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EFFICACY OF JAK-STAT INHIBITORS IN RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis (RA) is a leading cause of musculoskeletal disease worldwide. Disease Modifying Anti-Rheumatic Drugs have been used to treat RA. The treatment has advanced due to the introduction of biological disease modifying anti-rheumatic drugs. Janus kinase (JAK) inhibitors or JAKinhibs are orally available biological disease modifying anti- rheumatic drugs. Tofacitinib was the first FDA-approved JAK inhibitor. Another drug baricitinib also demonstrated efficacy in treating RA. Many other JAKinhibs are currently in clinical trials. These drugs act by inhibiting the JAK-STAT pathway which plays an important role in the pathophysiology of RA. JAK inhibitors differ by their selectivity towards JAKs. In this review, we summarize the efficacy and safety of JAK inhibitors in rheumatoid arthritis.

KEYWORDS: Rheumatoid arthritis, DMARDs, JAK-STAT pathway, Janus kinase inhibitors, Tofacitinib, Baricitinib.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disorder of the joints characterized by inflammatory arthritis as well as extra-articular involvement.[1] Clinical presentation is polyarticular and common symptoms of RA include pain, stiffness, swelling of the joint,

anorexia, weakness, or fatigue. The patient may note morning stiffness that lasts for an hour. The cause of rheumatoid arthritis is unknown.[2] The key molecules and signal mediators implicated in the pathogenesis of rheumatoid arthritis include cytokines (TNF-α, interleukin-1α and 1β, 6, 7, 15, 17A and 17F, 18, 21, 23, 32, and 33), growth and differential factors (a proliferation inducing ligand, B-lymphocyte stimulator, granulocyte-macrophage colony stimulating factor, macrophage colony stimulating factor and receptor activator of NF- κB ligand) and intracellular signaling molecule and transcription factors (janus kinase, spleen tyrosine kinase, phosphatidylinositol-3-kinase and Bruton's tyrosine kinase).[3]

Diseases modifying antirheumatic drugs (DMARDs) like methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide are used as the first-line therapy for the treatment of RA. Pain, inflammation, and stiffness associated with RA can be effectively managed with non-steroidal anti-inflammatory drugs and glucocorticoids. Moreover, other groups of drugs called biological response modifiers can be used for the treatment of rheumatoid arthritis.

These biological response modifiers like infliximab, adalimumab, etanercept, anakinra, abatacept, and rituximab are targeted agents that selectively inhibit specific molecules of the immune system.[4] Recent studies have highlighted the role of the JAK signal transducer and activator of the transcription (STAT) pathway in the pathophysiology of RA. This led to the implementation of new biological agents called JAK inhibitors (Jakinhib) in the treatment of rheumatoid arthritis.[5] This review will discuss the efficacy of JAK inhibitors in treating RA.

JAK-STAT SIGNAL PATHWAY

JAK-STAT pathways play an important role in the progression of RA. Janus kinases (JAK) are cytoplasmic tyrosine kinases that can phosphorylate tyrosine residue either on themselves (autophosphorylation) or on adjacent molecules like STATs and mediate a variety of cytokine signals affecting cell growth and differentiation.[6] JAK1, JAK2, JAK3, and TYK2 are the widely expressed janus kinases. Among these, JAK3 is predominantly expressed in hematopoietic cells and is activated by IL2, 4, 7, 9, and 15 which are essential for lymphoid differentiation. Mutation of JAK3 results in reduced lymphocytes and causes immunodeficiency.[7] TYK2 mutation in patients diagnosed with hyper IgE syndrome showed defects in multiple cytokine signaling pathways. Thus TYK3 deficiency leads to impaired helper T cell differentiation.[8] However, mutation of JAK1 and JAK2 produced a lethal phenotype in mice. Therefore JAK inhibitors are effective for treating RA and other immune mediated diseases.[9] The JAK inhibitors can be subcategorized into the first generation

(baricitinib, tofacitinib) and second generation (upadacitinib, filotinib, peficitinib, decernotinib, and itacitinib). The currently available FDA approved JAK inhibitors are tofacitinib, baricitinib, and upadacitinib.[10]

TOFACITINIB

Tofacitinib is an oral jakinhib that primarily inhibits signaling by cytokines receptors associated with JAK3 or JAK1 with functional selectivity over receptors that signal via JAK2 homodimeric pairs and exert its anti-inflammatory effect.[11,12] JAK1 inhibition plays an important role in clinical efficacy and side effects. Clinical studies a significant reduction in inflammatory cell influx and cartilage damage when the tofacitinib is administered at the time of disease onset. Moreover, it reduced the human IL6, IL8, and matrix metalloproteinase levels in mouse sera.[13] Tofacitinib alone or in combination with non-biological DMARDs, mainly methotrexate showed a potential therapeutic effect in patients with RA and its effect is comparable to that of adalimumab, a TNF inhibitor.[14,15] In RA patients, tofacitinib decreased the synovial mRNA expression of matrix metalloproteinases(MMP1 and MMP3) and synovial STAT1 and STAT2 phosphorylation.[16] Clinical studies in methotrexate naïve patients with early RA indicated that tofacitinib reduced synovial and bone marrow inflammation as well as inhibited the progression of disease in patients with early RA.[17]

Tofacitinib is rapidly absorbed from the GIT with a time to peak concentration of 0.5 to 1 hour and it has an oral bioavailability of 74%. Food is not expected to affect the extent of absorption. It is mainly metabolized by cytochrome P450 3A4. 70% of tofacitinib is eliminated non-renally and the remaining 30% is eliminated via renally. The elimination half-life of tofacitinib is 3 hours.[18-19]

Many clinical studies were conducted to evaluate the efficacy of tofacitinib (table1). A phase Ⅱ trial was conducted in RA patients who have had an inadequate response to methotrexate, etanercept, infliximab, and adalimumab. The patients were randomly treated with tofacitinib 5, 15, and 30 mg twice daily or a placebo for 6 weeks, and they were followed up for an additional 6 weeks. The primary efficacy endpoint was the American College of Rheumatology 20% improvement criteria (ACR20) response rate at 6 weeks. By week 6, the ACR20 response rate was 70.5%, 81.2%, and 76.8% in the 5 mg, 15 mg, and 30mg groups, respectively, compared with 29.2% in the placebo group. Adverse effects produced were infections, neutropenia, and immunosuppression; however, these adverse effects were treatable or reversible with discontinuation.[20]

In a phase IIb clinical study patients taking methotrexate were randomized to receive tofacitinib 1, 3, 5 10, or 15mg twice daily or 20mg once daily or placebo. At week 12, the ACR20 response rate was higher for patients taking tofacitinib at a dose greater than 3mg compared to placebo (52.9%, 50.7%, 58.1%, 56.0%, 53.8%, and 33.3% for tofacitinib 3mg, 5mg, 10mg, 15mg, 20mg, and placebo respectively).[21]

A 24-week, phase IIb study was conducted to compare the efficacy, safety, and tolerability of tofacitinib and adalimumab monotherapy with placebo for the treatment of RA in patients with inadequate response to DMARDs. The patients were randomly assigned to five doses of tofacitinib (1,3,5,10 or 15mg) twice daily or adalimumab 40mg subcutaneous injection every 2 weeks (total of 6injections) followed by oral tofacitinib 5mg twice daily for 12 weeks. The primary endpoint was ACR20 at week 12. Tofacitinib monotherapy at a dose greater than 3mg twice daily (39.2% for 3mg, 59.2% for 5mg, 70.5% for 10mg, and 71.9% for 15mg) and adalimumab (35.9%) had higher ACR response rate than placebo (22%).[22]

A phase II study was conducted on 140 patients receiving methotrexate who were randomized to receive 1, 3, 5, and 10mg of tofacitinib twice daily or placebo for 12 weeks. ACR20 at week 12 was the primary efficacy endpoint. The ACR20 response rate was significant in the tofacitinib group (64.3%, 77.8%, 96.3%, and 80.8% in the 1mg, 3mg, 5mg, and 10mg groups respectively) compared to the placebo group (14.3%). The commonly reported adverse effects were nasopharyngitis and increased ALT and ASP.[23]

Table1: Published clinical trials

Study	Study period	N	Treatment	Primary endpoint	Results		
					ACR20	HAQ-DI (mean change from baseline)	DAS28 (mean changefrom baseline)
Phase IIa	12	264	Tofacitinib	ACR20 at	5mg; 70.5%	5mg;-0.6	N/A
Kremer et	weeks		5,15or30mg	week 6	15mg;81.2%	15mg;-0.7	
al					30mg;76.8%	30mg;-0.7	
					PCB;29.2%	PCB;-0.3	
Phase IIb	24	507	Methotrexate+	ACRat	1mg;45.7%	1mg;-0.34	1mg; N/A
Kremer et	weeks		Tofacitinib	week 12	3mg;52.9%	3mg;-0.48	3mg;23.1%
al			(1,3,5,10,15		5mg;50.7%	5mg;-0.49	5mg; N/A
			Mg b.i.d or		10mg;58.1%	10mg;-0.39	10mg;27.5%
			20mg o.d)		15mg;56.0%	15mg;-0.43	15mg;29.2%
					20mg;53.8%	20mg;-0.53	20mg;20.8%
					PCB;33.3%	PCB;-0.16	PCB; 6.1%

Phase Ⅱb	12	384	Tofacitinib	ACR 20 at	1mg;31.5%		1mg;7.7%
Fleishman	weeks		(1,3,5,10or15	week 12	3mg;39.2%		3mg;5.9%
et al			mg b.i.d) +		5mg;59.2%		5mg;12.5%
			Adalimumab		10mg;70.5%		10mg;14.8%
			40mg		15mg;71.9%		15mg;19.3%
					Adalimumab;		Adalimumab;
					35.9%		3.95
					PCB;22.0%		PCB;3.6%
Phase Ⅱ	12	140	Methotrexate+	ACR 20 at	1mg;64.3%	1mg;-0.38	N/A
Tanka et	weeks		Tofacitinib	week 12	3mg;77.8%	3mg;-0.41	
al			(1,3,5 or 10mg		5mg;96.3%	5mg;-0.49	
			b.i.d)		10mg;80.8%	10mg;-0.57	
					PCB;14.3%	PCB;-0.05	

Safety Profile

The safety profile of tofacitinib is similar to other biological DMARDs except for some events like thromboembolism and increased risk of certain infections, most importantly herpes zoster. The most frequently reported adverse events (AEs) were headache, upper respiratory tract infection, nasopharyngitis, diarrhea, nausea, and hypertension and the most serious adverse events were infection events. The risk for developing serious infection was increased in older patients and those receiving tofacitinib in combination with biological DMARDs or glucocorticoids. The herpes zoster infection in patients treated with tofacitinib is due to decreased lymphocyte activation and proliferation.[24-25] Several studies reported malignancies in patients treated with tofacitinib. Dose-related increases in total cholesterol, HDL cholesterol, and LDL cholesterol were observed and the ratio of total cholesterol to HDL cholesterol (a measure of atherogenic risk) remained consistent from baseline.[26]

A pooled analysis evaluated tofacitinib safety up to March 2017 using data from clinical trials and the incidence rate (IR) for adverse events and mortality were 9.0 and 0.3 respectively.[27] In a phase Ⅲ clinical study, serious infections were reported in patients who were receiving tofacitinib. The common adverse events reported were headache and upper respiratory tract infection. It was also associated with laboratory abnormalities like increased LDL cholesterol and decreased neutrophil count.[28] *Wollenhaupt et al* in an ORAL Sequel long-term extension (LTE) study evaluating the safety and efficacy of tofacitinib 5mg and 10mg twice daily up to 9.5 years showed that 52% discontinued the treatment (24% due to AEs and 4% due to inadequate clinical response). IR for discontinuation of therapy due to AEs was 6.8.[29] A post-hoc, pooled analysis of phase Ⅲ studies of tofacitinib revealed that IR for selected AEs, discontinuation due to AEs, and serious infection were lower in patients who received

monotherapy compared to combination therapy.[30]

BARICITINIB

Baricitinib is an oral, once daily jakinhib developed by Eli Lilly and Incyte Corporation for the treatment of moderate to severe rheumatoid arthritis.[31] This small molecular weight compound has high selectivity for JAK2 and JAK1 and less selectivity for JAK3 and TYK2. It inhibits the IL-6 and IL-23 induced STAT3 phosphorylation.[32] in animal models, baricitinib showed significant anti-inflammatory effects without suppression of humoral immunity or adverse hematological effects.[33] In a clinical study involving patients who had an inadequate response to biological DMARDs, baricitinib 4mg was associated with clinical improvement.[34] Although baricitinib 4mg has high efficacy compared to 2mg dose, only 2mg dose is approved by Food and Drug Administration (FDA) because of the adverse effects associated with 4mg dose. Baricitinib attains peak plasma concentration within 1 hour post-dose. It demonstrates a dose dependent pharmacokinetics with a mean renal clearance of approximately 12L/h. baricitinib is well tolerated with no serious adverse effects. However, a reversible, dose related decrease in the neutrophil count was observed with baricitinib.[35]

In a phase αb study, 301 patients were randomized to receive a placebo or baricitinib 1, 2, 4, or 8mg once daily for 12 weeks. After 12 weeks, patients treated with placebo and 1mg baricitinib were changed to 2 mg baricitinib twice daily or 4mg once daily. More patients in the combined 4 mg and 8mg groups achieved ACR20 compared to placebo at week 20. Serious infections were developed in 3 patients and dose dependent decrease in hemoglobin was also observed with baricitinib.[36]

In a 24 week phase β study, 684 biological DMARD naïve patients with inadequate response or intolerance to more than one conventional DMARDs were randomly assigned to receive a placebo or baricitinib 2mg or 4mg once daily. Significantly higher ACR 20 response rates were observed with baricitinib 4mg compared to placebo. Significant improvements were also observed in ACR50 and ACR70 response rate, DAS28 <2.6 as well as HAQ-DI in the baricitinib group compared with placebo. Radiographic progression of structural joint damage was reduced in patients with baricitinib.[37]

In another phase Ⅲ study, 527 patients with inadequate response to one or more tumor necrosis factor inhibitors or other biological agents were randomized to baricitinib (2mg or 4mg daily) or placebo for 24 weeks. More patients achieved ACR20 at week 12 with

baricitinib 4mg than placebo. Adverse event rates were higher for patients receiving baricitinib than for those receiving placebo. A small reduction in neutrophil levels and increases in creatinine and low density lipoprotein levels were observed in the baricitinib group.[38]

An integrated analysis was performed to assess the safety of baricitinib across all completed clinical studies. Among 3464 patients exposed to baricitinib, no increase in deaths, adverse events leading to discontinuation, malignancies, MACE, or infections were reported. Herpes zoster was the most frequently reported adverse event. Baricitinib treatment was associated with few laboratory abnormalities. There was no increased risk over time for adverse events with longer exposure.[39]

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