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A REVIEW ON BARICITINIB TREATMENT FOR RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis (RA) is a common inflammatory disease with several implications on health, disability and economy. Conventional treatment for RA centres on anti-inflammatory drugs and specific targeting of tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6). Baricitinib is a novel, Food and Drug Administration (FDA) approved, once daily oral drug that is effective in combination with current treatment and results in significantly reduced symptoms with good safety profile. Further studies are required to find rare side effects and evaluate the long-term efficacy in disease modulation and patient symptom reduction. This is a comprehensive review of the literature on baricitinib for the treatment of RA. This review provides an update on the pathophysiology, diagnosis and conventional treatment of RA, then proceeds to introduce baricitinib and the data that exists to support or refute its use in RA. The presented study also indicated clinical trials confirming the effectiveness of baricitinib in this indication.

KEYWORDS: Rheumatoid Arthritis, novel treatment, baricitinib, Janus kinase / signalling transducer and activator of transcription, kinase inhibitor.

RHEUMATOID ARTHIRITIS

INTRODUCTION

Arthritis is not a single disease; The term refers to joint pain or joint disease and there are the more than 100 types are arthritis and related condition peoples of ages and sexes live with arthritis and it is leading cause of disability in the U.S. common arthritis symptoms include swelling, pain, stiffness and administration range of motion in joints. Sever arthritis can result in chronic pain, difficulty performing daily activities and make walking.

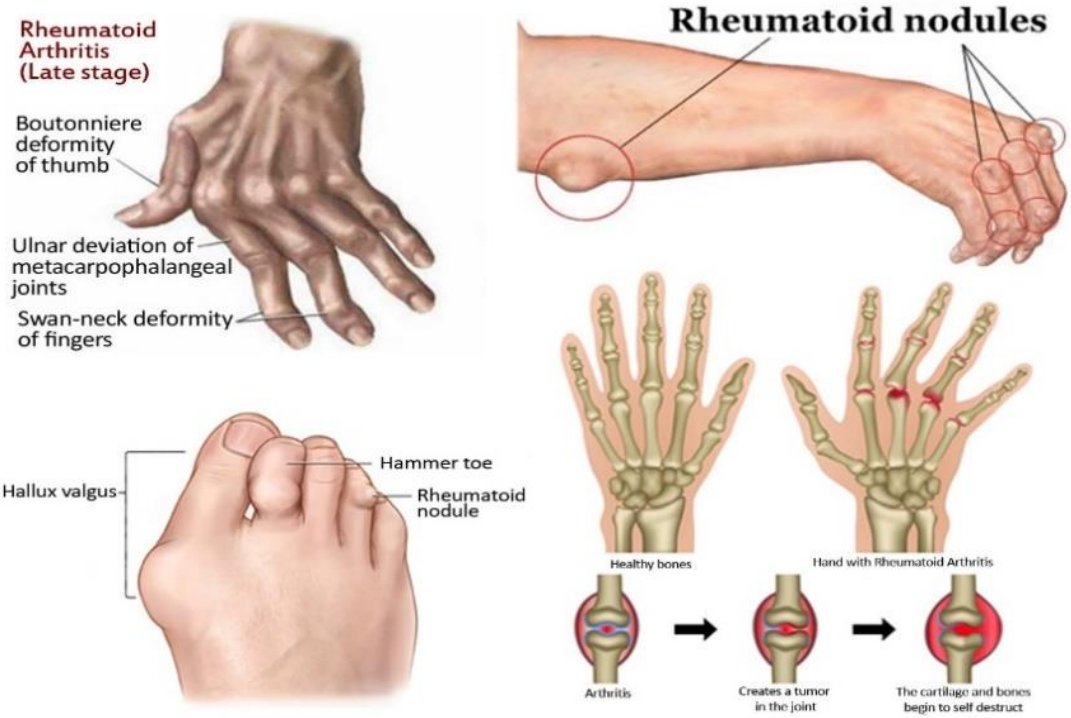
Types of arthritis

1. Rheumatoid arthritis
2. Osteoarthritis
3. Infection arthritis
4. Gout [Metabolic arthritis]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that arises more frequently in females than males, being predominantly observed in the elderly. That causes joint pain, joint swelling, joint stiffness and loss of functions in various joints. The clinical manifestation of symmetrical joint involvement includes arthritis, swelling, redness and even limiting the range of motion. Early diagnosis is considered as the key improvement index for the most desirable outcomes i.,e reduce joint destruction, less radiologic progression, no function disability and disease modifying anti rheumatic drug. Here we dissect the etiology and pathology at specific stages.

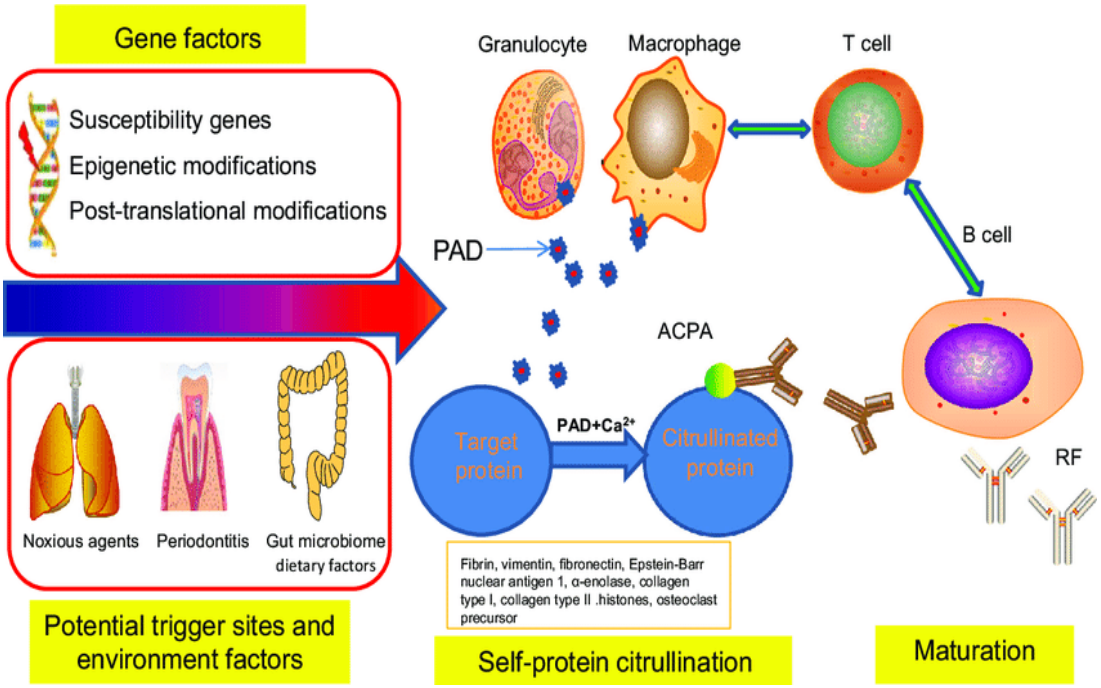
1. Triggering stage
2. Maturation stage
3. Targeting stage
4. Fulminant stage



1. Triggering stage

The appearance of ACPA is now widely used to diagnose and predict RA due to its high specificity (>97%) in clinical practice. ACPA occurs as a result of an abnormal antibody response to a range of citrullinated proteins, including fibrin, vimentin, fibronectin, Epstein-Barr Nuclear Antigen 1 (EBNA-1), α-enolase, type II collagen, and histones, all of which are distributed throughout the whole body. ACPA production has been associated with genetic and environmental factors.

The environment acts as a triggering factor for ACPA production in RA and the epigenetic regulation combines environment with genes. Gene–environment interaction influences the reactivity of autoantibodies to citrullinated antigens in RA. ACPAs can be detected long before the onset of the joint symptoms. This phenomenon suggests that the joints may not be the triggering spot for autoimmunity. Lung exposure to noxious agents, including smoke, silica dust, nanosized silica, or carbon-derived nanomaterials can trigger mucosal toll-like receptors (TLRs) that activate Ca^{2+}-mediated PADs, but also antigen-presenting cells (APCs), such as classical dendritic cells (DCs) and B cells. The coatomer subunit α gene mutations could disrupt the endoplasmic reticulum (ER)–Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis, thereby providing a connection between the lung and the joint diseases.



A can be triggered in the potential trigger sites (lung, oral, gut, et al.) by the interaction between the genes and environmental factors, which is characterized by the onset of self-protein citrullination resulting in the production of autoantibodies against citrullinated peptides. Lung exposure to noxious agents, infectious agents (Porphyromonas gingival is Aggregatibacter actinomycetemcomitans, and Epstein-Barr virus), gut microbiome, and dietary factors may induce the self-protein citrullination and maturation of ACPA. Citrullination is catalysed by the calcium-dependent enzyme PAD, changing a positively charged arginine to a polar but neutral citrulline as the result of a post-translational modification. In RA, PAD can be secreted by the granulocyte and macrophage. ACPA occurs as a result of an abnormal antibody response to a range of citrullinated proteins, including fibrin, vimentin, fibronectin, Epstein-Barr Nuclear Antigen 1, α-enolase, type II collagen, and histones, all of which are distributed throughout the whole body. Many citrullination neoantigens would activate MHC class II-dependent T cells that in turn would help B cells produce more ACPA. The stage is also called loss of tolerance. RA rheumatoid arthritis, PAD peptidyl-arginine-deiminase, ACPA anti-citrullinated protein antibodies, RF rheumatoid factor.

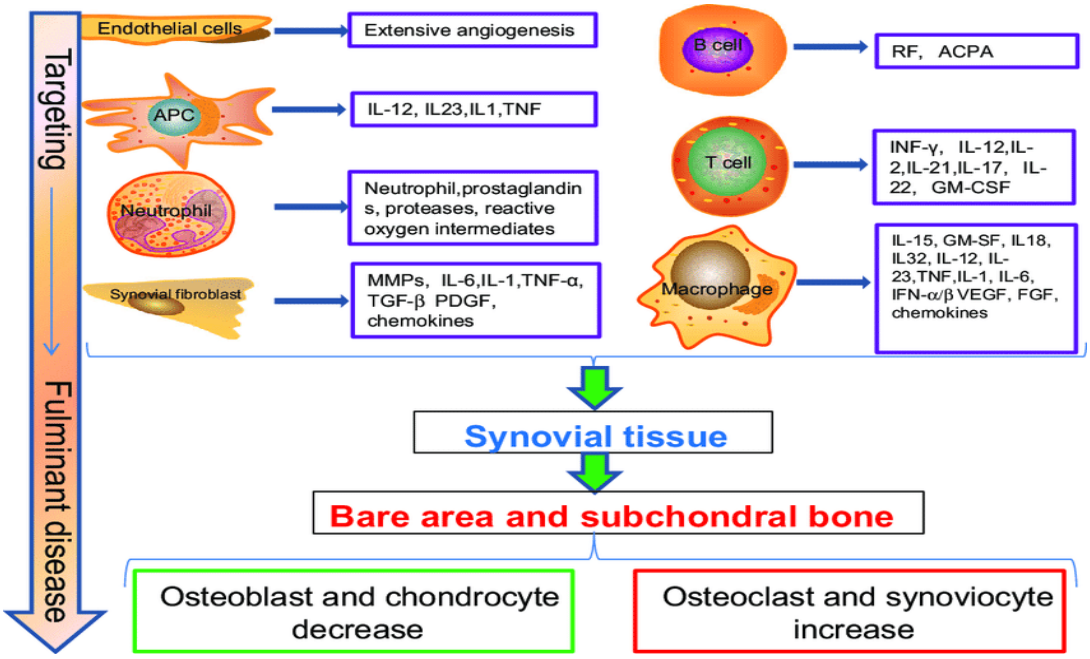
2. Maturation stage

This stage is initiated at the site of secondary lymphoid tissues or bone marrow. Epitope spreading refers to the development of immune responses to endogenous epitopes resulting from the release of self-antigens. The immune response to autoantigens may exist many years before disease onset and lay outside the joints. In this stage, epitope spreading and a gradually increased titer of ACPA can last several years before the onset of joint symptoms. Initial ACCP levels appear to be of great importance in predicting the interval time to disease onset. The production of ACPA reflects break of immunological tolerance. As a result, many citrullination neoantigens would activate MHC class II-dependent T cells that in turn would help B cells produce more ACPA. ACPA can induce pain, bone loss, and inflammation in RA. One study has identified that two RA-specific autoantigens N-acetylglucosamine-6-sulfatase (GNS) and filamin A (FLNA) correlate microbial immunity with autoimmune responses in the joint.

3. Targeting stage

The involvement of RA in joints usually has a characteristic presentation with synovitis occurring in symmetrical small joints. Joint swelling is the external reflection of synovial

membrane inflammation following immune activation. The normal synovial compartment is infiltrated by leukocytes and the synovial fluid is inundated with pro-inflammatory mediators that interact to produce an inflammatory cascade, which is characterized by the interactions of fibroblast-like synoviocytes (FLSs) with the cells of the innate immune system, including monocytes, macrophages, mast cells, and so on, as well as cells of adaptive immune system such as T lymphocytes (cell mediated immunity) and B cells (humoral immunity). The two immune systems and their interactions are intimately involved in the development of ACPA-positive RA.



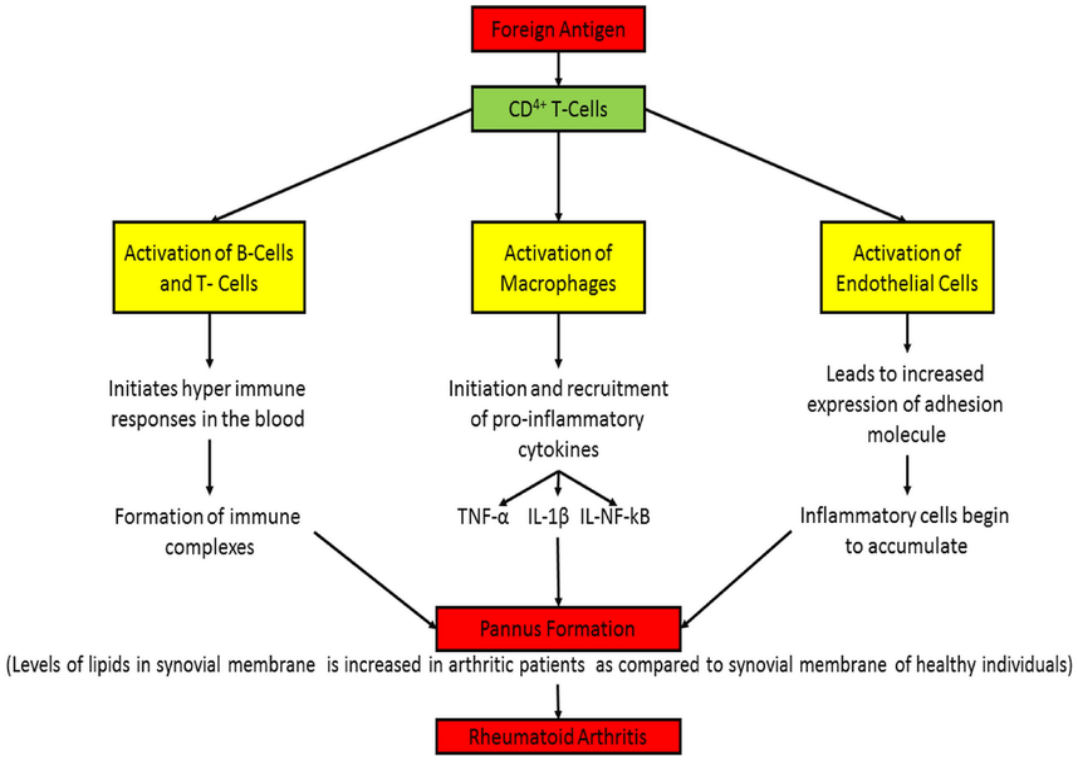
Many cells and their cytokines play critical roles in the development of RA. The synovial compartment is infiltrated by leukocytes and the synovial fluid is inundated with pro-inflammatory mediators that are produced to induce an inflammatory cascade, which is characterized by interactions of fibroblast-like synoviocytes with the cells of the innate immune system, including monocytes, macrophages, mast cells, dendritic cells, and so on, as well as cells of adaptive immune system such as T cells and B cells. Endothelial cells contribute to the extensive angiogenesis. The fulminant stage contains hyperplastic synovium, cartilage damage, bone erosion, and systemic consequence. Bone resorption virtually creates bone erosions, which are usually found at spots where the synovial membrane inserts into the periosteum, which is known as a bare area according to certain anatomical features. The destruction of the subchondral bone can eventually result in the degeneration of the articular cartilage as the result of a decrease in osteoblasts and an increase

in osteoclasts and synoviocytes. IL interleukin, TNF tumor necrosis factor, MMP matrix metalloproteinase, TGF transforming growth factor, PDGF platelet-derived growth factor, IFN interferon, GM-CSF granulocyte–macrophage colony-stimulating factor, VEGF vascular endothelial growth factor, FGF fibroblast growth factor.

4. Fulminant stage

synovium is characterized by a mixture of bone marrow-derived macrophages and specialized FLSs. Synovial cells maintain the steady state of the joint by secreting hyaluronic acid and lubricin for joint lubrication and function, as well as processing waste products. In RA, the dysfunction of FLS leads to hyperplastic synovium. The abnormal proliferation of FLS results from a loss of contact inhibition that plays a critical role in RA by producing inflammatory cytokines and proteinases, such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) that perpetuate joint destruction. They create a microenvironment that allows for the survival of T cell and B cell and neutrophil accumulation. Another hypothesis regarding the cause of hyperplastic synovium is likely due to the resistance to apoptosis associated with distinctive pathways. Such pathways include abnormalities of tumor protein p53 function, which contributes to synovial lining expansion and joint destruction in RA.

Pathophysiology of rheumatoid arthritis



Immune activation and RA disease progression is a complex process that involves interaction between components of both the adaptive and innate immune pathway. The nature of these interaction is gently affected by the local cytokine and chemokine environment of the synovium in which they take place. In established Rathe synovial membrane is populated by a variety of inflammation cell types that work together to cause joint.

The importance of the adaptive immune pathway in RA is suggested by the presence of dendritic cells, a major class of antigen presenting cell that express a variety of cytokines, HAL class 11 molecule and costimulatory molecule in close proximity to cluster of T cells in the synovium. Dendritic cell present antigen to T cell that are present in the synovium and also sever as one component of the T cell activation process. Activation of T cells requires 2 signals. The first signal is antigen presentation of the T cell. The second the costimulatory signal requires interaction of the cell surface protein CD80/86 on the antigen presenting (dendritic) cell with the CD28 protein on the T cell. Blockade of the costimulatory signal through competitive inhibition of CD80/86 Interferes with T cell activation and downstream events. The effectiveness of CD80/86 blockade as a treatment for RA validates the concept that T cell plays an active role in the pathophysiology of RA.

When T cell activation does occur native T helper (TH) cells differentiate into 3 major subpopulations (Th1, Th2, Th3 and Th17) with distinct cytokine population profile and function. Although RA has a long been considered to be disease that is mediated by Th1 cells recent interest has been focused on the Th17 subpopulation. Dendritic cells and macrophages both secrete transforming growth factor beta, interleukin (1L) 1beta, IL -6, IL- 21, IL-23, cytokine that support Th17 differentiation and suppress production of regulatory T cells thus shifting the homeostatic balance in the synovium toward inflammation. In turn Th17 cells produce IL-17A, IL-7F, IL-22, IL-26, Interferon -g, the chemokine CCL20, and the transcription factor ROR -g. production of IL-17A stimulates fibroblast like synoviocytes (FLS) macrophages like synoviocytes to upregulate production of IL-26 which induces production of the inflammatory cytokine IL-1BETA, IL-6, and TNF -ALPHA by monocyte these cytokines stimulate further differentiation of TH17 cells. In addition to antigen – driven inflammatory pathways, inflammation can be mediate through antigen nonspecific pathways initiated by cell to cell contact between activated T cells and macrophages and fibroblast.

Humoral adaptive immunity also plays an integral role in the pathogenesis of RA. The contribution of B cells to autoimmune disease can be mediated through several potential

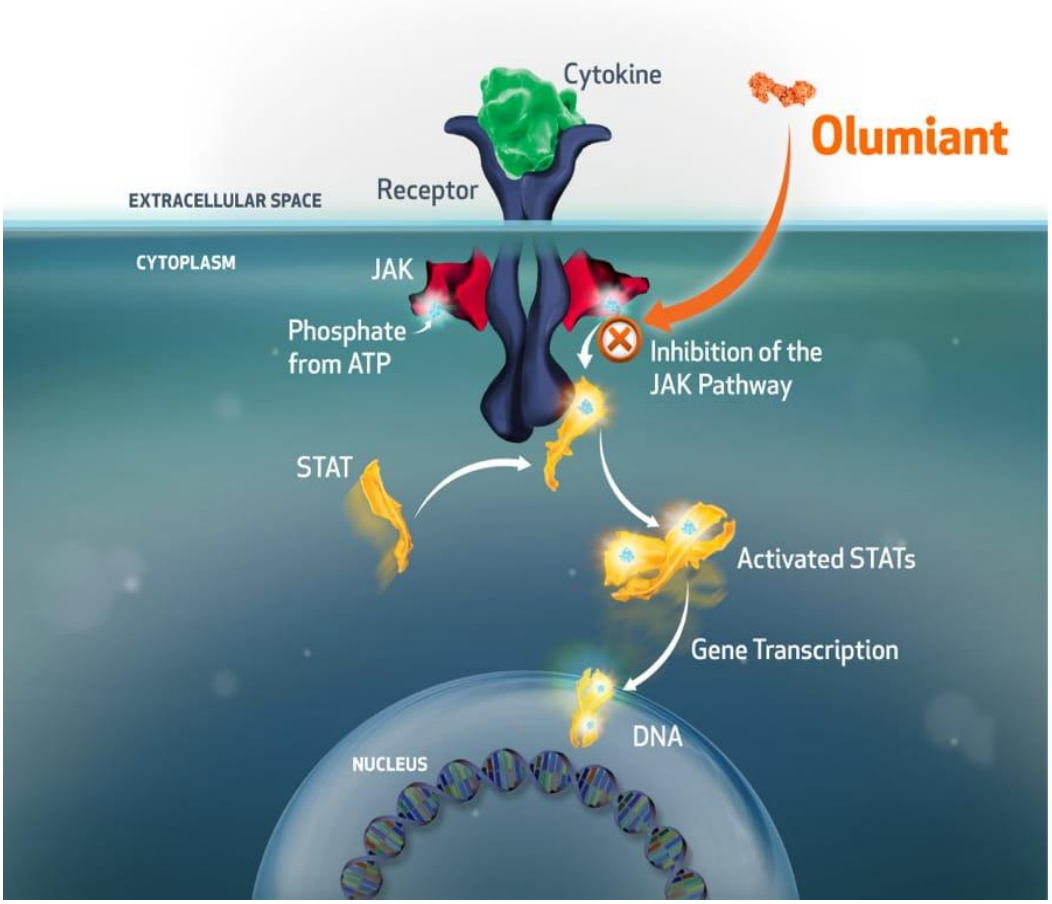
mechanism. Defects in B – cell tolerance checkpoints can result in autoreactive B cell that act as antigen presenting cells that are capable to activating T cells. B cells can also produce both pro- and anti-inflammatory cytokine. finally, B cell can function as antibody producing cells. separately or in combination this mechanism can contribute to RA pathogenesis. 30 Addition support for involvement of B cell In RA is provided by the successful use of agent that deplete specific B cell populations for the management of RA. Rituximab, a monoclonal antibody directed against CD20 positive B cell has demonstrated success in RA clinical trials and is currently approved for use in patient with RA who are refractory to TNF inhibitors.

Baricitinib

Baricitinib is a disease modifying anti Rheumatic drug and FDA approved for treating adult patients with moderately to severely active rheumatoid arthritis who had an inadequate response to others diseases modifying antirheumatic drugs, including TNF antagonist therapies. Several clinical trials have shown marked clinical improvement of the disease's progression compared to placebo.

Future use: Clinical trials has shown the efficacy of baricitinib and topical corticosteroid in improving signs and symptoms of several atopic dermatitis .it is currently under review by FDA for approval. similarly, clinical trials have shown promising results of baricitinib in the treatment of rheumatoid arthritis.

Mechnism action for baricitinib

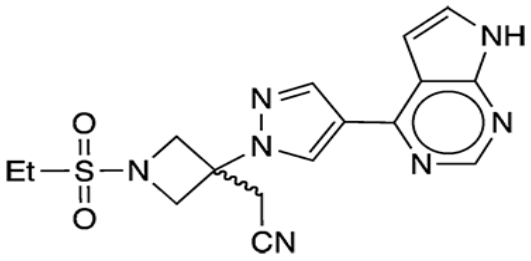


Baricitinib is an oral selective and reversible inhibitor of Janus kinase (JAKS). Janus kinase is an intracellular enzyme that belongs to the tyrosine protein kinase family and molecules signals for cytokines and growth factor receptor involved in immune cell function.

There are four JAK Proteins (JAK1, JAK2, JAK3 and TYK2). These protein pair differently in different cell receptor and form homodimer or heterodimer. These JAK dimers phosphorylate the transcription proteins (STATS) and active intracellular activity, including gene transcription of inflammatory mediates leading to an autoimmune response.

Baricitinib has a higher affinity for JAK1 and JAK2. It inhibits the JAK protein prevents phosphorylation and activation of STATS and modulates the signalling pathway of various interleukins, interferons and growth factor. Baricitinib also decreases the proliferation of JAK1/JAK2 expression in muted cell and induces cell apoptosis.

Drug profie for baricitinib



FDA Approval: Approved May 31, 2018

Brand name: Olumiant

Generic name: Baricitinib

Dosage form: Tablets

Class: Jak Inhibitor

Company: Elly Lilly and company

Formula: C16H17N702S

Baricitinib is a Janus kinase (JAK) inhibitor. JAKs are tyrosine protein kinases that play an important role in pro-inflammatory signalling pathways. Overactive JAKs have been implicated in autoimmune disorders, such as rheumatoid arthritis.

Litrature review

1. Peter C. Taylor, Ernest choy et al 2023. A JAK Inhibitor for treatment of Rheumatoid Arthritis: The Baricitinib Experience. In This article approved as monotherapy or in combination with baricitinib for treating adults with moderate to severe active rheumatoid arthritis and provides improvement in clinical signs and symptoms and patient reported outcomes. Currently, baricitinib is approved for treating RA in more than 75 countries. In several pivotal Phase II and III RA trials (RA-BALANCE, RA-BEGIN, RA-BEAM, RA-BUILD, RA-BEACON, RA-BEYOND), up to seven years of baricitinib treatment was well tolerated and provided rapid and sustained efficacy, which was confirmed in real-world settings.

2. Annine Stuart, Jabeen Begum et al. April 12, 2023. Rheumatoid Arthritis Drug Guide. In This article approved on the Arthritis medication play an essential role in

controlling the progression and symptoms of rheumatoid arthritis and the best medical care combination rheumatoid arthritis medication and other approaches.

3. Anam Ahmad, Muhammad Zaheer, Fred J. Balis et at. July 27 2022. Baricitinib: In This article approved on the indications, action, and contraindication for baricitinib as a valuable agent in managing rheumatoid arthritis in clinical setting.

4. Pawel Kawalec, Katarzyna sladowska, Iwona Malinowska- lipien et al. DEC 24 2022. New alternative in the treatment of rheumatoid arthritis: Clinical utility of baricitinib. In This article approved for use as monotherapy or in combination with methotrexate in the treatment of adults with moderate to severely active rheumatoid arthritis. The aim of this reviews the studies on pharmacology, mode of action, pharmacokinetics, efficacy and safety of baricitinib in patient with RA. Baricitinib provides an innovative approach to modulating the immune and inflammatory response in patient with Rheumatoid Arthritis.

5. Brett king, M.D., Ph.D., Manabu ohyama, M.D., Ph.D., et al May 5, 2022. Two phase 3 trials of Baricitinib for Alopecia Areata. In This article approved on alopecia areate is an autoimmune condition by rapidly hair loss in scalp, eyebrows, and eyelashes for which treatment are limitited. Baricitinib, an oral, selective, reversible inhibitor of Janus kinases 1 and 2, may interrupt cytokine signalling implicated in the pathogenesis of alopecia areata.

6. Linda Rath et al. June 9, 2022. What is Arthritis: In this article refers to joint pain or joint disease and there are more than 100 types of arthritis and related condition. People of all ages, races and sexes live with arthritis, and it is the leading cause of disability in the U.S. It’s most common among women, and although it’s not a disease of aging, some types of arthritis occur in older people more than younger people.

7. Sara Assadiasl, MD, Ph.D., Yousef fatahi et al. JUN 12 2021. Baricitinib: From Rheumatoid arthritis to COVID 19. In This article approved for treating moderates to severe rheumatoid arthritis but that later showed considerable efficacy in the control of exaggerated inflammatory response that occur in a wide range of disease. There is a growing body of evidence, obtained from clinical trials and case reports, demonstrating clinical and paraclinical improvement in patients following administration of baricitinib including RA, systemic lupus erythematosus, psoriasis, atopic dermatitis, alopecia areata,

interferon-mediated autoinflammatory diseases, graft-versus-host disease, diabetic kidney disease, and, recently, coronavirus disease-1.

8. Ivan Urits, Jacob israel, et al. DEC 23, 2020. Baricitinib for treatment of rheumatoid arthritis: In This article provides an update on the pathophysiology, diagnosis, and conventional treatment of Rheumatoid arthritis, then proceeds to introduce baricitinib and the data that exit to support or refute in use of Rheumatoid arthritis. The presented study also indicated clinical trials confirming the effectiveness of baricitinib in this indication.

9. Omar Viswanath, Alan kaye et al. DEC 2020. Baricitinib treatment of Rheumatoid arthritis. This article provides approved of the literature on baricitinib for the treatment of RA. The present study also indicated clinical trials conforming the effectiveness of baricitinib in this indication.

10. Nikita Khanna Anil Kumar et. al. 2020. A Review on Rheumatoid Arthritis intervention and current development. This review provides a general understanding of the challenges and uncertainties in the treatment of RA.

11. Linda Dresser et.al 2020. Baricitinib: A review of pharmacology, safety, emerging clinical experience in COVID 19. This article they available data on baricitinib with an emphasis on immunosuppressive and pharmacokinetic, safety and current progress in COVID-19 clinical trials.

12. Sultan s. Ahmed.et.al. 2019. Rheumatoid arthritis: A brief overview of the treatment. In this article provides explained various past and present treatment modalities to address the complication associated with RA.

13. Qiang Guo, Yuxianga Wang et al. April 27 2018. Rheumatoid Arthritis: Pathological mechanism and modern pharmclolgical therapies. This artical provides a contempory appraisal of recent literature on the pathogenesis of RA and the potential of new pharmacological intervention for optimizing RA treatment regimes. The review discusses recent advances of our understanding of RA pathogenesis, disease modifying drugs, and provides perspectives on next generation therapeutics for RA.

14. Gautham Rambha et. al. 2015. Literature review of rheumatoid arthritis in India. This artical provides focuced on descriptive epidermiology, comorbidities and extra-articular

manifestation, functioning abilities and quality of life and treatment patterns of RA patients in India.

15. Allan Gibofsky, MD, JD, et al may 13, 2014. Epidemiology, pathophysiology, and diagnosis of Rheumatoid arthritis: A synopsis. This article is the first in a 3- article supplement that will review the pathophysiology, treatment and damage and managed care implication of RA. This article will examine the epidemiology and pathophysiology of RA and provide guidance regarding diagnosis based on current disease classification criteria.

AIM AND OBJECTIVES

- The present aim of the review is to study the recently approved drug Baricitinib which is used to treat Rheumatoid arthritis.

OBJECTIVES

- To study the different drugs used for Rheumatoid Arthritis.
- To study the pharmacodynamic and pharmacokinetic properties of Baricitinib

Different drugs used for rheumatoid arthris

Name	Brand name (S)	Precaution	Potential side effects
Hydroxychloroquine sulphate	Plaquenil	Vision may be damaged with high doses or long-term use.	Blurry vision or increased light sensitivity • Headache • Belly cramps or pain • Loss of appetite, nausea, vomiting, or diarrhoea • Itching or rashes
leflunomide	Arava	Active infection • Liver or kidney disease • Cancer • Stop taking leflunomide before trying to conceive.	Dizziness • Hair loss • Headache • Heartburn • High blood pressure • Gastrointestinal or liver problems • Low blood cell count • Neuropathy • Skin rash
methotrexate	Rheumatrex, Trexall	Abnormal blood counts • Liver or lung disease	Belly pain • Chills or fever • Dizziness

		• Alcoholism • Active infection or hepatitis • Active plans to conceive	• Hair loss • Headache • Light sensitivity • Itching • Liver problems • Low blood counts Rare, but serious: Dry cough, fever.
tofacitinib	Xeljanz	Xeljanz adds to risk of serious infections, cancers, lymphoma • May increase chole sterol levels and live r enzymes • May lower blood count	Upper respiratory tract infection • Headache • Diarrhoea • Inflammation of the nasal passage and the upper part of the throat • Blood clots and tears in the intestine
baricitinib	Olumiant	Olumiant increases the risk of serious infections, cancers, lymphoma • May raise cholester ol levels and liver enzymes • May lower blood count	Upper respiratory tract infection • Headache • Diarrhoea • Inflammation of the nasal passage and the upper part of the throat • Blood clot and tears in the intestine
Upadacitinib	Rinvoq	• Rinvoq increases the risk of serious infections, cancers, lymp homa, and skin cancers.	Upper respiratory infections • Cough • Fever • Nausea • May cause blood clots • Tears in the stomach and intestines are possible.

Pharmacodynamic and Pharmacokinetics of baricitinib

In Vitro Baricitinib inhibits JAK1 having (IC_{50} 5.9nmol/L) and JAK2 (IC_{50} 5.7 nmol/L) but has lower potency against tyrosine kinase 2 (IC_{50} 53 nmol/L) and JAK3 (IC_{50} 560 nmol/L) In vitro analyses also showed that baricitinib inhibited JAK1/3 signalling to a lesser extent than

upadacitinib and tofacitinib, with all three JAK is inhibiting the signalling of JAK2/2-dependent cytokines.

In vitro, baricitinib inhibits JAK1 (half-maximal inhibitory concentration [IC_{50}] 5.9 The relatively short half-life of baricitinib (12.5 h) and convenient once daily oral administration, brought a substantial change to the current treatment options for RA. Improvements in the American College of Rheumatology 20% (ACR20) response rate, the Disease Activity Score in 28 joints (DAS28) and other clinical outcomes were seen as early as the first week with baricitinib treatment as compared to MTX.

The synthetic nature of baricitinib eliminates the risk of immunogenicity (neutralising antibody response) and the temporary interruption of baricitinib does not cause a loss of response. Importantly, when there is a need for drug discontinuation, 90% of the baricitinib dose is eliminated within 24 h. Although baricitinib is contraindicated during pregnancy, in contrast to many other available therapies, it may be stopped as late as one week prior to a planned pregnancy.

Dosa fexibility of baricitinib

Baricitinib is available in two dosage strengths (2 mg and 4 mg), each administered once daily. Baricitinib 4 mg is the indicated starting dose, with potential to taper to 2 mg, in all countries except the US, Canada and China, where a dose of 2 mg is approved for treating RA. Patients aged ≥65 years and those with a history of chronic or recurrent infections should receive a dose of 2 mg according to EU recommendations. Both baricitinib 4 mg and 2 mg are efficacious among different treatment populations.

A reduced dosage of baricitinib 2 mg/day is recommended in patients aged ≥65 years and those with moderate renal impairment, and may be appropriate for patients with a history of chronic or recurrent infections and is also in line with the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommendation to use a lower effective dose for all JAKs across all indications when treating populations at risk of venous thromboembolism (VTE), cancer or major cardiovascular (CV) problems.

Dose adjustment of baricitinib

Baricitinib is mainly excreted via the kidneys, in patients with moderate renal impairment with glomerular filtration rate (GFR) between 30 to 60 mL/minute /1.73. The dose should be

reduced to 1 mg oral daily. The drug is not recommended for patients who have GFR less than 30 mL/minute /1.73.

Mild to moderate liver impairment does not require any dose adjustment. Baricitinib should be avoided in patients with severe hepatic impairment due to a lack of clinical data.
No specific dose adjustment has been recommended for the geriatric population.

Adverse effects of baricitinib

Baricitinib is generally considered safe and well-tolerated, but it can increase the risk of serious infections as it is an immunosuppressive drug. The most common infections are upper respiratory and urinary tract infections, but there is also an increased incidence of herpes zoster infections. Among opportunistic infections, tuberculosis, histoplasmosis, pneumocystosis, candidiasis, BK virus infection, and cytomegalovirus infections have been reported.

Baricitinib is reportedly associated with bone marrow suppression and hematological abnormalities, including anemia, neutropenia, and lymphopenia, and requires regular lab monitoring. Another side effect that has typically been observed after 12 weeks of use of baricitinib is an increase in mean cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels without elevation of LDL to HDL ratio. A rise in CPK levels has also been observed in some patients.

Among gastrointestinal side effects, nausea, vomiting, abdominal pain has been commonly reported. However, serious side effects such as GI perforation are rare but have been reported in patients with prior history of diverticulitis. Transient elevation in liver enzymes has been observed with baricitinib as compared to placebo.

Contraindication

Patients with severe active local or systemic infections, including hepatitis, HIV, or fungal infections, should avoid its use until the active infection has been adequately treated. It should not be used in patients with active tuberculosis.

Baricitinib is contraindicated in patients with chronic kidney disease with GFR less than 30 mL/minute /1.73. It is not recommended for patients with severe hepatic impairment.

Patients with significant anemia with hemoglobin below 8mg/dL, lymphopenia with absolute lymphocyte count (ALC) less than 500 cells, or neutropenia with absolute neutrophil count (ANC) less than 1,000 cells should avoid Baricitinib until the counts recover.

Baricitinib should not be used in combination with biologic disease-modifying antirheumatic drugs. Due to the lack of clinical data on human pregnancy and breastfeeding, it's been recommended to avoid its use during pregnancy and nursing. Female patients of reproductive age should use effective contraception and should inform their clinicians if they become pregnant

Toxicity

In clinical trials, single doses up to 40 mg and multiple doses of up to 20 mg for ten days were evaluated, but no dose-limiting toxicity was observed. Adverse events were similar to those with lower doses, including nausea, vomiting, recurrent infections, hypersensitivity reactions, and myelosuppression.

In case of overdose, patients should be monitored for signs and symptoms of adverse reactions and seek medical attention accordingly.

Clinical study of baricitinib is treating for rheumatoid arthritis

1. 2015 a phase IIb trial investigated the efficacy of baricitinib at 1 mg, 2 mg, 4 mg, or 8 mg vs. placebo.[38]
2. The study involved 301 patients from 69 institu- tions in 9 countries who had failed prior treatment with methotrexate.
3. The primary endpoint was the pro-portion of study volunteers in the 4 mg or 8 mg cohort
4. That received a positive result on the American Col- lege of Rheumatology 20% (ACR20) score at 12 weeks.
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1. In 2014 two randomized controlled trials were conducted in healthy volunteers to demonstrate the pharmacokinetics and safety of baricitinib. Multiple ascending doses between 1 mg and 20 mg were studied. The results showed dose-linear and time-invariant pharmacokinetics with insignificant effects from a high fat diet. The plasma concentration of baricitinib peaks 1.5 hours after oral ingestion and mean renal clearance is 11.8 l/h. This study also demonstrated a dose related decline in absolute neutrophil count.

In 2015 a phase IIb trial investigated the efficacy of baricitinib at 1 mg, 2 mg, 4 mg, or 8 mg vs. placebo. The study involved 301 patients from 69 institutions in 9 countries who had failed prior treatment with methotrexate. The primary endpoint was the proportion of study volunteers in the 4 mg or 8 mg cohort that received a positive result on the American College of Rheumatology 20% (ACR20) score at 12 weeks. The ACR20 is a tool that uses multiple measures to objectively evaluate improvement in rheumatoid arthritis symptoms.

Phase III RA-BEACON trial in 2016 involving 527 patients compared the use of 2 mg or 4 mg of daily baricitinib with placebo at 24 weeks. The primary end point used the ACR20 response to determine clinical improvement at 12 weeks. The study population consisted of patients > 18 years old with moderate-to-severe RA who had discontinued prior treatment with conventional tumor necrosis factor inhibitors (TNFis) or biologic disease-modifying antirheumatic drugs (bDMARDs) due to insufficient response or intolerance after > 3 months The results showed significantly more patients in the 4 mg baricitinib group had an ACR20 our response than the placebo group (55% vs. 27%).

2. Large Phase III trials assessing the efficacy and safety of baricitinib at a registered dose of 2 or 4 mg once daily in patients with RA were identified: RA-BEACON, RA-BUILD, RA-BEAM and RA-BEGI In the randomized double-blind RA-BEACON trial, 527 patients with moderate-to-severe RA were assigned in a 1:1:1 ratio to baricitinib at a dose of 2 mg, baricitinib at a dose of 4 mg, or placebo. Before the study, patients showed an inadequate response or intolerance to at least one therapy with TNF inhibitors. Patients who received baricitinib had significantly higher ACR20 and ACR50 response rates than patients given placebo. At 12 weeks, the percentage of patients who achieved

the ACR20 response was significantly higher in the group treated with baricitinib (2 and 4 mg) than in the placebo group (49% and 55% vs 27%).

CONCLUSION

Rheumatoid Arthritis is a common autoimmune disease is associated with inflammatory and swelling of the synovium of the joint. And if untreated often results is destruction of both the joint and cartilaginous elements of joint and resultant disability. A comorbidity associated with systemic inflammation contribute to increased mortality seen in patient with RA compared with the general population.

Baricitinib has proven to be an effective treatment for Rheumatoid arthritis. It belongs to class of Janus kinase inhibitor and has demonstrated its ability to reduce inflammation, pain of joints. Improve overall quality of life for many patients with this condition. However, like any medication, it comes with potential side effects and should be prescribed and monitored by healthcare professional. Individual response to Baricitinib may vary, so it is important for patient to work closely with their healthcare team to determine if it is the right choice for their specific case.

In real-life data of Baricitinib in RA, with a better response to therapy in patients with an elevated disease activity at baseline, as well as its ability to allow a significant reduction of pain and concomitant steroid dose. In addition, US was confirmed to be useful in monitoring disease activity and treatment response.

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