist as distinct stereoisomers[100]. The medication works as the S-enantiomer, a particular stereoisomer with strong activity and selectivity against JAK enzymes. Ruxolitinib inhibits JAK1 and JAK2, which in turn prevents inflammatory response-related cytokines including interleukin-6 (IL-6), interleukin-12 (IL-12) and interferon-γ from signalling[101]. This disturbance of the JAK-STAT signalling pathway reduces cytokine-driven inflammation, particularly in conditions such as myeloproliferative neoplasms (MPNs), in which aberrant JAK signalling results in excessive blood cell synthesis and bone marrow fibrosis[102]. Orally administered ruxolitinib has a peak plasma concentration that occurs one to two hours after dosing[103]. The cytochrome P450 3A4 (CYP3A4) enzyme and, to a lesser extent, CYP2C9 are the primary enzymes involved in the drug's liver metabolism. Inactive metabolites are produced by this metabolism. Because of the medication's brief elimination half-life (about 3-6 hours), twice-daily administration is required. The kidneys eliminate the majority of ruxolitinib, with faeces excreting a smaller amount. By blocking the JAK-STAT pathway, it regulates haematopoiesis and the immune system, which makes it useful in conditions marked by aberrant cell proliferation and excessive cytokine signalling. When hydroxyurea is not tolerated or resistant in PV patients, ruxolitinib is used to reduce the need for phlebotomy and manage symptoms. In patients who do not respond to conventional corticosteroid therapy, it is also licensed for the treatment of acute and chronic GVHD. The main drawback of this medication is that long-term users are more likely to develop skin cancer, most likely as a result of its immunosuppressive

qualities[104]. Since CYP3A4 is responsible for the metabolism of ruxolitinib, medications that inhibit or promote this enzyme, such as rifampin or ketoconazole, may alter the body's levels of ruxolitinib and necessitate dosage modifications[105].

6.3. Baricitinib

The selective inhibitor baricitinib acts on the Janus kinase (JAK) enzymes, namely JAK1 and JAK2. It has demonstrated effectiveness in treating several inflammatory disorders, although its main usage is in the treatment of rheumatoid arthritis[106]. Two structural elements that are essential to its biological activity are the bicyclic system and the pyrimidine ring. JAK1 and JAK2, which are important in the signalling pathways of several cytokines involved in inflammation and immunological response, are inhibited by it[107]. Baricitinib decreases the synthesis of pro-inflammatory mediators by inhibiting these enzymes. Orally administered baricitinib is well absorbed; peak plasma concentrations are obtained in about an hour[108]. It is attached to plasma proteins and has a volume of distribution of around 1 L/kg. mostly metabolized by UDP-glucuronosyltransferases and CYP3A4, with a tiny amount excreted undigested. Because of the half-life, which is around 12 hours, dosage can be done once day[109]. It is common for patients on baricitinib to need to have their liver function, cholesterol and infection symptoms checked[110]. It is mainly authorized for the management of persons with moderate-to-severe rheumatoid arthritis whose response to one or more disease-modifying antirheumatic medications (DMARDs) was insufficient[111]. It was approved for use in COVID-19 emergency situations and has also been studied for usage in alopecia areata[112]. Infections, nausea, headaches and elevated liver enzymes are a few of the frequent side effects. Due to its immunosuppressive qualities, there is a risk of significant infections and thrombosis[113].

6.4. Upadacitinib

A selective Janus kinase (JAK) inhibitor, upadacitinib is mainly used to treat inflammatory diseases like rheumatoid arthritis[114]. Its amine group, pyrimidine ring and other functional groups all contribute to its increased bioactivity. Upadacitinib disrupts the JAK-STAT signalling pathway, which is essential for the activity of several cytokines in the immune response, by specifically blocking JAK[77]. As a result, immunological response and inflammation are reduced. After oral treatment, Upadacitinib is quickly absorbed; peak plasma concentrations happen in 1-4 hours. It shows excellent tissue penetration with a modest volume of dispersion. Mostly metabolized by the liver via CYP3A4, however a few other small routes are also involved. A few active metabolites are present[115]. Because of the half-life, which is around 12 hours, dosage can be done once day. To reduce possible dangers related to JAK inhibition, patients taking Upadacitinib need to have their blood counts, liver function tests and infection symptoms closely monitored[116]. Elevated liver enzymes, headaches, nausea and upper respiratory tract infections are a few of the prevalent side effects. In addition, there's a chance of developing thrombosis, cancer and severe infections.

6.5. Fedratinib

Another JAK inhibitor for RA is fedratinib, a little chemical mostly used to treat myelofibrosis, a kind of cancer of the bone marrow[117]. The complicated structure of fedratinib, which consists of an amine group and a pyrimidine, helps it to block certain kinases. It inhibits Janus kinase 2 (JAK2) and JAK1 to a lesser degree [68]. The signalling pathways that encourage the growth of malignant hematopoietic cells are disrupted by this suppression. JAK2, which is involved in the signalling pathways of several hematopoietic growth factors and cytokines, is blocked by fedratinib in order to exert its effect. Proliferation is lowered as a result. The treatment of people with intermediate-2 or high-risk myelofibrosis with fedratinib is authorized[117]. It can also help reduce symptoms such as splenomegaly. Following oral dosing, fedratinib is well absorbed and peak plasma concentrations are usually attained in 4-6 hours. Its wide distribution volume suggests that the tissue is widely distributed. CYP3A4 and other liver enzymes are primarily responsible for the drug's metabolism, but other active metabolites also play a role in its pharmacological actions. Because of the half-life, which is around 19 to 24 hours, once-daily dosage is possible[68]. It is advised to periodically check liver function tests, blood counts and any indications of neurological problems while on fedratinib therapy. It is a targeted therapeutic option for myelofibrosis, helping patients with this difficult illness to achieve better results[118]. Diarrhoea, nausea, exhaustion and increased liver enzymes are a few frequent side effects. Thrombocytopenia and encephalopathy are more severe side effects that may require monitoring[48].

7. Discussion and Conclusion

Eleven JAK inhibitors that were approved to treat inflammatory, autoimmune and myeloproliferative neoplasms were included in the current review. These medications' synthetic routes, including their original and/or modified routes, were explained.

JAK inhibitors target STAT-mediated cytokine pathways, providing immunomodulatory effects on diverse illnesses, leading to a paradigm shift in refractory systemic autoimmune treatments. JAKs are crucial intracellular signalling molecules that convert extracellular inputs into cellular responses, crucial for understanding the interplays involved in various immunological and haematological diseases. JAK inhibitors, by disrupting the JAK-STAT signalling pathway, provide a therapeutic alternative for rheumatoid arthritis, reducing inflammation and improving symptoms by influencing cytokine-driven processes. JAK inhibitors, targeting inflammatory signalling pathways, are a significant development in RA treatment, regulating disease activity and easing symptoms. Tofacitinib, Baricitinib and Upadacitinib are common JAK inhibitors used in RA. Through their targeting of these inflammatory mediators' signalling pathways, they aid in the management of symptoms and alter the course of the disease. However, careful evaluation and continuous monitoring are crucial for long-term outcomes. JAK inhibitors offer tailored treatment for autoimmune and inflammatory illnesses, improving symptoms and quality of life, but their use requires careful management due to potential adverse effects. The summary provides a summary of eleven medications, categorized as selective or nonselective JAK inhibitors, based on their pharmacological applications and kinase inhibitory actions.

8. List of Abbreviations

Table 4: List of abbreviations.

S.No.	ABBREVIATIONS	MEANINGS
1.	JAK	Janus kinase
2.	OIs	Opportunistic infections
3.	RA	Rheumatoid arthritis
4.	TyK2	Tyrosine kinase
5.	JAK STAT	Janus kinase-signal transducer and activator of transcription
6.	IL	Interleukins
7.	JH	Janus homology domain
8.	ATP	Adenosine tri-phosphate
9.	DMARDs	Disease -modifying anti rheumatic medications
10.	TNF α	Tumour necrosis factor- α
11.	GM-CSF	Granulocyte-macrophage colony-stimulating-factor
12.	MAPK	Mitogen-activated protein kinase
13.	HLA-DRB1	Human leukocyte antigen, major histocompatibility complex, Class 2, DR beta1
14.	GWAS	Genome wide association studies
15.	M-CSF	Macrophage colony-stimulating factor
16.	PV	Polycythemia Vera
17.	GVHD	Graft- Versus- Host- Disease
18.	CYP	Cytochrome P450

Conflict of Interest

The authors declare no conflict of interest.

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9. Reference

1. World Health Organization, Rheumatoid arthritis.
2. Parish LC. An historical approach to the nomenclature of rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 1963;6:138-158.
3. VanItallie TB. Gout: epitome of painful arthritis. Metabolism, 2010;59:32-36.
4. Ciofoaia EI, Pillarisetty A, Constantinescu F. Health disparities in rheumatoid arthritis. Therapeutic Advances in Musculoskeletal Disease 2022;14.
5. Sohn SJ. The role of the protein-tyrosine kinase Jak3 in murine T cell differentiation and function. University of Washington, 1998.
6. Yamaoka K, Saharinen P, Pesu M, Holt VE, Silvennoinen O, O'Shea JJ. The janus kinases (jaks). Genome biology, 2004;5:1-6.
7. Rodig SJ, Meraz MA, White JM, Lampe PA, Riley JK, Arthur CD, King KL, Sheehan KC, Yin L, Pennica D, Johnson EM. Disruption of the Jak1 gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses. Cell, 1998;93:373-383.
8. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signalling. Immunological reviews, 2009;228:273-287.
9. Pellegrini S, Dusanter-Fourt I. The structure, regulation and function of the Janus kinases (JAKs) and the signal transducers and activators of transcription (STATs). European journal of biochemistry, 1997;248:615-633.
10. Elliott NE. The role of activating mutations in the FERM domain of janus kinase 3 in the development of adult t-cell leukemia/lymphoma. Vanderbilt University, 2013.
11. O'Shea JJ, Murray PJ. Cytokine signalling modules in inflammatory responses. Immunity, 2008;28:477-87.
12. Parganas E, Wang D, Stravopodis D, Topham DJ, Marine JC, Teglund S, Vanin EF, Bodner S, Colamonici OR, Van Deursen JM, Grosveld G. Jak2 is essential for signaling through a variety of cytokine receptors. Cell, 1998;93:385-395.
13. Russell SM, Tayebi N, Nakajima H, Riedy MC, Roberts JL, Aman MJ, Migone TS, Noguchi M, Markert ML, Buckley RH, O'Shea JJ. Mutation of Jak3 in a patient with SCID: essential role of Jak3 in lymphoid development. Science, 1995;270:797-800.
14. Shimoda K, Kato K, Aoki K, et al. Tyk2 plays a restricted role in IFNα signaling, although it is required for IL-12-mediated T cell function. Immunity, 2000;13:561-571.
15. Piessevaux J. SOCS proteins and cytokine signalling: The many faces of the SOCS box (Doctoral dissertation, Ghent University).
16. Hanks SK, Hunter T. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification 1. The FASEB journal, 1995;9:576-596.
17. Boudeau J, Miranda-Saavedra D, Barton GJ, Alessi DR. Emerging roles of pseudokinases. Trends in cell biology, 2006;16:443-452.
18. Saharinen P. Signalling through the Jak-Stat pathway: Regulation of tyrosine kinase activity (Doctoral dissertation, Helsingin yliopisto).
19. Haan C, Kreis S, Margue C, Behrmann I. Jaks and cytokine receptors—an intimate relationship. Biochemical pharmacology, 2006;72:1538-1546.
20. Murray PJ. The JAK-STAT signalling pathway: input and output integration. The Journal of Immunology, 2007;178:2623-2629.
21. Walker JG, Smith MD. The Jak-STAT pathway in rheumatoid arthritis. The Journal of rheumatology, 2005;32:1650-1653.
22. Rane SG, Reddy EP. Janus kinases: components of multiple signalling pathways. Oncogene, 2000;19:5662-5679.
23. Darnell Jr JE, Kerr LM, Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signalling proteins. Science, 1994;264:1415-1421.
24. Leonard WJ. Role of Jak kinases and STATs in cytokine signal transduction. International journal of hematology, 2001;73:271-277.
25. Villarino AV, Kanno Y, O'Shea JJ. Mechanisms and consequences of Jak–STAT signalling in the immune system. Nature immunology, 2017;18:374-384.
26. Geddis AE, Linden HM, Kaushansky K. Thrombopoietin: a pan-hematopoietic cytokine. Cytokine & growth factor reviews, 2002;13:61-73.

27. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT signalling as a target for inflammatory and autoimmune diseases: current and future prospects. Drugs, 2017;77:521-546.

28. Cazzola M, Kralovics R. From Janus kinase 2 to calreticulin: the clinically relevant genomic landscape of myeloproliferative neoplasms. Blood, The Journal of the American Society of Haematology, 2014;123:3714-3719.

29. Levine RL, Pardanani A, Tefferi A, Gilliland DG. Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. Nature reviews cancer, 2007;7:673-683.

30. Tanaka Y, Luo Y, O'Shea JJ, Nakayamada S. Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. Nature Reviews Rheumatology, 2022;18:133-145.

31. Axelrad JE, Lichtiger S, Yajnik V. Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression and cancer treatment. World journal of gastroenterology, 2016;22:4794.

32. Sopjani M, Morina R, Uka V, Xuan NT, Dërmaku-Sopjani M. JAK2-mediated intracellular signaling. Current Molecular Medicine, 2021;21:417-425.

33. Turner MD, Nedjai B, Hurst T, Pennington DJ. Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. Biochemical et Biophysical Acta (BBA)-Molecular Cell Research, 2014;1843:2563-2582.

34. Aittomäki S, Pesu M. Therapeutic targeting of the Jak/STAT pathway. Basic & clinical pharmacology and toxicology, 2014;114:18-23.

35. Bajusz D, G Ferenczy G, M Keseru G. Structure-based virtual screening approaches in kinase-directed drug discovery. Current topics in medicinal chemistry, 2017;17:2235-2259.

36. Xu P, Shen P, Yu B, Xu X, Ge R, Cheng X, Chen Q, Bian J, Li Z, Wang J. Janus kinases (JAKs): The efficient therapeutic targets for autoimmune diseases and myeloproliferative disorders. European Journal of Medicinal Chemistry, 2020;192:112155.

37. Favoino E, Prete M, Catacchio G, Ruscitti P, Navarini L, Giacomelli R, Perosa F. Working and safety profiles of JAK/STAT signalling inhibitors. Are these small molecules also smart? Autoimmunity reviews, 2021;20:102750.

38. Vainchenker W, Leroy E, Gilles L, Marty C, Plo I, Constantinescu SN. JAK inhibitors for the treatment of myeloproliferative neoplasms and other disorders. F1000Research, 2018;7.

39. Wrobleski ST, Moslin R, Lin S, Zhang Y, Spergel S, Kempson J, Tokarski JS, Strnad J, Zupa-Fernandez A, Cheng L, Shuster D. Highly selective inhibition of tyrosine kinase 2 (TYK2) for the treatment of autoimmune diseases: discovery of the allosteric inhibitor BMS-986165. Journal of Medicinal Chemistry, 2019;62:8973-8995.

40. Leroy E, Constantinescu SN. Rethinking JAK2 inhibition: towards novel strategies of more specific and versatile janus kinase inhibition. Leukemia, 2017;31:1023-1038.

41. Burke JR, Cheng L, Gillooly KM, Strnad J, Zupa-Fernandez A, Catlett IM, Zhang Y, Heimrich EM, McIntyre KW, Cunningham MD, Carman JA. Autoimmune pathways in mice and humans are blocked by pharmacological stabilization of the TYK2 pseudo kinase domain. Science translational medicine, 2019;11.

42. Alexander M, Luo Y, Raimondi G, O'shea JJ, Gadina M. Jakinibs of all trades: inhibiting cytokine signaling in immune-mediated pathologies. Pharmaceuticals, 2021;15:48

43. Goedken ER, Argiriadi MA, Banach DL, Fiamengo BA, Foley SE, Frank KE, George JS, Harris CM, Hobson AD, Ihle DC, Marcotte D. Tricyclic covalent inhibitors selectively target Jak3 through an active site thiol. Journal of Biological Chemistry, 2015;290:4573-4589.

44. Gehringer M, Laufer SA. Emerging and re-emerging warheads for targeted covalent inhibitors: applications in medicinal chemistry and chemical biology. Journal of medicinal chemistry, 2018;62:5673-5724.

45. Burmester GR, Cohen SB, Winthrop KL, Nash P, Irvine AD, Deodhar A, Mysler E, Tanaka Y, Liu J, Lacerda AP, Palac H. Safety profile of Upadacitinib over 15 000 patient-years across rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis. RMD open, 2023;9:002735.

46. Jaekel N, Behre G, Behning A, Wickenhauser C, Lange T, Niederwieser D, Al-Ali HK. Allogeneic hematopoietic cell transplantation for myelofibrosis in patients pretreated with the JAK1 and JAK2 inhibitor ruxolitinib. Bone marrow transplantation, 2014;49:179-184.

47. Convertino I, Tuccori M, Ferraro S, Valdiserra G, Cappello E, Focosi D, Blandizzi C. Exploring pharmacological approaches for managing cytokine storm associated with pneumonia and acute respiratory distress syndrome in COVID-19 patients. Critical Care, 2020;24:1-6.

48. Mullally A, Hood J, Harrison C, Mesa R. Fedratinib in myelofibrosis. Blood advances. 2020 Apr 28;4:1792-1800.

49. Le M, Berman-Rosa M, Ghazawi FM, Bourcier M, Fiorillo L, Gooderham M, Guenther L, Hanna S, Hong HC, Landells I, Lansang P. Systematic review on the efficacy and safety of oral janus kinase inhibitors for the treatment of atopic dermatitis. Frontiers in medicine, 2021;8:682547.

50. Crow YJ, Neven B, Frémond ML. JAK inhibition in the type I interferonopathies. Journal of Allergy and Clinical Immunology, 2021;148:991-993.

51. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nature reviews Drug discovery, 2017;16:843-862.

52. Chovatiya R, Paller AS. JAK inhibitors in the treatment of atopic dermatitis. Journal of Allergy and Clinical Immunology, 2021;148:927-940.

53. Davis JS, Ferreira D, Paige E, Gedye C, Boyle M. Infectious complications of biological and small molecule targeted immunomodulatory therapies. Clinical microbiology reviews, 2020;33:110-128.

54. Solimani F, Meier K, Ghoreschi K. Emerging topical and systemic JAK inhibitors in dermatology. Frontiers in immunology, 2019;10:2847.

55. Sekhon SS, Roy V. Thrombocytopenia in adults: a practical approach to evaluation and management. Southern Medical Journal-Birmingham Alabama, 2006;99:491.

56. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, Li Y. Inflammation and tumour progression: signalling pathways and targeted intervention. Signal transduction and targeted therapy, 2021;6:263.

57. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone research, 2018;6:15.

58. Kondo N, Kuroda T, Kobayashi D. Cytokine networks in the pathogenesis of rheumatoid arthritis. International journal of molecular sciences, 2021;22:10922.

59. Lee JY. Regulation of cytokine expression during the inflammatory process. University of Pennsylvania, 2002.

60. Ding Q, Hu W, Wang R, Yang Q, Zhu M, Li M, Cai J, Rose P, Mao J, Zhu YZ. Signalling pathways in rheumatoid arthritis: implications for targeted therapy. Signal transduction and targeted therapy, 2023;8:68.

61. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. New England Journal of Medicine, 2001;344:907-916.

62. Kesharwani D, Paliwal R, Satapathy T, Paul SD. Rheumatoid arthritis: an updated overview of latest therapy and drug delivery. Journal of pharmacopuncture, 2019;22:210.

63. Jamilloux Y, El Jammal T, Vuitton L, Gerfaud-Valentin M, Kerever S, Sève P. JAK inhibitors for the treatment of autoimmune and inflammatory diseases. Autoimmunity reviews, 2019;18:102390.

64. Popiolek-Barczyk K, Mika J. Targeting the microglial signalling pathways: new insights in the modulation of neuropathic pain. Current Medicinal Chemistry, 2016;23:2908-2928.

65. Andratsch M, Mair N, Constantin CE, Scherbakov N, Benetti C, Quarta S, Vogl C, Sailer CA, Üceyler N, Brockhaus J, Martini R. A key role for gp130 expressed on peripheral sensory nerves in pathological pain. Journal of Neuroscience, 2009;29:13473-13483.

66. Andrade P, Hoogland G, Garcia MA, Steinbusch HW, Daemen MA, Visser-Vandewalle V. Elevated IL-1β and IL-6 levels in lumbar herniated discs in patients with sciatic pain. European spine journal, 2013;22:714-720.

67. Mika J, Zychowska M, Popiolek-Barczyk K, Rojewska E, Przewlocka B. Importance of glial activation in neuropathic pain. European journal of pharmacology, 2013;716:106-119.

68. Roskoski Jr R. Janus kinase (JAK) inhibitors in the treatment of inflammatory and neoplastic diseases. Pharmacological research, 2016;111:784-803.

69. Danese S, Argollo M, Le Berre C, Peyrin-Biroulet L. JAK selectivity for inflammatory bowel disease treatment: does it clinically matter? Gut, 2019;68:1893-1899.

70. O'Neill LA. Targeting signal transduction as a strategy to treat inflammatory diseases. Nature reviews Drug discovery, 2006;5:549-563.

71. Simon LS, Taylor PC, Choy EH, Sebba A, Quebe A, Knopp KL, Porreca F. The Jak/STAT pathway: A focus on pain in rheumatoid arthritis. In Seminars in arthritis and rheumatism, 2021;51:278-284.

72. Groner B, von Manstein V. Jak Stat signaling and cancer: Opportunities, benefits and side effects of targeted inhibition. Molecular and cellular endocrinology, 2017;451:1-4.

73. Newton RC, Decicco CP. Therapeutic potential and strategies for inhibiting tumor necrosis factor-α. Journal of medicinal chemistry, 1999;42:2295-2314.

74. Malemud CJ. The role of the JAK/STAT signal pathway in rheumatoid arthritis. Therapeutic advances in musculoskeletal disease, 2018;10:117-127.

75. O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. Annual review of medicine, 2015;66:311-328.

76. Hodge DR, Hurt EM, Farrar WL. The role of IL-6 and STAT3 in inflammation and cancer. European journal of cancer, 2005;41:2502-2512.

77. Xin P, Xu X, Deng C, Liu S, Wang Y, Zhou X, Ma H, Wei D, Sun S. The role of JAK/STAT signaling pathway and its inhibitors in diseases. International immunopharmacology, 2020;80:106210.

78. Ivanenkov AY, Balakin VK, Lavrovsky Y. Small Molecule Inhibitors of NF-□ B and JAK/STAT Signal Transduction Pathways as Promising Anti-Inflammatory Therapeutics. Mini reviews in medicinal chemistry, 2011;11:55-78.

79. Moura RA, Fonseca JE. JAK inhibitors and modulation of B cell immune responses in rheumatoid arthritis. Frontiers in Medicine, 2021;7:607725.

80. Siegel RJ. The Role of Extracellular Sulfatase-2 in the Pathogenesis of Rheumatoid Arthritis. Washington State University, 2021.

81. Fouser LA, Wright JF, Dunussi-Joannopoulos K, Collins M. Th17 cytokines and their emerging roles in inflammation and autoimmunity. Immunological reviews, 2008;226:87-102.

82. Firdous SM, Ghosh S, Nath P, Khan H. Molecular basis of diabetic nephropathy. Diabetes and diabetic complications. Nova Science Publishers, Hauppauge, 2021.

83. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nature Reviews Rheumatology, 2017;13:234-243.

84. Gómez R, Conde J, Scotece M, Gómez-Reino JJ, Lago F, Gualillo O. What's new in our understanding of the role of adipokines in rheumatic diseases? Nature Reviews Rheumatology, 2011;7:528-536.

85. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nature reviews immunology, 2011;11:85-97.

86. Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. Frontiers in endocrinology, 2013;4:71.

87. Hornburg D, Wu S, Moqri M, Zhou X, Contrepois K, Bararpour N, Traber GM, Su B, Metwally AA, Avina M, Zhou W. Dynamic lipidome alterations associated with human health, disease and ageing. Nature Metabolism, 2023;5:1578-1594

88. Kurkó J, Besenyei T, Laki J, Glant TT, Mikecz K, Szekanecz Z. Genetics of rheumatoid arthritis-a comprehensive review. Clinical reviews in allergy & immunology, 2013;45:170-179.

89. Uysal H, Nandakumar KS, Kessel C, Haag S, Carlsen S, Burkhardt H, Holmdahl R. Antibodies to citrullinated proteins: molecular interactions and arthritogenicity. Immunological reviews, 2010;233:9-33.

90. Bery AI, Shepherd HM, Li W, Krupnick AS, Gelman AE, Kreisel D. Role of tertiary lymphoid organs in the regulation of immune responses in the periphery. Cellular and Molecular Life Sciences, 2022;79:359.

91. Siouti E andreakos E. The many facets of macrophages in rheumatoid arthritis. Biochemical pharmacology, 2019;165:152-169.

92. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, Danese S, Feagan BG, Reinisch W, Niezychowski W, Friedman G. Tofacitinib as induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine, 2017;376:1723-1736.

93. Chaudhari K, Rizvi S, Syed BA. Rheumatoid arthritis: current and future trends. Nat Rev Drug Discov, 2016;15:305-306

94. Nair PC, Piehler J, Tvorogov D, Ross DM, Lopez AF, Gotlib J, Thomas D. Next-generation JAK2 inhibitors for the treatment of myeloproliferative neoplasms: lessons from structure-based drug discovery approaches. Blood Cancer Discovery, 2023;4:352-364.

95. Stark GR, Darnell JE. The JAK-STAT pathway at twenty. Immunity, 2012;36:503-514.

96. Angelini J, Talotta R, Roncato R, Fornasier G, Barbiero G, Dal Cin L, Brancati S, Scaglione F. JAK-inhibitors for the treatment of rheumatoid arthritis: a focus on the present and an outlook on the future. Biomolecules, 2020;10:1002.

97. Bibi Z. Role of cytochrome P450 in drug interactions. Nutrition and metabolism, 2008;5:1-10.

98. Elli EM, Baratè C, Mendicino F, Palandri F, Palumbo GA. Mechanisms underlying the anti-inflammatory and immunosuppressive activity of ruxolitinib. Frontiers in oncology, 2019;9:1186.

99. Shawky AM, Almalki FA, Abdalla AN, Abdelazeem AH, Gouda AM. A comprehensive overview of globally approved JAK inhibitors. Pharmaceutics, 2022;14:1001.

100. Ceramella J, Iacopetta D, Franchini A, De Luca M, Saturnino C andreu I, Sinicropi MS, Catalano A. A look at the importance of chirality in drug activity: Some significative examples. Applied Sciences, 2022;12:10909.

101. Kleppe M, Kwak M, Koppikar P, Riester M, Keller M, Bastian L, Hricik T, Bhagwat N, McKenney AS, Papalexi E, Abdel-Wahab O. JAK–STAT pathway activation in malignant and non-malignant cells contributes to MPN pathogenesis and therapeutic response. Cancer discovery, 2015;5:316-331.

102. Chen X, Shi JG, Emm T, Scherle PA, McGee RF, Lo Y, Landman RR, Punwani NG, Williams WV, Yeleswaram S. Pharmacokinetics and pharmacodynamics of orally administered ruxolitinib (INCB018424 phosphate) in renal and hepatic impairment patients. Clinical pharmacology in drug development, 2014;3:34-42.

103. Ward AC, Touw I, Yoshimura A. The Jak-Stat pathway in normal and perturbed hematopoiesis. Blood, The Journal of the American Society of Haematology, 2000;95:19-29.

104. Kesharwani D, Paul SD, Paliwal R, Satapathy T. Exploring potential of diacerin nanogel for topical application in arthritis: Formulation development, QbD based optimization and pre-clinical evaluation. Colloids and Surfaces B: Biointerfaces, 2023;223:113160.

105. Azanza JR, Mensa J, Barberán J, Vázquez L, de Oteyza JP, Kwon M, Yáñez L, Aguado JM, Gracian AC, Solano C, Camps IR. Recommendations on the use of azole antifungals in hematology-oncology patients. Revista Española de Quimioterapia, 2023;36:236.

106. Harigai M, Honda S. Selectivity of Janus kinase inhibitors in rheumatoid arthritis and other immune-mediated inflammatory diseases: is expectation the root of all headache? Drugs, 2020;80:1183-1201.

107. Fensome A, Ambler CM, Arnold E, Banker ME, Brown MF, Chrencik J, Clark JD, Dowty ME, Efremov IV, Flick A, Gerstenberger BS. Dual inhibition of TYK2 and JAK1 for the treatment of autoimmune diseases: discovery of ((S)-2, 2-difluorocyclopropyl)((1 R, 5 S)-3-(2-((1-methyl-1 H-pyrazol-4-yl) amino) pyrimidin-4-yl)-3, 8-diazabicyclo [3.2. 1] octan-8-yl) methanone (PF-06700841). Journal of medicinal chemistry, 2018;61:8597-8612.

108. Jorgensen SC, Tse CL, Burry L, Dresser LD. Baricitinib: a review of pharmacology, safety and emerging clinical experience in COVID-19. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2020;40:843-856.

109. De Zwart LL, Haenen HE, Versantvoort CH, Sips AJ. Pharmacokinetics of ingested xenobiotics in children: A comparison with adults.

110. Assadiasl S, Fatahi Y, Mosharmovahed B, Mohebbi B, Nicknam MH. Baricitinib: from rheumatoid arthritis to COVID-19. The Journal of Clinical Pharmacology, 2021;61:1274-1285.

111. Singh JA, Hossain A, Tanjong Ghogomu E, Kotb A, Christensen R, Mudano AS, Maxwell LJ, Shah NP, Tugwell P, Wells GA, Cochrane Musculoskeletal Group. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network meta-analysis. Cochrane Database of Systematic Reviews, 1996;2016.

112. Nguyen B, Tosti A. Alopecia in patients with COVID-19: A systematic review and meta-analysis. JAAD international, 2022;7:67-77.

113. Ozkurt Z, Tanrıverdi EÇ. COVID-19: Gastrointestinal manifestations, liver injury and recommendations. World Journal of Clinical Cases, 2022;10:1140.

114. Radu AF, Bungau SG, Negru AP, Uivaraseanu B, Bogdan MA. Novel potential janus kinase inhibitors with therapeutic prospects in rheumatoid arthritis addressed by in silico studies. Molecules, 2023;28:4699.

115. Lefevre PL, Vande Casteele N. Clinical pharmacology of janus kinase inhibitors in inflammatory bowel disease. Journal of Crohn's and Colitis, 2020;14:725-736.

116. Nash P, Kerschbaumer A, Dörner T, Dougados M, Fleischmann RM, Geissler K, McInnes I, Pope JE, Van Der Heijde D, Stoffer-Marx M, Takeuchi T. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. Annals of the rheumatic diseases, 2021;80:71-87.

117. Talpaz M, Kiladjian JJ. Fedratinib, a newly approved treatment for patients with myeloproliferative neoplasm-associated myelofibrosis. Leukaemia, 2021;35:1-7.

118. Zhang M, Xu CR, Shamiyeh E, Liu F, Yin JY, von Moltke LL, Smith WB. A randomized, placebo-controlled study of the pharmacokinetics, pharmacodynamics and tolerability of the oral JAK 2 inhibitor fedratinib (SAR 302503) in healthy volunteers. The Journal of Clinical Pharmacology, 2014;54:415-21.