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Review Article

A review on potential adverse effects associated with Janus-kinase inhibitors

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, symmetrical, inflammatory autoimmune disease that affects small joints. RA has a population prevalence of 0.5% to 1% in the U.S. The annual cost of care for chronic treatment of RA in the United States is estimated at $12,509. Pharmaceutical companies have developed drugs to treat RA using Janus kinase (JAK) inhibitors. These drugs can have potential adverse effects. Forecasting a better output to JAK inhibitors (JAKI's). Therapy duration of JAKI's and Problems regarding to strategies of dose reduction or if the discontinuation of therapy takes place in case of low disease activity. The accurate pharmacological profile and interactions of other drugs with JAKI's have to establish. Proper safety, efficacy profile of JAKI's and when administered in combination with DMARD's. The safety, efficacy data of JAKI's when compared to non-anti-TNF biologics. Obtaining of experience on JAKI's that were already existed in the market and further experimental findings on newer compounds and which may clarify many of the aspects which are to be solved in nearer future as these JAKI will have greater application in treatment of RA. Regardless of significant developments in latest years in the pharmacotherapy of RA in the use of JAK inhibitors, yet the adverse effects of JAK inhibitors are unanswered. Therefore, one of the main concerns associated with JAK inhibitor is the potential adverse effects. The challenges can be addressed by clinical pharmacist mediated interventions related to dosing of JAK inhibitors and proper management of adverse drug reactions (ADRs).

Keywords: JAKI's, Rheumatoid arthritis, DMARD's, Safety, Efficacy, Pharmacotherapy

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, symmetrical, inflammatory autoimmune disease that affects small joints initially, then deeper joints, eventually affecting the skin, eyes, heart, kidneys, and lungs. Joint bone and cartilage are frequently damaged, while ligaments and tendons also weaken.[1] All of this degeneration of joints develops deformities and bone degradation, which are frequently quite painful for individuals. Common symptoms of RA include morning stiffness of the affected joints for >30 min, fatigue, fever, and weight loss. In RA joints are tender, swollen, warm and rheumatoid nodules are present under the skin. The disorder tends to appear between the ages of 35 and 60, with periods of remission and aggravation.[2-5] The yearly cost of care for the chronic treatment of RA in the United States is estimated at $12,509 (direct treatments costs of $3,725) in patients using non-biologic treatments and $36,053 (direct treatment costs of $20,262) in patients using biologic agents. It has been suggested that these high treatment costs may negatively affect medication adherence in patients with RA.[6] Pharmaceutical drug companies have developed therapeutics to target the Janus-kinase (JAK) STAT pathway for treatment of RA, primarily comprising of JAK inhibitors and also known as JAKI.[7] JAK inhibitors belong to a family of medicine called disease-modifying antirheumatic drugs (DMARDs). Three JAK inhibitors, Baricitinib (Olumiant), Tofacitinib (Xeljanz), and Upadacitinib (Rinvoq), are approved by the FDA to treat

rheumatoid arthritis.[8] JAK inhibitors put the brakes on some immune system actions, they can leave you open to different kinds of infections.[8]In this article we are going to list out potential adverse-effects associated with JAK inhibitors.

EPIDEMIOLOGY

Based on descriptive epidemiological data, the population prevalence of RA varies from 0.5% and 1%, with a highly varied every year incidence (12-1200 per 100,000 individuals) based on gender, race/ethnicity, and calendar year.[9]

The majority of patients are women, with an average diseases duration of 10 years. They are married, non-smokers, and have completed secondary education. We report a high (>80%) over-use of Methotrexate (MTX) and steroids among our RA population, while the over-use of DMARDs and TNF-inhibitors average around 67% and 33% respectively. RA treatment usage varies all over the five nation locations. Highest utilization of steroids is identified in Jordan and KSA (p value <0.001), while the highest ever-use of TNF-inhibitors is reported in KSA (p value <0.001).[10]

Worldwide, the prevalence of RA is at 0.5% to 1%, yet it may be declining in the United States. Using data from 1995 and 2005, the prevalence of RA in adult Americans was estimated at 1.29 million (0.6%) and down from the previous estimate of 2.1 million. In 1995, the prevalence of RA in American women (1.06%) was nearly double that in men (0.61%). Interestingly, considering the majority of the data came from Minnesota patients, it's likely they're not suitable for anyone other than Caucasians.[9] The prevalence of RA varies by location. The incidence appears to be highest in Pima Indians (5.3%) and Chippewa Indians (6.8%) and lowest in people from China and Japan (0.2-0.3%), suggesting the possibility that genetic factors contribute to RA.[10] These differences in regional RA prevalence also may suggest a role for environmental factors.

TREATMENT HISTORY OF RHEUMATOID ARTHRITIS

Treatment for RA has advanced considerably over the past twenty-five years, from symptomatic treatment to the use of therapeutic regimens that change disease activity and have been showed to delay or stop structural damage to joints. Drug treatment for RA has progressed from salicylates to NSAIDs, CSS, DMARDs, MTX, and now biologic response modifiers. Physiological response modifiers (biologics) were accessible in the late 1990s. Current RA therapy is such that progression from symptom starting to major damage is no longer unavoidable, and RA patients can expect to live pleasant and productive lives while on medication.

A new category of drugs for the management of rheumatoid arthritis is now available in the form of JAK inhibitors. These targeted, synthetic DMARDS (tsDMARDS) are effective in inflammatory diseases by intracellularly blocking tyrosine kinase.[11] According to the EULAR Guidelines, both JAK inhibitors can be utilised in rheumatoid arthritis when csDMARD treatment is inadequate or must be terminated because of adverse effects. Both Tofacitinib and Baricitinib have been shown to be more efficient than a placebo in the treatment of rheumatoid arthritis.[12-14]

MECHANISM OF ACTION

Baricitinib

Baricitinib belongs to JAK inhibitor class. JAKs are the intracellular enzymes, which can transmit the signals arising from cytokines interactions on the cell membrane. These JAKs are responsible for signal transcription and can modulates gene expression. Baricinib can inhibit the phosphorylation, pairing and signaling pathway of JAKs. But, the inhibition of which enzyme will bring about therapeutic action is still unknown.[17,18]

Tofacitinib

Tofacitinib can shows its action through inhibition of phosphorylation, pairing and signaling pathway of JAKs like JAK1/JAK2, JAK1/JAK3.[19,20]

Upadacitinib

Upadacitinib mainly inhibits intracellular activities like phosphorylation, pairing and signaling pathway JAKs like JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2. Upadacitinib has a higher potential to inhibit JAK1 and JAK2 compared to JAK3 and TYK2.[21,22]

Table 1: Dosing.

S. no.	Drug	Dose	Comment
01	Baricitinib	2 mg/day- oral-with or without food	Baricitinib cannot be recommended during when patient is suffered with severe infection and when the patient is having neutropenia, lymphopenia, and anemia. This drug has to prescribed only after the infection got cured. Baricitinib cannot be administered if the patients have glomerular filtration rate less than 60 ml/min/1.73 m^2
02	Tofacitinib		
A	Adults	5 mg/twice daily	

Continued.

S. no.	Drug	Dose	Comment
B	For the patients who are receiving the strong CYP3A4 inhibitors like ketoconazole or moderate CYP3A4 inhibitors like fluconazole	5 mg/once daily	
C	Patients with severe renal impairment	5 mg/once daily	
D	Patients with lymphocyte count less than 500 cells/mm^3 and absolute neutrophil count (ANC) less than 500 cells/mm^3	Discontinue the dosing	
E	Patients who have low hemoglobin levels less than 8 g/dl	The drug has to be administered only after hemoglobin values get normalized	
3	Upadacitinib	15 mg/once daily with or without food	Administration of upadacitinib can be interrupted when the ANC value less than 1,000 cells/mm^3 and when hemoglobin 8 g/dl.

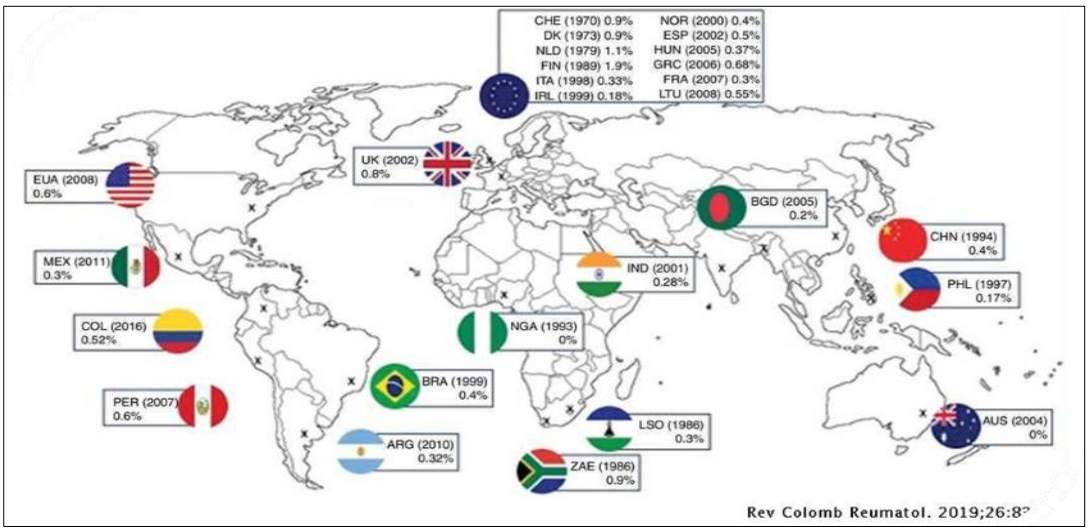

Figure 1: Prevalence of rheumatoid arthritis in various countries around the world.[10]

Table 2: Drug interactions.

S. no	Drug	Affending agent	comment
01	Baricitinib	Strong OAT3 inhibitors	The exposure of Baricitinib can be increased when OAT3 Inhibitors such as Probenecid can be given in combination or at a time with Baricitinib.
02	Tofacitinib	Strong CYP3A4 inhibitors like ketoconazole or moderate CYP3A4 inhibitors like fluconazole.	The exposure of Tofacitinib can be increased. During this condition dosage adjustment is recommended
03	Upadacitinib	Strong CYP3A4 inhibitors like ketoconazole, strong CYP3A4 inducers like rifampin	The exposure of the Upadacitinib can be increased when it can be co-administered with Ketoconazole and hence which can be prescribed with caution. The exposure of the Upadacitinib can be increased when it can be co-administered with Rifampin and which can also decrease the therapeutic effectiveness of Upadacitinib. Hence, these two drugs' co-administration cannot be recommended.

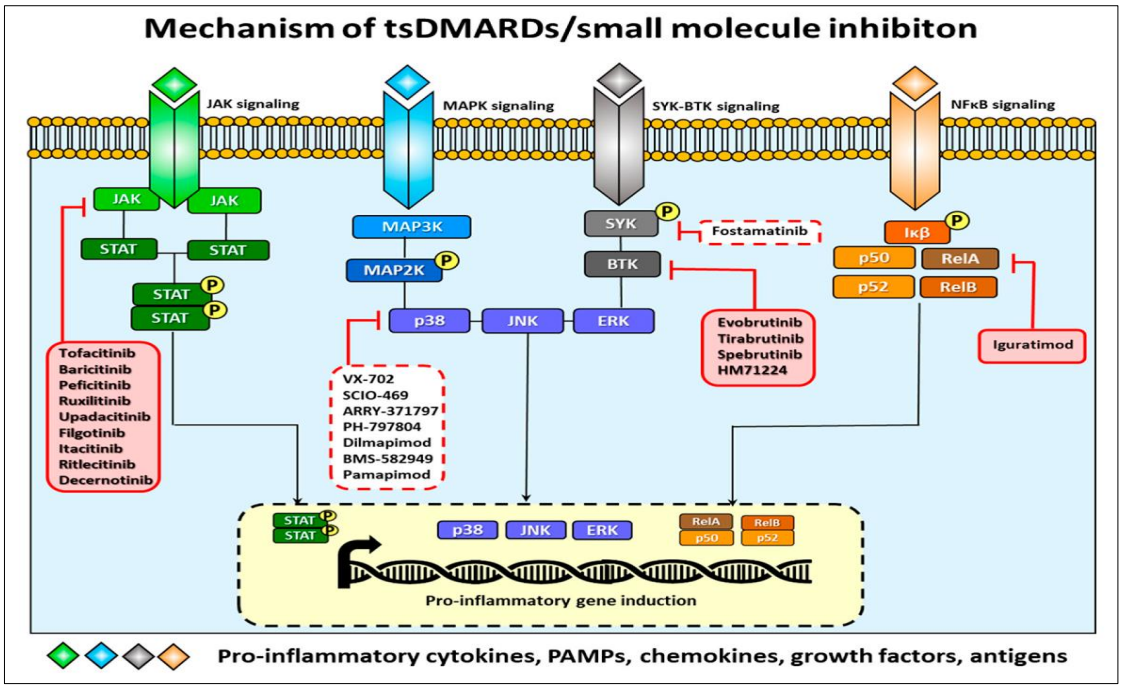

Figure 2: Mechanism of action of tsDMARDS.[23]

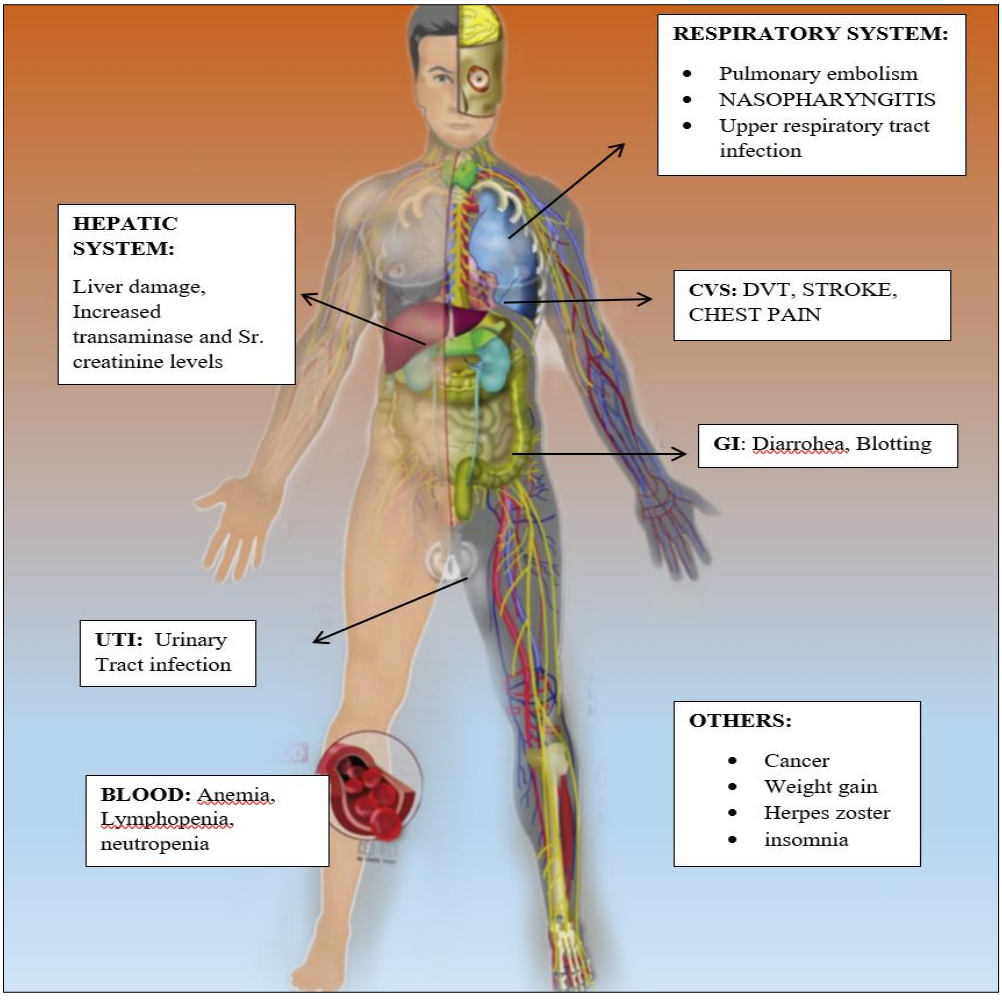

Figure 3: Adverse effects broadly system wise).[24-26]

Table 3: Adverse drug reactions of JAK inhibitors.[16-19]

S. no.	Drug	Post-marketing ADRS	Clinical trials ADRS
1	Baricitinib	Rash, drug hypersensitivity, angioedema, urticaria, immune system suppression, upper respiratory tract infection, urinary tract infections, arterial thromboembolic event, cerebro-cardiovascular event, opportunistic infection, folliculitis, intervertebral disc protrusion, gastrointestinal disorders, abdominal pain, infections and infestations, eye infection toxoplasmal, postoperative abscess	Upper respiratory tract infection, nausea, herpes zoster infection, acne, neutropenia, increased LFTS, platelet elevations, opportunistic infection, malignancy, venous thrombosis. Laboratory abnormalities: neutropenia, platelet elevation, liver enzyme elevation, lipid elevation, creatinine phosphokinase
2	Tofacitinib	Drug hypersensitivity, upper respiratory infection, urinary tract infections, immune system suppression, dermatotome, Herpes zoster infection, blood clots, stroke, non-Hodgkin's, lymphoma, colon cancer, chronic lymphocytic leukemia, prostate cancer, gastric cancer, opportunistic infection	Nasopharyngitis, diarrhea, headache, hypertension, insomnia, vomiting, gastritis, nausea, dyspepsia, dyspnea, cough, sinus congestion, interstitial lung disease, hepatic steatosis, rash, erythema, pruritis, joint swelling, tendonitis, arthralgia, musculoskeletal pain, non-melanoma, skin cancers, pyrexia, fatigue, peripheral edema
3	Upadacitinib	Increased risk of herpes zoster infection, creatine phosphokinase elevations, pneumonia, herpes zoster infection, anemia, lymphopenia, neutropenia	Upper respiratory tract infection, nausea, cough, pyrexia, pneumonia, herpes zoster, herpes simplex, oral candidiasis, anemia, tuberculosis, venous thrombosis. Laboratory abnormalities: elevated LDL, elevated HDL, elevated AST, elevated creatine phosphokinase, neutropenia, lymphopenia

DISCUSSION

Future perspectives and challenges of JAKI's in RA treatment

Since the advent in technology from 1990's the biologics containing of monoclonal antibodies targeting certain specific cellular pathways and which can play an important role in remission or decreasing the disease activity.[27,28]

Among small molecules, JAKs can represent the newer class of drugs and due to their highly centralized role in the Immune response and inhibition of JAKs seems to be the clinical strategy in the treatment of RA.[29,30]

The safety and efficacy profile of JAKs are more efficacious when compared to the biologics and the manufacturing cost of JAKIs are also more economical than biologics and their usage in the regular practice is increasing day by day.[31,32]

The spectrum of activity of JAK's are not just limited to RA, but it is showing better pharmacological benefits in the treatment of spondylarthritis.

Inflammatory bowel disease and in many types of arthritis.[33,34]

According to the therapeutic guidelines of EULAR which are updated in 2020 recommend the prescribing of JAK's as an alternative therapy in the patients who are refractory to DMARD's or in the patients in whom previous DMARD's therapy have been failed. [35]

There are several questions to be answered and several challenges to be solved in near future. These are: recognition of biomarkers (ACCP antibodies) forecasting a better output to JAKI's; therapy duration of JAKI's and problems regarding to strategies of dose reduction or if the discontinuation of therapy takes place in case of low disease activity; the accurate pharmacological profile and interactions of other drugs with JAKI's have to establish; proper safety, efficacy profile of JAKI's and when administered in combination with DMARD's; and the safety, efficacy data of JAKI's when compared to non-anti-TNF biologic's.[36-41]

Obtaining of experience on JAKI's that were already existed in the market and further experimental findings on newer compounds and which may clarify many of the aspects which are to be solved in nearer future as these JAKI will have greater application in treatment of RA.

CONCLUSION

Regardless of significant developments in latest years in the pharmacotherapy of RA in the use of JAK inhibitors, yet the adverse effects of JAK inhibitors are unanswered. Therefore, one of the main concerns associated with JAK inhibitor is the potential adverse effects.

The most commonly reported side effects include infections such as nasopharyngitis, hypercholesterolemia, high serum transaminase and creatinine levels, low neutrophil count and anaemia. Although cases of serious opportunistic infections, such as herpes zoster, tuberculosis, cryptococcal pneumonia and pneumocystis pneumonitis, were reported, the majority of the side effects were tolerable and managed. In this article we have discussed adverse effects associated with JAK inhibitors. This challenge can be addressed by clinical pharmacist mediated interventions related to dosing of JAK inhibitors and proper management of ADRs.

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