IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

JAK INHIBITORS: A NEW ERA TREATMENT FOR RHEUMATOID ARTHRITIS

[1]Shikha Shukla, [1]Nimisha Kakadia, [1]Shrikalp Deshpande
[1]Department of Pharmacology and Pharmacy Practice
[1]Kadi Sarva Vishwavidhyalaya, Gujarat, India

Abstract : One frequent immune-mediated inflammatory disease (IMID) that causes pain, swelling, and stiffness in synovial joints is rheumatoid arthritis (RA). csDMARDs are still very important in the treatment of RA, but in the last five years, the number of people taking newer drugs such JAKs has increased double. The limited utilization of triple therapy indicates that prescribers are more inclined to use mono and dual biologic medicines. Small-molecule inhibitors that target the JAK family of kinases have shown promise in the treatment of a variety of illnesses. Eleven JAK inhibitors that have been approved for clinical usage have been covered in this review. These drugs are fedratinib, filgotinib, oclacitinib, pacritinib, peficitinib, ruxolitinib, baricitinib, fedratinib, tofacitinib, and upadacitinib. More selective JAK inhibitors, such as JAK3 selective inhibitors with potential efficacy and a corresponding decrease in side effects, have been developed in an effort to prevent unwanted occurrences.

Index Terms **- Immune-mediated inflammatory disease (IMID), Anti-citrullinated peptide autoantibodies (ACPAs), DMARDs (Disease Modifying Antirhuematic Drugs), JAK (Janus Kinase), STAT (signal transducers and activators of transcription).**

I. INTRODUCTION

One frequent immune-mediated inflammatory disease (IMID) that causes pain, swelling, and stiffness in synovial joints is rheumatoid arthritis (RA). The hands and feet are frequently affected by the early symptoms, especially around the metatarsophalangeal and metacarpophalangeal joints. The presence of autoantibodies (rheumatoid factor or anti-citrullinated peptide autoantibodies (ACPAs), or both), and evidence of systemic inflammation (increased erythrocyte sedimentation rate or C reactive protein, or both) are supportive but not necessary for the diagnosis, which is based on the pattern and type of joint involvement. The 2010 European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) classification criteria, which place an emphasis on the significance of joint pattern, seropositivity, and inflammation, are used to classify the condition for research purposes.[1,2]

II. WHAT IS RHEUMATOID ARTHRITIS?

Rheumatoid arthritis (RA) is a chronic, symmetrical, inflammatory autoimmune disease that initially affects small joints, progressing to larger joints, and eventually the skin, eyes, heart, kidneys, and lungs. Joint cartilage and bone are frequently damaged, and ligaments and tendons deteriorate. Deformities and bone erosion result from all of this joint deterioration, which is typically extremely painful for the patient. Rheumatoid nodules beneath the skin, tiredness, fever, weight loss, and morning stiffness of the afflicted joints lasting more than thirty minutes are typical signs of RA.[3,4]

The global lifetime prevalence is up to 1%; the condition can start at any age and peaks between the ages of 30 and 50. The prevalence of RA is highest in people over 40, with women up to five times more likely than men to have it. The prevalence of rheumatoid arthritis ranges from 0.5% to 1% globally, with 0.7% occurring in India.[5,6]

Diagnosis of RA[7]

Typical Presentation

Many joints are usually painful and stiff when RA patients first arrive. Most frequently affected joints are the wrists, metacarpophalangeal joints, and proximal interphalangeal joints. More than an hour of morning stiffness points to an inflammatory cause. When a joint is examined, a slight thickening of the synovium may be felt or there may be obvious boggy swelling from synovitis. Patients may also have more subclinical arthralgias prior to the development of clearly noticeable joint edema. When a disease is active, systemic symptoms including weariness, weight loss, and low-grade fever can appear.

Diagnostic Criteria

In 2010, the American College of Rheumatology and European League Against Rheumatism collaborated to create new classification criteria for RA. In an attempt to diagnose RA early in patients who might not fit the 1987 American College of Rheumatology classification criteria, new criteria have been developed. The 2010 criteria do not include radiographic erosive

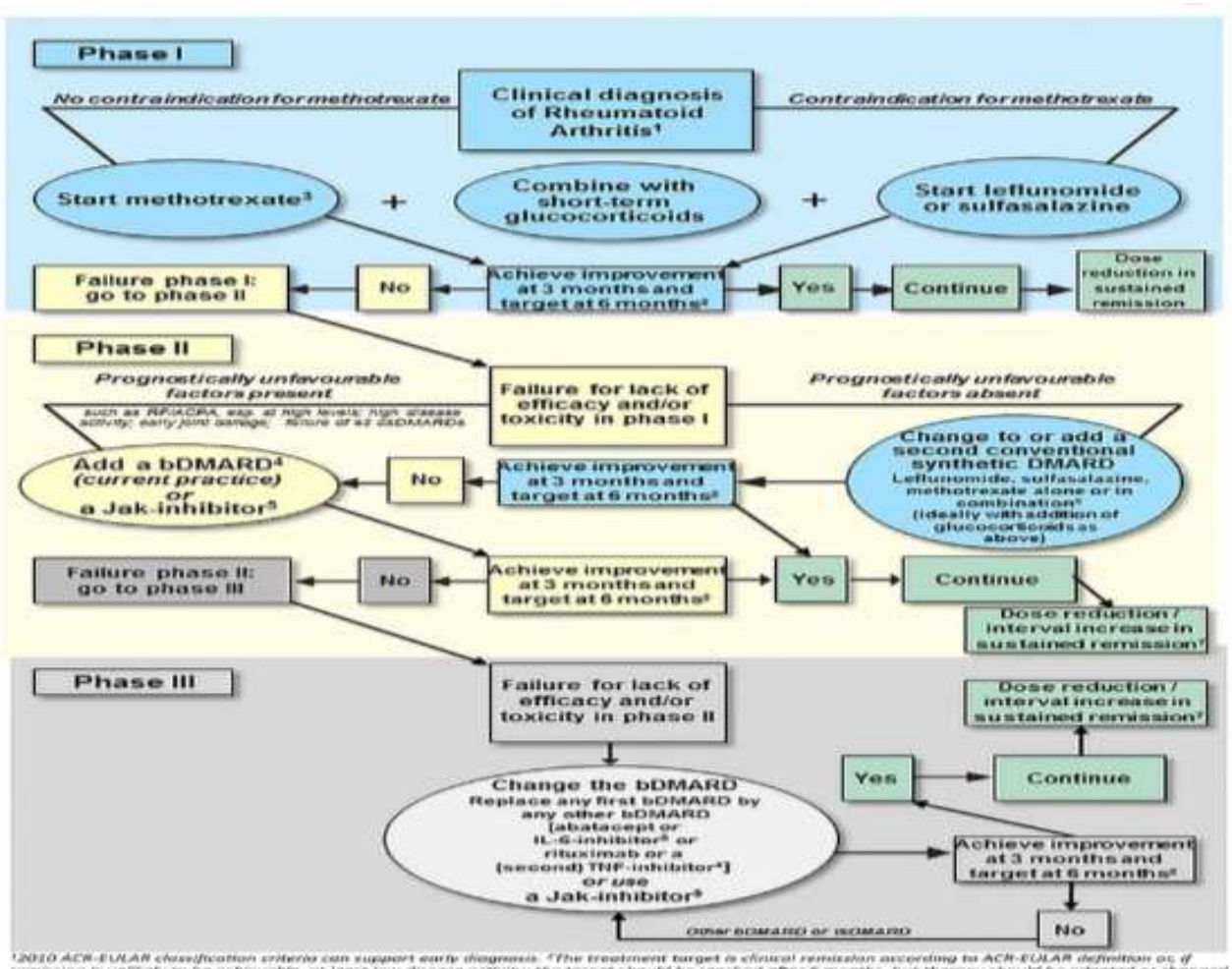
changes or the appearance of rheumatoid nodules, both of which are less common in the early stages of RA. The 2010 criteria also do not need symmetric arthritis, which permits an early asymmetric presentation.

Diagnostic Tests

Autoantibodies are frequently seen in autoimmune disorders, including RA. Rheumatoid factor is not unique to RA; it can also be found in elderly, healthy people and individuals with other illnesses like hepatitis C. The pathophysiology of RA may be influenced by anti-citrullinated protein antibody, which is more specific for the condition. Between 50 and 80 percent of RA patients have either anti-citrullinated protein antibody, rheumatoid factor, or both. Antinuclear antibody test results can be positive in patients with RA, and in younger versions of the disease, the test has predictive value.

The revised RA classification criteria include acute phase reactants, such as C-reactive protein levels and erythrocyte sedimentation rate, which are frequently elevated in active RA. Erythrocyte sedimentation rate and C-reactive protein levels can also be used to monitor the course of a disease and how well a treatment is working. Assessment of renal and hepatic function as well as a baseline complete blood count with differential are useful because the results may affect available treatments.

Standard Treatment Guideline for RA[8]



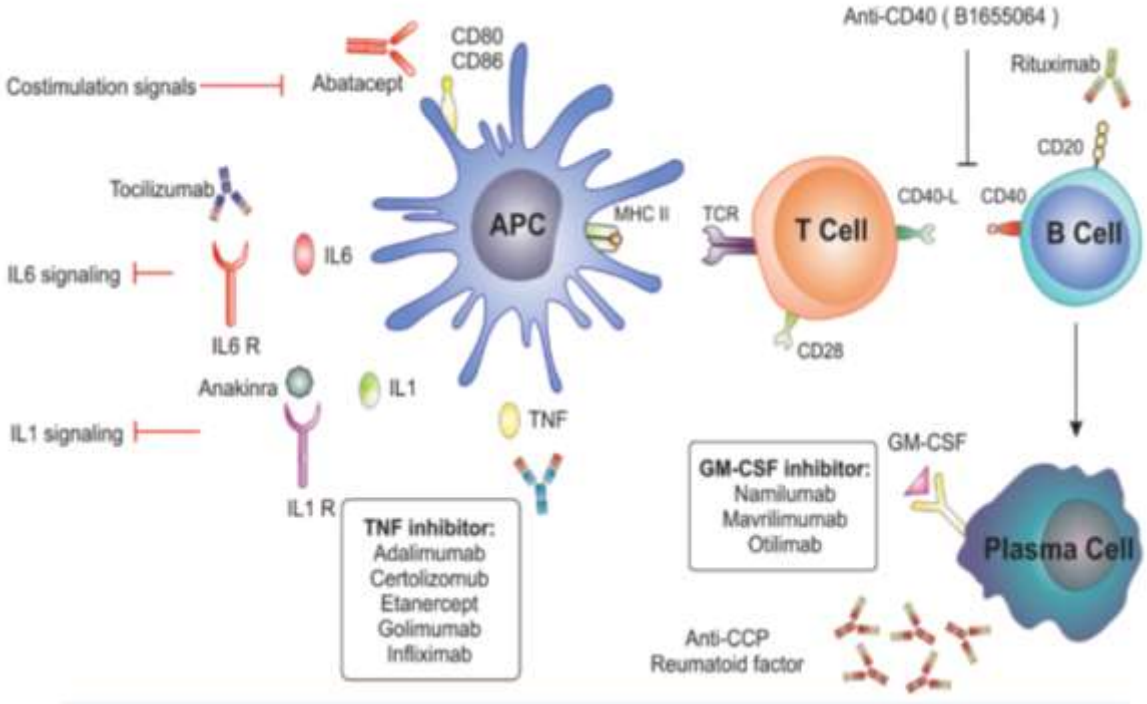
¹2010 ACR-EULAR classification criteria can support early diagnosis. ²The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. ³"Methotrexate should be part of the first treatment strategy"; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. ⁴TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved biosimilars), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. ⁵Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). ⁶The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. ⁷Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. ⁸Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. ⁹Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.

III. DMARDs:

Mechanism of Action of DMARDs:

Similar to antibodies, biologic DMARDs bind to external targets such as cell surface receptors or circulating cytokines: Five biologic drugs target TNF, which is important in the pathophysiology of RA: adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Anakinra, a human recombinant IL-1Ra, is a molecule that blocks the biological effects of IL-1. A humanized monoclonal antibody called tocilizumab binds to both the soluble and membrane-bound versions of the IL-6 receptor, preventing IL-6 from attaching to the receptor. Rituximab is an anti-CD20 chimeric monoclonal antibody that reduces B-lymphocyte counts. Abatacept is a fusion protein made of the recombinant, dimerized cytotoxic T-lymphocyte antigen 4 (CTLA-4), a natural inhibitor of T-cell activation, and the hinge, CH2, and CH3 domains of IgG1. By obstructing the communication between CD28 on a T cell and B7 on an antigen-presenting cell, abatacept stops T-cell co-stimulation. Granulocyte macrophage colony-stimulating factor (GM-CSF) has been proposed as a potential treatment target in trials for chronic autoimmune diseases including rheumatoid arthritis. GM-CSF stimulates the production of pro-inflammatory cytokines such as interleukin-6 and signals

through the JAK-STAT pathway. DMARDs stand for disease-modifying antirheumatic medications; TNF stands for tumor necrosis factor; RA stands for rheumatoid arthritis; and IgG stands for immunoglobulin G.[9]



Type of DMARDs and date of availability:

Table 1:

Type	Drugs	First year of EU marketing authorization
Conventional (csDMARD)	Methotrexate (MTX)	12/1953
	Hydroxychloroquine (HCQ)	04/1955
	Sulfasalazine (SUL)	1940s
	Leflunomide (LEF)	09/1998
	Azathioprine	Prior to 1982
Biologics Tumor necrosis factor (TNF)	Adalimumab	12/2002
	Etanercept	11/1998
	Certolizumab	04/2008
	Golimumab	04/2009
	Infliximab	08/1998
Non-TNF	Abatacept	08/2011
	Tocilizumab	01/2010
	Sarilumab	05/2017
	Rituximab	11/1997
	Anakinra	11/2001
JAK Inhibitors	Tofacitinib	11/2012
	Baricitinib	05/2018
	Upadacitinib	08/2019
	Filgotinib	2020

IV. JAK/STAT PATHWAY:

The JAK family consists of multiple subtypes, including JAK1, JAK2, JAK3, and TYK2, as well as several STAT proteins, including STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. The pathway is started when a ligand or cytokine binds to a cell membrane receptor in response to an external signal. This binding results in a structural or conformational change, which activates the homodimers or heterodimers of the relevant JAK isoforms. The JAK auto-phosphorylation process generates a docking site for the STAT protein, which phosphorylates itself upon binding. The JAKs help the STAT proteins move or translocate into the cell nucleus, whereupon protein synthesis and gene expression are triggered.

Interleukins IL4, IL-6, IL 10, IL 12, IL-23, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), erythropoietin (EPO), thrombopoietin (TPO), leptin, and growth hormone (GH) are the primary cytokines that function via the JAK/STAT system.[10]

V. JAKs INHIBITORS:

JAKs are cytoplasmic tyrosine kinases that are found inside cells that transmit cytokine signals from membrane receptors to the cell nucleus. There are four recognized varieties of JAKs: Tyk2, JAK1, JAK2, and JAK3. While JAK2 signals for a broader range of cytokines and is downstream of several growth factors involved in hematopoiesis, JAK1 and JAK3 transduce pro-inflammatory cytokine signaling. The sole medication in this family that is presently licensed for use in the United States is tofacitinib, a pan-JAK inhibitor. Another pan-JAK inhibitor, baracitinib, was not approved by the FDA in April 2017 due to insufficient safety and dosage information.[11]

More selective JAK inhibitors, such as JAK3 selective inhibitors with potential efficacy and a corresponding decrease in side effects, have been developed in an effort to prevent unwanted occurrences. Decernotinib was one such JAK3 selective inhibitor that survived phase II trials for RA and has five times higher JAK3 selectivity than other JAKi. Only Type I receptors of the common γ chain subgroup (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) are linked to JAK3. These focus on memory, T-cell survival and proliferation, regulatory cell function, B-cell function, and NK-cell activity. JAK3 is predominantly expressed in the hematological system and in lymphocytes. Consequently, JAK3 selective inhibitors were considered to be therapeutically promising for RA due to their effects.[12]

VI. JAK INHIBITORS IN TREATMENT OF RHEUMATOID ARTHRITIS:

Ruxolitinib

Mechanism of Action:

A significant advancement in our understanding of the pathophysiology of myeloproliferative disorders, such as polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF), was the identification that these disorders are caused by gain-of-function mutations in the JAK2 gene. The discovery of these mutations also gave rise to a justification for specifically focusing on this enzyme. The FDA has officially approved roxolitinib, a Jak1/2 inhibitor, for the treatment of intermediate- and high-risk MF. Ruxolitinib increases overall survival while lowering systemic symptoms and splenomegaly. Nonetheless, ruxolitinib has also been investigated in RA, where phase IIa trial results showed promise in terms of safety and efficacy. Promising outcomes have also been shown when roxolitinib is applied topically to treat psoriasis.[13]

Baricitinib

Mechanism of Action:

An oral, selective, and reversible JAK inhibitor is called baricitinib. The tyrosine-protein kinase family of intracellular enzymes, JAK, regulates signals from growth factor receptors and cytokines that are important for immune cell activity. There is an increased affinity of baricitinib for JAK1 and JAK2. The medication works by blocking these JAK proteins, which stops STATs from becoming phosphorylated and activated. Furthermore, baricitinib modifies the signaling route of certain growth factors, interleukins, and interferons. Additionally, baricitinib causes cell death and reduces the growth of JAK1/JAK2 expression in mutant cells. Within one week of starting therapy, baricitinib dramatically lowered blood C-reactive protein levels in rheumatoid arthritis patients.[14]

Tofacitinib

Mechanism of Action:

Inhibiting intracellular cytoplasmic nonreceptor tyrosine kinase (JAK) enzymes, which are implicated in both innate and adaptive immunological responses along the course of immune-mediated inflammatory disorders (IMIDs), is how tofacitinib works. There are four tyrosine kinase subtypes that make up the Janus kinases: JAK1, JAK2, JAK3, and TYK2. Tofacitinib further limits the intracellular growth factor and cytokine-mediated signals that can be transduced by the JAK-STAT pathway by specifically inhibiting the JAK1 and JAK3 enzymes. The natural function of intracellular Janus kinases is to phosphorylate the enzymes known as signal transducers and activators of transcription (STATs), which in turn affects immune cell activity, hematopoiesis, and gene expression. A significant part of the development of autoimmune illnesses like RA is attributed to the JAK-STAT signaling pathway. Tofacitinib, like other JAK inhibitors, further reduces the inflammatory effects of signal transducers and activators of transcription by inhibiting their phosphorylation and intracellular activation.[15]

Upadacitinib

Mechanism of Action:

Inhibiting intracellular cytoplasmic enzymes Janus kinases (JAK), a family of four tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) implicated in the development of immune-mediated inflammatory disorders (IMIDs), is how upadacitinib works. The JAK-STAT pathway's ability to transduce growth factor and cytokine-mediated signals intracellularly is further hampered by JAK inhibition.

JAKS modulates hematopoiesis and immune cell activity, phosphorylates signal transducers and activators of transcription (STATs), and controls gene expression. Upadacitinib further reduces the inflammatory effects of STATs by blocking their phosphorylation and intracellular activation. Compared to JAK2, JAK3, and TYK2 subtypes, upadacitinib selectively and more strongly inhibits JAK1.[16]

VII. AUTHORSHIP CONTRIBUTIONS

Participation in literature review and writing: Shukla Shikha
Supervision and writing: Nimisha Patel, Shrikalp Deshpande
All authors have read and agreed to the published version of the manuscript

VIII. CONFLICT OF INTEREST

There are no conflicts of interest among the authors that would be thought to compromise the objectivity of this review.

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