Review Article

Clinical perspectives of Janus Kinase Inhibitors: A review

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Abstract

JAK inhibitors are small-molecule drugs that inhibit Janus kinases (Jakinibs) widely used in multiple therapeutic areas like rheumatoid arthritis, psoriasis, inflammatory bowel disease, cancer and recently tried with antiviral agents for COVID-19 treatment and have gained traction as safe and efficacious options for these treatments. The JAK inhibitors are considered as new players in many treatments hence this review highlights the use of major JAK inhibitors in various therapeutic areas; their uses and associated risk and limitations in clinical settings. For collection of clinical data recent articles were taken in consideration.

Keywords: Janus kinase inhibitors, JAK-STAT pathway, tyrosine kinase-2, tofacitinib, rheumatoid arthritis

Introduction

JAK inhibitors block cytokine mediated signalling via the JAK-STAT pathway, which plays an important role in immune regulation and growth. These 'small molecule' drugs are highly specific for blocking targets identified within cells that cause chronic inflammation.

Rheumatoid arthritis (RA) is chronic autoimmune disorder characterized by severe destructive inflammation of the distal joints, particularly of the hands. The inflammation breaks down cartilage and bone, resulting in severe pain, stiffness, deformities, and disability. The inflammation can affect other areas as well, including the eyes, lungs, heart, or skin. RA can strike at any age but is more commonly seen in adulthood (Changelian et al., 2003).

JAKs are intracellular enzymes that transmit signals from cytokines binding to receptors on the cell surface to signal transducers and activators of transcription (STATs), which drive pro-inflammatory cellular responses the JAK–STAT pathway.

The JAK/STAT pathway: JAKs, named after the two-faced Roman God Janus, form a family consisting of four members: JAK1, JAK2, JAK3 and TYK2. They are all cytoplasmic tyrosine kinases able to phosphorylate tyrosine residues either on themselves (auto-phosphorylation) or on adjacent molecules (trans-phosphorylation), including the STATs. The latter is a family of transcription factors, acting downstream of JAKs and consisting of 7 members (O'Shea et al., 2013). Schematic representation of the various cytokines and their receptors signalling via the JAK/STAT. Figure 1, shows overview of the JAK–STAT signalling pathway.

Binding of cytokines (yellow) to their receptors on the cell surface results in Janus kinase (JAK) activation and subsequent cross-phosphorylation of the receptors. Signal transducers and activators of transcription (STATs) then attach to the phosphorylated receptors, dimerize, and translocate to the nucleus where they drive the expression of proteins involved in inflammatory processes, including those leading to autoimmune diseases such as rheumatoid arthritis (Vashkiv and Hu, 2006).

Methods

The review of articles was done with articles published from 2003 to 2020 on JAK inhibitors which have clinical significance.

JAK inhibitors used in arthritis and different therapeutic areas:

Tofacitinib is an effective oral JAK2/1/3 inhibitor that was

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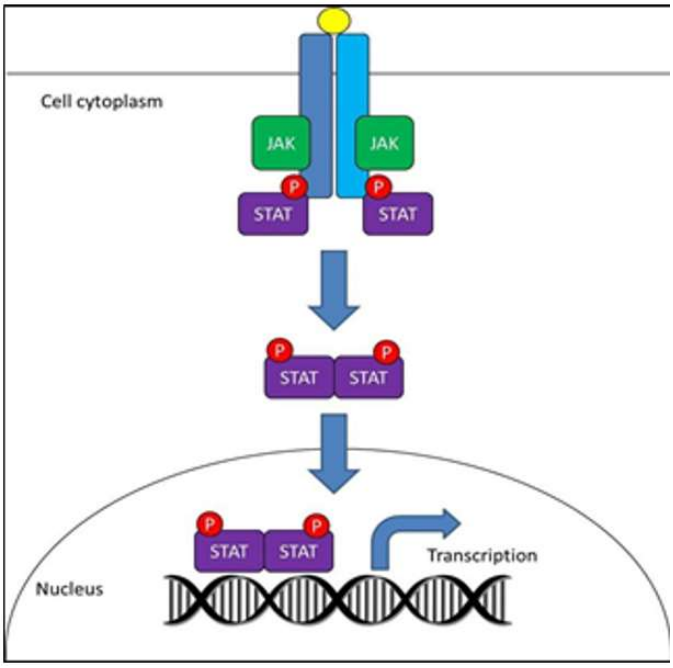

Figure 1. Signal-transduction pathway. JAK: Janus kinase; TYK: tyrosine kinase; P: phosphorus; STAT: Signal Transducer and Activation of Transcription (rheumatology.medicinematters.com).

Table 1. First-generation Janus kinase inhibitors

Drugs	Details
Tofacitinib	First studied as an anti rejection agent in organ transplant (Changelian PS et al., 2003), First FDA approved JAK inhibitor for the treatment of RA.
Ruxolitinib	FDA approved for the treatment of myelodysplastic disorders.
Baricitinib	Approved by the FDA for RA in June 2018 However, currently in phase 2 trials for psoriasis and AD (Papp KA et al.,2016)
Oclacitinib	No approved indications in humans; Has been used to treat AD in dogs (Cosgrove SB et al 2013 and Gonzales AJ et al.,2014)

approved by the FDA for the treatment of rheumatoid arthritis (RA) in 2012 (Seif et al., 2017)

Since JAK3 is limited to cytokines using the common γ chain family, tofacitinib can effectively block IL-2, IL-7, and IL-6. However, herpes zoster and cellulitis infections may occur. Both low-density lipoprotein and high-density lipoprotein levels increase while blood neutrophils are decreased. In a study in patients with RA it decreased erythrocyte sedimentation rates and C-reactive protein levels (Lee et al., 2014).

Tofacitinib efficiently blocks common γ-chain cytokines including IL-2, IL-4, IL-15, and IL-21. Since both JAK1 and JAK2 are inhibited, tofacitinib also constrains signalling by IFN-γ, IL-6, and to a lesser extent IL-12, and IL-23. As a result of this rather broader activity, tofacitinib impairs differentiation of CD4+ T helper cells (Th1 and Th2), and limits the generation of pathogenic Th17 cells (Ghoreschi et al., 2011).

Tofacitinib inhibits activation of mouse and human macrophages and is efficacious in K/BxN serum-transfer arthritis, a model that is dependent on macrophages, but not on lymphocytes (Rosengren et al., 2012).

Tofacitinib appeared to be efficacious in a mouse model of celiac disease (Yokoyama et al., 2012). Tofacitinib (previously known as CP-690,550) was the second JAK inhibitor approved by the FDA for use in a clinical setting. Tofacitinib inhibits JAK family members with a high degree of kinome selectivity (Kontzias et al., 2012; Karman et al., 2012) and was developed by Pfizer as a JAK3 inhibitor to be used as immunosuppressant in organ transplantation and possibly for the treatment of autoimmune diseases. It was soon clear that Tofacitinib inhibits not only JAK3 (IC50, 1nM) but can also inhibit JAK1 (IC50, 112nM) as well as JAK2 (IC50, 20nM) enzymatic activity (Kaur et al., 2014). These result show that tofacitinib blocks multiple steps of RA by inhibiting both innate and adaptive immunity.

Tofacitinib is an efficacious drug for the management of moderate to severe RA among patients with an inadequate response to methotrexate and tumor necrosis factor inhibitors. Long-term studies can help in understanding the risk/benefit profile of tofacitinib (McAndrew et al., 2015).

As an oral medication, tofacitinib provides patients with an alternative to parenteral therapy. Tofacitinib has a similar efficacy profile to biologics, while also offering patients convenience and independence, potentially improving medication compliance and decreasing healthcare costs. Tofacitinib is an alternative to apremilast, an oral phosphodiesterase-4 inhibitor also indicated for psoriatic arthritis (Curtis et al., 2019).

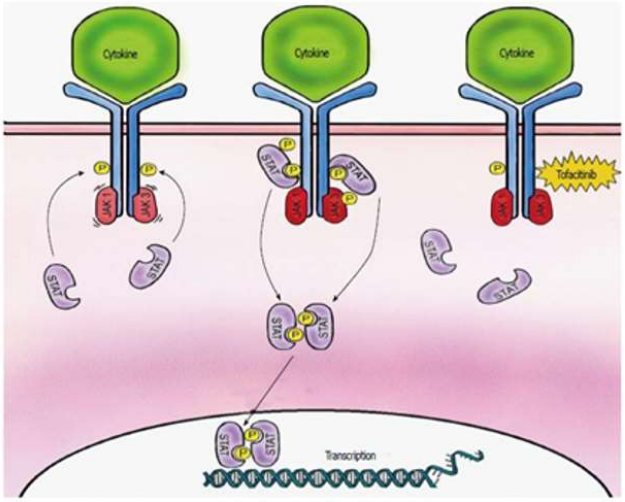

Figure 2. Mechanism of action of tofacitinib (Lundquist et al., 2014)

Table 2. Summary of published phase 3 tofacitinib studies (Lundquist et al., 2014)

Study	Duration	Participants	Demographics	Intervention	Primary outcome
ORAL solo	6 months	Active RA patients with inadequate response to at least one DMARD (biologic or nonbiologic) receiving stable doses of antimalarial	n = 611 Age: 49.7-52.4 yr Female: 85.2%-88.2% Duration of RA: 7.7-8.6 Baseline HAQ-DI: 1.50-1.53 Baseline DAS-28: 6.65-6.71	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; placebo for 3 mo then Tofacitinib 5 mg bid; placebo for 3 mo then Tofacitinib 10 mg bid	ACR20 response at month 3; DAS 28-4 ESR < 2.6 at month 3; HAQ-DI at month 3 (change from baseline)
ORAL step	6 months	Moderate to severe RA patients with inadequate response to TNF alpha inhibitors	n = 399 Age: 54.4-55.4 yr Female: 80.3%-86.36% Duration of RA: 11.3-13.0 yr Baseline HAQ-DI: 1.5-1.6 Baseline DAS-28: 6.4-6.5	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; placebo for 3 mo then Tofacitinib 5 mg bid; placebo for 3 mo then Tofacitinib 10 mg bid	ACR20 response at month 3; DAS 28-4 ESR < 2.6 at month 3; HAQ-DI at month 3 (change from baseline)
ORAL standard	12 months	Active RA patients receiving stable doses of methotrexate	n = 717 Age: 51.9-55.5 yr Female: 75.0%-85.3% Duration of RA: 6.9-9.0 yr Baseline HAQ-DI: 1.4-1.5 Baseline DAS-28: 6.3-6.6	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; adalimumab 40 mg SC every 2 wk; placebo for 6 mo then Tofacitinib 5 mg bid; placebo for 6 mo then Tofacitinib 10 mg bid	ACR20 response at month 6; DAS 28-4 ESR < 2.6 at month 6; HAQ-DI at month 3 (change from baseline)
ORAL sync	12 months	Active RA patients with inadequate response to one or more DMARD	n = 792 Age: 50.8-53.3 yr Female: 75.0%-83.8% Duration of RA: 8.1-10.2 yr Baseline HAQ-DI: 1.24-1.45 Baseline DAS-28: 6.14-6.44	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; Placebo	ACR20 response at month 6; DAS 28-4 ESR < 2.6 at month 6; HAQ-DI at month 3 (change from baseline)
ORAL scan	24	Active RA patients receiving background methotrexate	n = 797 Age: 52.0-53.7 yr Female: 80.2%-91.1% Duration of RA: 8.8-9.5 yr Baseline HAQ-DI: 1.23-1.41 Baseline DAS-28: 6.25-6.34	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; placebo for 3 mo then Tofacitinib 5 mg bid; placebo for 3 mo then Tofacitinib 10 mg bid	ACR20 response at month 6; DAS 28-4 ESR < 2.6 at month 6; HAQ-DI at month 3 (change from baseline); SHS at month 6 (change from baseline)
ORAL start	24	Methotrexate naïve patients with active RA	n = 952 Baseline TSS: 16.51-20.30	Tofacitinib 5 mg bid; Tofacitinib 10 mg bid; methotrexate 10 mg per week with 5 mg increments every 4 wk to 20 mg per week	Modified Total Sharp Score at month 6; ACR70 response at month 6

Tofacitinib is also associated with an increased risk of herpes zoster infection (Huang et al.,2019; Noell et al., 2018; Winthrop et al., 2017) Risk factors include increased age, Asian race, tofacitinib dose, concomitant steroid therapy, and prior biologic exposure (Baumrin et al., 2019). The nonlive recombinant zoster vaccine (RZV) is the preferred herpes zoster vaccine for psoriasis and psoriatic arthritis patients. The vaccine administration is recommended prior to initiation of therapy but may be safely administered during concurrent tofacitinib treatment. The live-attenuated vaccine (Zostavax) can also be administered but should be given prior the start of therapy (Ly et al., 2019).

Tofacitinib is an oral Janus kinase inhibitor approved for the treatment of psoriatic arthritis (PsA). It provides an alternative option for patients who have had an inadequate response and tolerance to other disease modifying antirheumatic drugs (DMARDs). It has demonstrated comparable efficacy to biologics, is effective in the management of treatment resistant disease, and is reported to improve enthesitis, dactylitis, and radiographic progression. Tofacitinib is also associated with an increased risk of serious infections, malignancy, and laboratory abnormalities. There is currently a large armamentarium of therapies for psoriatic arthritis, and choosing among treatments can be challenging. Due to this wide selection, a thorough assessment of psoriatic disease phenotype, patient preference, disease presentation, and comorbidities is critical (Anniina et al., 2019).

The characteristics of JAKinib ssummarized in table 3. JAKinibs are classified by their selectivity to JAKs, which is based on preclinical data from enzymatic or biochemical assays. These assays can be impacted by substrate and their results may differ depending on clinical drug concentration. All JAKinibs presented in Table 1 inhibit JAK1. Tofacitinib has additional selectivity for JAK3; baricitinib for JAK2; and peficitinib for JAK2, JAK3, and Tyk2. All JAKinibs target the conserved adenosine triphosphate (ATP)-binding pocket of JAKs (Singh et al., 2015).

Plasma protein binding varies widely with each JAKinib, ranging from 20.4% for tofacitinib to 75.2% for peficitinib. Approximately 30% of tofacitinib is metabolized by the kidneys and 70% by the liver. The enzymes responsible for drug metabolism and the routes of excretion of JAKinibs were summarized in Table 1. According to characteristics of metabolism and excretion of tofacitinib and baricitinib, dose adjustment of these drugs is recommended in patients with liver dysfunction or renal impairment. Dose adjustment for peficitinib and upadacitinib is recommended in patients with liver dysfunction. These two JAKinibs need no dose adjustment for renal function, as their renal excretion is negligible, while filgotinib is mainly excreted in urine, and its dosage is currently under review.

Baricitanib

Baricitinib is a JAK inhibitor. JAK mediates the effects of cytokines and their production; thus, JAK inhibitors inhibit multiple cytokines rather than one specific cytokine, as seen with the bDMARDs. Because JAK inhibitors target cytokines, they have much in common with bDMARDs, and are often lumped in with them. However, they are in fact small molecules and will likely be considered a third group of DMARD. Unlike bDMARDs, JAK inhibitors are administered orally. Baricitinib 2 mg, once daily, in combination with methotrexate, for the treatment of adult patients with moderate-to-severe RA who have responded inadequately to one or more DMARDs. In the case of

Table 3. Summary of JAK inhibitors (Masayoshi and Suguru, 2020)

Parameters	Tofacitinib	Baricitinib	Upadacitinib	Peficitinib	Filgotinib
Selectivity to JAK	JAK1/3	JAK1/2	JAK1	Pan JAK	JAK 1
Molecular weight	312.4	371.4	380.4	326.4	541.6
Dosage for RA	5 mg (twice daily) 11 mg (once daily) for extended release tablets	2 or 4 mg (once daily) Only 2 mg is approved in US	15 mg (once daily) 7.5 mg (twice daily) is approved only in Japan	100–150 mg (once daily) Approved only in JPN and south korea	Under review
Plasma protein binding	39%	44–56%	52%	72.83–75.2%	20.40%
Metabolism	Kidney, 30%, Liver 70; Mediated by CYP3A4 and CYP2C19	Mediated by CYP3A4	Mediated by CYP3A4, CYP3A5, and CYP2D6	Mediated by NNMT and SULT2A1	Mediated by CES2 and weakly by CES1
Excretion	Urine 80% Faeces 14%	Urine 75.2% Faeces 19.9%	Urine 43% Faeces 53%	Urine 36.8% Faeces 56.6%	Urine >80%
Factors related to drug interaction	Substrate of Pgp and MDR1	Substrate of OAT3, Pgp, BCRP, and MATE2-K	Substrate of Pgp and BCRP	Substrate of Pgp Inhibits CYP3A, CYP2C8, BCRP, OATP1B1, and OCT1s	Substrate of Pgp and BCRP. Weak inhibitor of UGT1A1, OATP1B1, and OATP1B3
Drugs affecting plasma con- centration of JAKinibs	Increase exposure: ketoconazole, tacrolimus, cyclosporine due to inhibition of CYP3A4, and fuconazole due to inhibition of CYP3A4 and CYP2C19	Increase exposure: probene- cid and lefunomide due to inhibition of OAT3	none	Increase exposure: ketoconazole, tacrolimus, cyclo- sporine due to inhibition of CYP3A4, and fucona- zole due to inhibition of CYP3A4 and CYP2C19 Decrease exposure: rifampicin due to inducing CYP3A4	none
Dose adjustment	Reduced dose in patients with moderate liver dysfunction or severe renal impairment	Reduced dose in patients with moderate renal impairment Not recommended for patients with severe renal impair- ment and severe liver dysfunction	Not recommended for patients with severe liver dysfunction	Reduced dose in patients with moderate liver dysfunction	Under review

ND not done, JPN Japan, USA United State of America, BCRP breast cancer resistance protein, CES carboxylesterase, CYP cytochrome P450, GI gastrointestinal, JAK Janus kinase, MATE mul- tidrug and toxic extrusion protein, MDR multidrug resistance protein, NNMT nicotinamide N-methyltransferase, OAT organic anionic transporter, OATP organic anion transporting polypeptide, OCT organic cation transporter, Pgp P-glycoprotein, PK pharmacokinetics, RA rheumatoid arthritis, SULT sulfotransferase; UGT uridine 5'-diphospho-glucuronosyltransferase a. The dose of baricitinib is limited to 2 mg in the USA

intolerance to methotrexate, baricitinib may be used as monotherapy.

Recently FDA have approved an Emergency Use Authorization (EUA) for the distribution and emergency use of baricitinib to be used in combination with remdesivir in hospitalized adult and pediatric patients two years of age or older with suspected or laboratory confirmed COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Standard therapy

Treatment of RA consists of both acute therapies, used to address intense flares of the disease, and more chronic therapies, that are aimed at the underlying disease process itself, known as disease-modifying antirheumatic drugs (DMARDs). Conventional DMARDs (cDMARDs) consist of small molecules that address various pathways involved in inflammatory/immune processes and include a diverse array of drugs, such as antimalarials, sulfasalazine, leflunomide, and methotrexate. Gold injections are no longer used to treat arthritis, and immune suppressants, such as azathioprine and cyclosporine, are not highly effective yet are highly toxic, according to the clinical expert consulted by CADTH for this review. Recently, these drugs have been joined by biologic DMARDs (bDMARDs), a group of drugs with a shared design, being either monoclonal antibodies or fusion proteins. Tumour necrosis factor (TNF)-alpha inhibitors were the original biologics, but they have since been joined by drugs that target interleukins (IL-1, IL-6), as well as drugs that target stimulation of T cells, drugs that deplete B cells, and, now, drugs that target Janus kinases (JAKs), called JAK inhibitors. Typically, patients are started on one or more cDMARDs, most commonly methotrexate; if their disease progresses, they will work up to the biologics. Common limitations of all approaches are increased risk of infection and possibly an increased risk of certain cancers (Singh et al., 2015).

Ruxolitinib

The FDA approved dose of ruxolitinib for myelofibrosis and polycythemiavera ranges from 5mg to 25 mg twice daily. 20mg twice daily was used in the open-label clinical trial in AA26. As with tofacitinib, dose adjustment is required in the setting of concomitant CYP3A4 and CYP2C9 inhibitors, as well as with hepatic and renal impairment.

Prior to treatment with tofacitinib or ruxolitinib, serologic screening is recommended and includes complete blood count (CBC), creatinine and hepatic function panel (LFTs),

Table 4. Ruxolitinib clinical trials

Clinical trial	JAK inhibitor {Target (S)}	Second agent	Class second agent	Disease	Trial number (www.ClinicalTrials.gov)
Single agent trials	Pacritinib (JAK2.FLT3)	NA	NA	MF	NCT01773187
	Momelotinib (JAK1,JAK2)	NA	NA	MF, PV, ET	NCT01969838 (MF) NCT01998828 (PV and ET)
	NS-018 (JAK2)	NA	NA	MF	NCT01423851
	INCB-039110 (JAK1)	NA	NA	MF	NCT01633372
Ruxolitinib combination trials	Ruxolitinib	Danazol	Andragen	MF	NCT01732445
	Ruxolitinib	Pomalidpmide	IMID	MF	NCT01644110
	Ruxolitinib	Lanalidomide	IMID	MF	NCT01375140
	Ruxolitinib	Azacitadine	Hypomethylation	MF	NCT011787487
	Ruxolitinib	Panobinostat	HDAC inhibitor	MF	NCT01693601 (US)
	Ruxolitinib			MF	NCT01433445 (UK)
	Ruxolitinib	GS-6624	Antifibrosying	MF	NCT01369498
	Ruxolitinib	PRM-151	Antifibrosying	MF	NCT01981850
	Ruxolitinib	BKM-120	PI3 Kinase inhibitor	MF	NCT01730248
	Ruxolitinib	LDE-225	Hedehog inhibitor	MF	NCT01787552
	Ruxolitinib (MPD-RC Trial)	Allo-SCT	NA	MF	NCT01790295
	Ruxolitinib (GOELMAS trial,France)	Allo-SCT	NA	MF	NCT01795677

IMID: indicates immunomodulatory drugs; MF: myelofibrosis; NA: Not applicable (www.ClinicalTrials.gov)

and fasting lipid panel together with hepatitis B, hepatitis C, and tuberculosis testing. We also suggest screening for HIV. Subsequently, monitoring CBC, creatinine, LFTs, and fasting lipid panel after 1 month of treatment and then every 3 months thereafter is recommended. Tuberculosis screening should be performed annually (William, 2017).

Oclacitinib

Gonzales et al*.,* 2014 studied that Oclacitini inhibited the function of JAK1-dependent cytokines involved in allergy and inflammation (IL-2, IL-4, IL-6, and IL-13) as well as pruritus (IL-31) at IC50's ranging from 36 to 249 nM. Oclacitinib had minimal effects on cytokines that did not

Table 5. Safety profiles of JAK inhibitors (Calabrese et al., 2020)

Targets	Drug	Indication and dosage	Warnings and side effects
JAK-1, JAK 2	Baricitinib (Olumiant)	Rheumatoid arthritis: oral 2 mg once daily;	Warnings: Do not initiate in case of anemia< 8 g/dL, lymphopenia< 500/mm3, severe hepatic impairment, moderate or severe renal impairment Side effects: Infectious (tuberculosis), hematologic (lymphoma), thrombosis, gastrointestinal perforation
JAK-1, JAK 2	Ruxolitinib (Jakafi)	Myelofibrosis: 5 to 20 mg orally twice daily depending on platelets count Polycythemiavera: 10 mg orally twice daily. Acute graft-vs-host disease: 5 mg orally twice daily	Warnings: Adjustment on renal/hepatic impairment and platelet count Side effects: Hematologic (pancytopenia, thrombocytopenia, anemia, neutropenia), infectious (herpes zoster, opportunistic infections), oncologic (non- melanoma skin cancer), metabolic (weight gain, hypercholesterolemia), other (bruising, dizziness, headaches)
JAK-3 (and JAK-1, JAK 2)	Tofacitinib (Xeljanz)	Rheumatoid arthritis and psoriatic arthritis: orally, 5 mg twice daily or 11 mg once daily Ulcerative colitis: orally, 10 mg twice daily	Warnings: Avoid in patients at increased risk of thrombosis; avoid the combination with methotrexate or other disease-modifying anti-rheumatic drug or immunosuppressant; do not initiate if lymphocytes < 500/mm3, neutrophils < 1,000/mm3, or hemoglobin < 9 g/dL; adjust on renal or hepatic impairment Side effects: Thrombosis, infections (tuberculosis, opportunistic infections, herpes zoster), malignancy (lymphoma, skin cancer), gastrointestinal perforation, hematologic (anemia, lymphopenia, neutropenia)

*1 and 2 mg of baricitinib with remdesivir for COVID-19 with recently approved by FDA

activate the JAK1 enzyme in cells (erythropoietin, granulocyte/macrophage colony-stimulating factor, IL-12, IL-23; IC50's > 1000 nM). These results demonstrate that oclacitinib is a targeted therapy that selectively inhibits JAK1-dependent cytokines involved in allergy, inflammation, and pruritus and suggests these are the mechanisms by which oclacitinib effectively controls clinical signs associated with allergic skin disease in dogs (Przemysław et al*.,* 2020).

Safety issues of JAK inhibitors

JAK inhibitors showed a high level of efficacy and satisfactorily level of safety. As with all novel compounds many questions arise regarding the safety profile and potential influence of these drugs on the functioning of important internal organs, including the cardiovascular system. With the small synthetic compounds, we may block many cytokines belonging to several families, which exert both pro- and anti-inflammatory potentials. Parallel to this, we may change the expression of hundreds of related genes, creating a new environment for our patients (Calabrese et al., 2020).

Conclusion

JAKinibs represent significant therapeutic advances, as JAK inhibitors showed a high level of efficacy and satisfactorily level of safety but are relatively new drugs with evolving safety profiles. At the current level of knowledge, the careful consideration of the risks and benefits will be considered before start of treatment. JAK inhibitors are widely used in multiple therapeutic areas and repurposing of JAK inhibitors are new horizons in treatment like combination therapy with remdisavir for hospitalized patients for COVID-19.

Potential prothrombotic risk may be a class effect of JAKi, which is concerning given evidence of hypercoagulability with severe COVID-19; so required vigilance during treatment. As we still accumulate knowledge on JAK inhibitors, currently available data regarding safety are not yet conclusive and more studies in this field are required. At this moment, it is still unclear which mechanisms may drive JAK specific risk and this is the main concern regarding the administration of JAK inhibitors in patients with RA and other therapeutic areas.

Conflicting Interest: Nil

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