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Review

Janus Kinases and Autoimmunity: Bridging Pathways to Therapy

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Abstract: Janus kinase (JAK) is a family of intracellular non-receptor tyrosine kinases with four members (JAK1, JAK2, JAK3, and Tyk2). The JAK-STAT (signal transducer and activator of transcription) pathway is an evolutionary conserved mechanism of transmembrane signal transduction relaying over 50 cytokines signals to regulate the proliferation, immune response, inflammation, and malignancy. The dysfunction of JAK-STAT signaling pathway is directly associated with the pathogenesis of inflammatory and autoimmune disorders, as well as tumor progression. Studies have shown that targeting the JAK family with small-molecule inhibitors can treat inflammatory and autoimmune diseases and myeloproliferative neoplasms. In this review, we discuss the current understanding of the JAK-STAT signaling and approved JAK inhibitors.

Keywords: Janus kinase; JAK-STAT pathway; autoimmune disease; JAK inhibitor

1. Introduction

Janus kinases (JAKs) are one of the most extensively researched non-receptor tyrosine kinases that play a crucial role in cellular signaling. JAK family has four members (JAK1, JAK2, JAK3, and tyrosine kinase 2 (Tyk2)) [1]. These kinases participate in the transmission of signals from extracellular cytokines to the interior of the cell, thus changing gene expression governing cellular behavior [2]. JAK-STAT (signal transducer and activator of transcription) pathway is an evolutionarily conserved signaling pathway involved in various cell functions, including development, differentiation, hematopoiesis, metabolism, and immune regulation [3–5]. More than 50 cytokines, including interleukins (ILs), interferons (IFNs), colony-stimulating factors, hormones, and growth factors mediate cellular proliferation, differentiation, survival, and immune response through the JAK-STAT signaling pathway to [6,7].

Nonetheless, dysregulation of JAK kinases is associated with several diseases, such as autoimmune disorders (rheumatoid arthritis (RA) and myelofibrosis). Uncontrolled JAK-STAT signaling in these conditions results in excessive inflammation and dysregulated immune responses [8]. As a result, JAK kinases have become attractive targets for pharmacological intervention, leading to the development of JAK inhibitors to treat autoimmune diseases by dampening excessive cytokine signaling [9].

This review aims to comprehensively describe the major findings about the role of JAK-STAT pathway components in autoimmune and malignant diseases and discuss in detail the development and application of JAK inhibitors for the treatment of human diseases.

2. JAKs Family Architecture

Tyk2 was the first member of the JAK family to be discovered in the early 1990s [10]. JAK1, JAK2, and JAK3 were then discovered over the next three years in succession [11–13]. These subtypes contain highly homologous and relatively large proteins of the tyrosine kinase families. They possess seven structural

homologous regions (JH1–JH7), which are divided into four functional domains, including FERM domain, Src homology domain (SH2), pseudokinase domain, and kinase domain, with about 1100 amino acid residues [14, 15]. Kinase domain (JH1) and pseudokinase domain (JH2) are the characteristic features of the JAKs. JH1 domain is an active protein tyrosine kinase catalytic domain that phosphorylates a key component of the kinase domain of the substrate [16]. However, JH2 domain has no catalytic activity and mainly regulates the kinase action of JH1 [17].

JAK1 is the most ubiquitously expressed JAK family member. JAK1 is involved in signaling through various cytokine receptors that utilize the common beta chain and gp130 subunit, including IFNs, ILs, and colony-stimulating factors. Compared with other JAKs subtypes, JAK1 is activated by the highest number of cytokines, including cytokine receptors with the common gamma chain (γc) subunit, receptors with a gp130 subunit, and class II cytokine receptor and IL-10 family cytokine receptor [18]. JAK1 plays a crucial role in autoimmune and inflammatory diseases since it regulates many cytokine signals, becoming an important drug target for the treatment of these diseases.

Similarly, JAK2 can also be phosphorylated by gp130 receptor family and class II cytokine-receptor family [2]. JAK2 is essential for T-cell development and function, as well as the regulation of hematopoiesis. JAK2 mutations are associated with myeloproliferative neoplasms (MPN), such as polycythemia vera (PV) and essential thrombocythemia (ET) [19]. These hematologic disorders are characterized by excessive production of red blood cells in EPO and platelets by thrombopoietin through JAK2 signaling [20]. These characteristics of JAK2 form the basis for MPN treatment using JAK2 inhibitors.

JAK3 is exclusively expressed in hematopoietic cells and is primarily involved in signaling through cytokine receptors that utilize the common gamma chain (γc), such as IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. JAK3 plays a critical role in T-cell activation and proliferation [21]. JAK3 can also pair with JAK1 to transport different cytokines, thus participating in lymphoid activity, which is associated with severe combined immunodeficiency disease. JAK3 has become an attractive therapeutic target for immunosuppressive drugs used in transplantation and autoimmune diseases due to its restricted expression pattern and functional characteristics [22,23].

Tyk2 is the least understood member of the JAK family and has a more limited tissue distribution compared with other JAKs. Tyk2 regulates the phosphorylation of STAT proteins downstream of the receptors for the cytokines IL-12, IL-23, IL-10-like cytokines, and type I cytokines of IFNα and IFNβ [24, 25]. Tyk2 can also regulate the balance of Th1 and Th2 cells in mice. Tyk2 deletion in mice has a restricted phenotype with impaired responses, such as resistance to collagen-induced arthritis (CIA) and experimental autoimmune encephalomyelitis (EAE). The patients with high immunoglobulin E syndrome have defective signal transduction of IFNα and IL-12, which can be recovered through Tyk2 gene transduction treatment. Small molecule compounds targeted on Tyk2 pseudokinase domain to block Tyk2 signaling have become a trend for discovering selective Tyk2 inhibitors [26].

3. JAK-STAT Signaling Pathway

The JAK-STAT pathway was discovered in the 1990s and has attracted much interest due to its role in cellular signaling. This signaling pathway is activated by cytokines, growth factors, and hormones that bind to their respective cell surface receptors. These receptors are composed of two or more subunits, where at least one is associated with a JAK kinase. JAK kinases are activated upon ligand binding, then phosphorylating tyrosine residues on the receptor, creating docking sites for STAT proteins.

STAT proteins, found in the cytoplasm in an inactive form, are recruited to the phosphorylated receptors through Src homology 2 (SH2) domains. These proteins undergo tyrosine phosphorylation through the JAK kinases, leading to dimerization and dissociation from the receptor. The phosphorylated STAT dimers then translocate to the nucleus, where they bind to specific DNA sequences (STAT-binding elements (SBEs)) in the promoters of target genes [27, 28]. This binding leads to the transcriptional activation or repression of these genes, depending on the cellular context and the specific STAT protein involved.

The JAK-STAT pathway is highly regulated at multiple levels to ensure appropriate cellular responses. This regulation occurs through the negative feedback inhibition exerted by various proteins. For instance, JAK-STAT activation induces the suppressors of cytokine signaling (SOCS) family of proteins, which then

bind to phosphorylated tyrosine residues on the receptors or JAK kinases, thereby inhibiting further signaling. The protein inhibitors of activated STATs (PIAS) bind to activated STATs and prevent DNA binding activity [29]. Additionally, the JAK-STAT pathway is regulated by phosphatases dephosphorylating STAT proteins, leading to inactivation and export from the nucleus. Phosphatases, such as SHP-1 and SHP-2, play significant roles in this process. Moreover, the termination of JAK-STAT signaling occurs through the ubiquitin-mediated proteasomal degradation of STAT proteins [30].

4. The JAK-STAT Pathway and Diseases

The JAK-STAT pathway mediates the effects of numerous cytokines involved in immunity and blood cell formation. For instance, IFNs signal induces antiviral responses through JAKs. Also, ILs, such as IL-3 and IL-5, are critical for the development and function of immune cells, including T cells and B cells. Dysregulation of JAK kinases is associated with several diseases, particularly autoimmune disorders and myeloproliferative tumor. Uncontrolled JAK-STAT signaling results in excessive inflammation and dysregulated immune responses in such conditions. As a result, JAK kinases have become attractive targets for pharmacological intervention, leading to the development of JAK inhibitors as promising drugs for treating autoimmune diseases by dampening excessive cytokine signaling.

Dysfunctional JAK-STAT signaling can lead to uncontrolled immune responses, promoting the development and progression of various autoimmune diseases, as explained below. (1) Autoimmune diseases: JAK-STAT signaling plays a critical role in regulating immune cell function and differentiation. Mutations or overexpression of JAK proteins can lead to constitutive activation of JAK-STAT signaling, resulting in the overproduction of pro-inflammatory cytokines and the differentiation of autoreactive immune cells. This can lead to the development and progression of autoimmune diseases, such as RA, systemic lupus erythematosus (SLE), and multiple sclerosis (MS). (2) Neoplasms: The JAK-STAT pathway mediates abnormally elevated cytokines, resulting in the transcription of downstream effector molecules. Dysfunctional JAK-STAT signaling can also promote the development and progression of cancer. $JAK2^{V617F}$ mutation can lead to constitutive activation of JAK-STAT signaling, resulting in the overproduction of pro-inflammatory cytokines and the proliferation and recruitment of blood cells [19]. This can lead to the development and progression of hematological malignancies, including PV, ET, and primary myelofibrosis (PMF) [31,32]. (3) Other diseases: several studies have shown that inflammation may promote the pathogenesis and development of neurodegenerative diseases, such as Parkinson's disease (PD) [33]. Misfolded α-synuclein is crucial in PD progression. PD animal models and patients have indicated that aberrant expression of α-synuclein is associated with the activation of the JAK-STAT pathway. Hair follicle miniaturization and immune dysregulation promote disease pathogenesis in hair loss. Activation of the JAK-STAT pathway can drive hair follicles into a quiescent phase, thus decreasing hair growth capacity. JAK inhibitors can promote hair growth by inducing hair follicle exit from the resting state [34,35].

5. Approved JAK inhibitors

The JAK-STAT pathway participates in diverse biological processes, indicating that its dysregulation can lead to pathological conditions. Therefore, inhibiting the activation of the JAK-STAT signaling pathway may prevent the development of related diseases. JAK has become a key drug target for the treatment of inflammatory and autoimmune diseases, myeloproliferative tumors, and other diseases. Many JAKs inhibitors have been approved by Food and Drug Administration (FDA) or other country agencies for clinical medication.

JAK inhibitors can be divided into two generations based on the selective properties [36]. Non-selective or pan-JAK inhibitors are the first-generation small molecule JAKs inhibitors, and they include tofacitinib, baricitinib, ruxolitinib, etc. The second-generation JAK inhibitors, such as upadacitinib and ritlecitinib, have selective inhibitory activity against different JAK subtypes. The allosteric JAK inhibitors (Tyk2 inhibitor deucravacitinib) are a class of small molecule inhibitors that bind to other sites but not to competitive ATP-binding sites in JAKs with high selectivity [26,37–39]. Meanwhile, JAKs inhibitors can also be classified into competitive (reversible) and covalent (irreversible) inhibitors depending on their competitive binding mode with ATP. The approved JAK inhibitors are summarized in Table 1.

Table 1. Approved JAK inhibitors.

Classification	JAK Inhibitors	Targets	Indications
Pan-JAK inhibitors	Ruxolitinib	JAK1/2	Malignant tumors
			Acute graft-versus-host disease
			Primary myelofibrosis
			Polycythaemia vera
			Atopic dermatitis
			Vitiligo
	Tofacitinib	JAK1/2/3	Rheumatoid arthritis
			Psoriatic arthritis
			Juvenile idiopathic arthritis
			Ulcerative colitis
			Ankylosing spondylitis
	Baricitinib	JAK1/2 Tyk2	Rheumatoid arthritis
			Atopic dermatitis
			COVID-19
			Alopecia areata
	Peficitinib	JAK1/2/3 Tyk2	Rheumatoid arthritis
	Delgocitinib	JAK1/2/3 Tyk2	Atopic dermatitis
	Pacritinib	JAK2/JAK2^{V617F} Tyk2/FLT	Intermediate-or high-risk primary or secondary myelofibrosis
	Momelotinib	JAK1/2/ACVR1	Intermediate or high-risk myelofibrosis
Selective JAKs inhibitors	Upadacitinib	JAK1	Atopic dermatitis
			Ulcerative colitis
	Filgocitinib	JAK1	Rheumatoid arthritis
	Abrocitinib	JAK1	Atopic dermatitis
	Fedratinib	JAK2	Intermediate-2 or high-risk primary or secondary myelofibrosis
	Ritlecitinib	JAK3/TEC	Alopecia areata
	Deucravacitinib	Tyk2(JH2)	Plaque psoriasis

5.1. Pan-JAK Inhibitors

5.1.1. Ruxolitinib

Ruxolitinib was the first US FDA-approved JAK small molecule inhibitor developed by Incyte and Novartis in 2011 [39]. Ruxolitinib is a potent JAK1 (IC_{50} = 3.3 nM) and JAK2 (IC_{50} = 2.8 nM) inhibitor with 130-fold selectivity over JAK3 [39]. Ruxolitinib was approved for the treatment of malignant tumors, acute graft-versus-host disease, PMF, PV by the FDA and other agencies [40–43]. The JAK2^{V617F} mutation in the JAK2 JH2 pseudokinase domain results in constitutive JAK2 kinase activity, driving cell survival and proliferation independently from signals triggered by cytokine binding [31]. Active JAK2 plays a crucial role in tumor cell transformation and proliferation. Besides, the prevalence of JAK2^{V617F} mutation has increased in MPNs. As a result, JAK2 has become a potential molecular target for therapeutic intervention in MPN and other malignancies associated with abnormal JAK2-STAT signaling. Ruxolitinib can strongly inhibit JAK2^{V617F} mutation-positive cells. Several clinical trials have evaluated the efficacy of ruxolitinib in MPN treatment. A clinical trial (NCT00952289) showed that Ruxolitinib has significant therapeutic outcomes compared with placebo [44]. In addition, ruxolitinib cream was approved in 2021 and 2022 for the treatment of atopic dermatitis (AD) and vitiligo, respectively [45,46].

5.1.2. Tofacitinib

Tofacitinib, also known as CP690550 or Xeljanz, was developed by Pfizer and was the first JAK inhibitor approved by the FDA for RA treatment in 2012 [47]. Free-cell assay showed that tofacitinib, as a pan-JAKs inhibitor, has significant inhibitory activity against JAK1, JAK2, and JAK3 with IC_{50} values of 112, 20, and 1 nM, respectively [47]. Tofacitinib blocks the γc cytokine-receptor and gp130 cytokine-receptor signaling pathway through JAK1 and JAK3 subtypes. Clinical trials (NCT00814307, NCT00853385) have shown that tofacitinib can treat RA patients with poor responses to methotrexate or other DMARDs [48,49].

Nonetheless, some clinical trials have evaluated the efficacy of tofacitinib in other inflammatory and immune diseases. Two clinical trials (NCT01882439 and NCT01877668) assessed the efficacy of tofacitinib in patients with active psoriatic arthritis (PsA) with inadequate response to TNF inhibitors or DMARDs [50, 51]. Another clinical trial (NCT00787202) evaluated the efficacy of tofacitinib for patients with severely active ulcerative colitis (UC) [52]. As a result, tofacitinib was also approved for the treatment of PsA (2017), ulcerative colitis (2018), juvenile idiopathic arthritis (2020), and active ankylosing spondylitis (2021) [53].

5.1.3. Baricitinib

Baricitinib, developed by Incyte and Lilly, was first approved by the EMA (European Medicine Agency) for RA treatment in 2017 [54]. Besides, baricitinib was approved by the FDA for the treatment of moderate-to-severe RA in adults in 2018 [55]. Baricitinib is a pan-JAK inhibitor with potent inhibitory activity for JAK1 (IC_{50} = 5.9 nM), JAK2 (IC_{50} = 5.7 nM), and Tyk2 (IC_{50} = 53 nM) [56]. Baricitinib suppresses JAK-STAT pathway by inhibiting JAK1, JAK2, and Tyk2, leading to the production of the pro-inflammatory cytokines, thus preventing the development of inflammatory and autoimmune disease. Furthermore, the EMA approved baricitinib for the treatment of adult patients with moderate-to-severe AD in Nov 2020 [57]. A pilot study showed that baricitinib can alleviate respiratory symptoms in 12 patients with mild-to-moderate COVID-19 pneumonia. Also, the FDA approved an emergency use authorization for the combination of baricitinib and remdesivir to treat hospitalized patients with COVID-19 in April 2022 [53]. In addition, several phase 2 and phase 3 trials have concluded that baricitinib has a superior effect on hair growth (after 36 weeks of treatment) in adults with severe alopecia areata (AA) to placebo [58,59]. Subsequently, baricitinib was recently approved by the EMA and the FDA for the treatment of adults with severe AA (2022) [60].

5.1.4. Other Pan-JAK Inhibitors

Peficitinib, a pan-JAK inhibitor developed by Astellas Pharma Inc., was approved by the PMDA for RA treatment in Japan in 2019 [61]. Peficitinib has potent inhibitory activity against JAK1, JAK2, JAK3, and Tyk2, with IC_{50} values of 3.9 nM, 5.0 nM, 0.7 nM, and 4.8 nM, respectively [62]. Numerous clinical trials have shown that peficitinib has a significant response rate in patients with moderate-to-severe RA [53]. Delgocitinib, a pan-JAK inhibitor developed by Japan Tobacco, was approved for AD treatment in 2020 in Japan [63]. Delgocitinib has potent inhibitory activity against JAK1, JAK2, JAK3, and Tyk2 with IC_{50} values of 2.8 nM, 2.6 nM, 13 nM, and 58 nM, respectively [64]. Furthermore, delgocitinib has a significant therapeutic efficacy in the treatment of AD patients. Pacritinib, an orally administrated pan-JAK inhibitor developed by CTI BioPharma, was first approved by the FDA in February 2022 for the treatment of adults with intermediate- or high-risk primary or secondary (post-PV or post-ET) myelofibrosis (MF) with a platelet count below 50×10^9/L [65]. Besides its strong inhibitory activity against JAK2/$JAK2^{V617F}$ and Tyk2, pacritinib also has potential inhibitory effects on FLT kinase. Momelotinib, a JAK1/2 and activin A receptor 1 inhibitor developed by GSK, was first approved by FDA in September 2023 for the treatment of intermediate or high-risk MF, including PMF or secondary MF (post- PV and post- ET) [66].

5.2. Selective JAKs Inhibitors

5.2.1. JAK1 Inhibitors

Upadacitinib was the first approved selective JAK1 inhibitor by the FDA in 2019 for RA treatment. Upadacitinib inhibits JAK1 isoform (IC_{50}; 45 nM). Upadacitinib can also inhibit JAK2 isoform with IC_{50} of

109 nM [67] (about 2-fold lower selectivity compared with JAK1). Therefore, upadacitinib is not a highly selective JAK inhibitor. As a result, upadacitinib was approved by the FDA for the treatment of RA (2019), PsA (2021), AD (January 2022), moderate-to-severe UC (March 2022), Ankylosing Spondylitis (April 2022), non-radiographic Axial Spondyloarthritis (October 2022) and crohn's disease (2023) [53].

Filgotinib, discovered by Gliead as potent selective JAK1 inhibitor, was approved by the EMA and Japan in 2020 for RA treatment [68]. Besides, filgotinib can inhibit JAK1 and JAK2 with IC_{50} values of 10 nM and 28 nM, respectively [69]. Therefore, filgotinib may have potential risk of cardiovascular side effects due to its relatively strong inhibitory activity against JAK2 subtypes.

Abrocitinib, a selective JAK1 inhibitor discovered by Pfizer, was approved by UK and Japan in September 2021 and the FDA in January 2022 for the treatment of refractory, moderate-to-severe AD [70]. Abrocitinib is selective for JAK1 isoform with IC_{50} value of 29 nM. Compared with JAK1, cell-free assay has shown that abrocitinib has over-inhibitory activity on JAK2 (28-fold), JAK3 (340-fold), and Tyk2 (43-fold) [71]. Compared with the placebo, abrocitinib has higher therapeutic effectiveness in AD treatment.

5.2.2. JAK2 Inhibitors

Fedratinib is a JAK2-selective inhibitor approved by the FDA in 2019 for the treatment of patients with intermediate-2 or high-risk primary or secondary myelofibrosis [72]. Fedratinib has potent inhibitory activity against JAK2 and $JAK2^{V617F}$ with IC_{50} value of 3 nM (35-fold and 334-fold compared with inhibitory activity against JAK1 and JAK3) [73]. Moreover, fedratinib can significantly inhibit FMS-like tyrosine kinase 3 (FLT3) and RET kinase with IC_{50} of 15 nM and 48 nM, respectively.

5.2.3. JAK3 Inhibitors

Ritlecitinib (also known as PF-06651600) was developed by Pfizer, and was first approved by the FDA and Japan in July 2023 for the treatment of severe AA in adults and adolescents 12 years and older [74]. Ritlecitinib irreversibly and specifically inhibits JAK3 subtype with a high selectivity compared with the other three JAK isoforms. The covalent interaction between ritlecitinib and a unique cysteine residue (Cys909) in the catalytic domain of JAK3, which is replaced by a serine residue in the other JAK subtypes, explains the high selectivity [75]. Ritlecitinib also inhibits members of the TEC kinase family, including TEC, BTK, BMX, ITK, and RLK, indicating that it is a dual JAK3/TEC family kinase inhibitor. Several clinical trials (NCT03732804, NCT04006457, and NCT02974868) have revealed that ritlecitinib can treat [74].

5.2.4. Tyk2 Inhibitors

Deucravacitinib, a first-in-class oral inhibitor of Tyk2 developed by Bristol Myers Squibb (BMS), was approved by the FDA in September 2022 for the treatment of adults with moderate-to-severe plaque psoriasis undergoing systemic therapy or phototherapy [76]. Unlike other JAKs inhibitors, deucravacitinib binds to the catalytically inactive pseudokinase regulatory domain (JH2) through an allosteric inhibition that acts on the kinase domain (JH1) of Tyk2 [77]. IL-23/IL-17 axis may be involved in the pathogenesis of psoriasis. Tyk2 regulates cytokines signaling of IL-12, IL-23, and type I IFNs [78]. Therefore, targeting Tyk2 is suitable for the development of inhibitors for the treatment of psoriasis. Two clinical phase 3 trials (NCT03624127 and NCT03611751) have proven that deucravacitinib has superior performance against moderate-to-severe plaque psoriasis based on multiple efficacy endpoints to placebo or apremilast [79,80].

6. Adverse Effects of JAK Inhibitors

JAK inhibitors treat various chronic inflammation by simultaneously blocking signaling downstream of cytokines important for a range of physiological functions. As a result, their side effects are often mechanically related. Clinical trials have shown that severe opportunistic infections, including upper respiratory tract infections, pneumonia, urinary tract infections, and skin and soft tissue infections, are the most common adverse events related to JAK inhibitors.

The use of JAK inhibitors is also associated with cardiovascular events. Tofacitinib is the most

extensively studied JAK inhibitor with much available safety data. A large randomized safety clinical trial showed that the risk of serious heart-related events, such as heart attack or stroke, and blood clots (deep venous thrombosis and pulmonary embolism) is increased with the use of tofacitinib for RA and UC treatment [81]. Health Canada issued pharmacovigilance warning in June 2020 of the risk of venous thromboembolism (VTE) with clinical use of ruxolitinib and tofacitinib [82]. Anemia is one of the common side effects of pan-JAK inhibitors. JAK2 regulates the function of hematopoietic growth factor, such as erythropoietin, indicating that JAK2 inhibition may lead to the disturbance of hemoglobin production, resulting in anemia [23].

Furthermore, malignancy is a potential complication of JAK inhibitors. However, clinical trials have not revealed an increased risk of solid tumors with RA patients using JAK inhibitors [83]. In addition, gastrointestinal reactions, such as diarrhea, nausea, vomiting, and even gastrointestinal perforation, are associated with the use of tofacitinib, peficitinib, abrocitinib, and fedratinib [84–87].

As a result, the FDA warned (2021) about the increased risk of serious heart-related events, cancer, blood clots, and death related to the use of JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) to treat certain chronic inflammatory conditions [81]. Although no large safety clinical trials have evaluated the risk associated with other JAK inhibitors, the FDA has indicated that they may have a similar risk as tofacitinib because they have the same treatment mechanisms.

7. Conclusion and Future Perspective for JAK Inhibitors

Each JAK family member has its distinct role in cellular signaling, particularly in immune system regulation and hematopoiesis. Dysregulation of these kinases may cause diseases associated with various immune disorders, making them attractive targets for pharmacological intervention. The development of JAK inhibitors is a promising therapeutic approach for the treatment of these diseases. To date, 13 JAK inhibitors (ruxolitinib, tofacitinib, baricitinib, peficitinib, delgocitinib, upadacitinib, filgotinib, fedratinib, abrocitinib, pacritinib, momelotinib, deucravacitinib, and ritlecitinib) have been approved by various agencies for the treatment of inflammatory and autoimmune diseases and MPN.

Cytokine signaling is critical for cellular growth, development and differentiation, immune homeostasis, and host defense. Therefore, inhibition of multiple cytokines using non-selective pan-JAK inhibitors causes adverse events, such as severe opportunistic infections, anemia, and other side effects. Severe infection events, including upper respiratory tract infections, pneumonia, urinary tract infections, and skin and soft tissue infections occur in patients using JAK inhibitors. Non-selective JAK inhibitors can also decrease hemoglobin levels, possibly due to inhibition of signaling by erythropoietin and other cytokines dependent on JAK2 isoform. Therefore, selective JAK inhibitors may avoid such side effects. To date, only two selective JAK inhibitors, deucravacitinib, and ritlecitinib, have been approved for the treatment of inflammatory and autoimmune diseases. However, their side effects are unclear since they have been used in the clinic for a short time.

More personalized treatments may be developed in the future depending on the patient's genetic makeup and disease characteristics using advances in genomics and bioinformatics, thus improving outcomes and use of healthcare resources.

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