IJAPB International Journal of Advances in Pharmacy and Biotechnology

Journal homepage: http://ijapbjournal.com/

Review Article

Target Directed Drug Discovery and Development of Baricitinib

Rehima Mohammad*, Rajasekhar Reddy Alavala, Koteswara Rao GSN

K L College of Pharmacy,K L E F Deemed to be University, Guntur, Andhra Pradesh -522502, INDIA.

ARTICLE INFO

Article history:
Received 20 April 2021
Received in revised form 05 May 2021
Accepted 02 June 2021
doi.org/10.38111/ijapb.20210702003

Keywords:
Doxycycline, Antibiotic tetracycline, Chlamydia, Gonorrhea, Syphilis, Periodontitis

ABSTRACT

Baricitinib is a reversible Janus - associated kinase (JAK) - inhibitor that interrupts the signaling of multiple cytokines implicated in COVID - 19 immunopathology. It may also have antiviral effects by targeting host factors that viruses rely for cell entry and by suppressing type I interferon driven angiotensin - converting - enzyme - 2 up regulation. However, baricitinib's immunosuppressive effects may be detrimental during acute viral infections by delaying viral clearance and increasing vulnerability to secondary opportunistic infections. The lack of reliable biomarkers to monitor patients' immune status as illness evolves complicates deployment of immunosuppressive drugs like baricitinib. Furthermore, baricitinib carries the risk of increased thromboembolic events which is concerning given the proclivity towards a hyper - coagulable state in COVID - 19 patients. In this article we review available data on baricitinib with an emphasis on immunosuppressive and antiviral pharmacology, pharmacokinetics, safety, and current progress in COVID - 19 clinical trials.

Introduction

Baricitinib is a novel and reversible, selective, first-generation, oral JAK1& JAK 2 inhibitor with moderate affinity towards TYK2 and significantly less affinity towards JAK3 enzymes [1]. It was achieved by substituting the part of the tofacitinib molecule (another drug for RA) that showed JAK1/JAK3 selectivity with a different chemical moiety, resulting in a new structure that exhibited specificity for JAK1 and JAK2 over JAK3.it was developed for the treatment of inflammatory diseases, such as rheumatoid arthritis (RA) [2].

Recently, baricitinib has been proposed as a potential treatment for COVID-19 (the disease caused by SARS-CoV-2) due to its anti - inflammatory and antiviral activities. Baricitinib is expected to have a high binding affinity to AAK1 (AP2-associated protein kinase-1) and GAK (G-associated kinase) and interrupt the passage and intracellular assembly of SARS-CoV-2 into the target cells mediated by ACE2 receptor, it is also expected to block cytokine storms by suppressing JAK1 and JAK 2 receptors [3]. Correspondingly, baricitinib is proposed for trial in SARS-CoV-2 acute respiratory disease patients to minimize the viral entry and related inflammation [4].

Baricitinib administration results in inhibition of IL-6 stimulated STAT3 phosphorylation. It was used as a monotherapy and/or in combination with methotrexate, 2 mg, and 4 mg once daily for the treatment of moderate to severe rheumatoid arthritis in adult patients who are intolerant to one or more DMARDs (disease-modifying anti-rheumatic drugs) after approval by EU [5]. Following oral administration peak plasma concentration is reached approximately at 1 hour. The total half-life of the drug is approximately 12 hours [6].

Target Directed Drug Discovery:

Rheumatoid arthritis (RA) is a common, systemic autoimmune inflammatory disorder affecting approximately 1% of the worldwide population with high prevalence in women than men [7]. The treatment of this disease relies on the use of drugs acting against the activation of the immune system and includes anti-inflammatory and analgesic drugs, steroids, immunosuppressive agents, disease-modifying anti-rheumatic drugs (DMARDs), biologics and synthetic small molecules [8].

* *Corresponding author*. Tel.: +91 7093777360.
E-mail address: rehimamohammed07@gmail.com

The Janus kinase inhibitors (JAKi) or (Jakinibs) are among those synthetic small molecules that prevent the activation of JAKs and are cytosolic enzymes that play an important role in activation of the inflammatory cascade in immune cells [9]. The name "JAK" was taken from the two-faced Roman God of gates, "Janus" (Lanus in latin) since the enzyme have two near-identical phosphate-transferring parts: One part manifests the kinase activity while the other part modulates the kinase activity of the first reversibly [10].

Our knowledge of existence of JAK/STAT pathway is < 3 decades old. JAK1and JAK2 receptors were identified in 1989, and the first member of JAK family of proteins was cloned and synthesized in 1990. The gene was given a name TYK2, and draws the interest of scientists due to a "kinase-like" domain next to the common protein tyrosine kinase domain. The inhibition of JAKs appeared to be a promising strategy in autoimmune diseases Due to their significant role in the immune response and their connection with several cytokine receptors [11].

JAKi blocks the specific adenosine triphosphate (ATP)-binding site by interfering in the JAK-Signal Transducer and Activator of Transcription (STAT) intracellular signaling cascade which will results the activation of immune cells and their progression towards a pro-inflammatory phase [12]. Baricitinib and tofacitinib are the first generation JAKi (jak inhibitors) which are commonly active against JAK 1, JAK 2 and JAK 3 enzymes. Whereas the second generation JAKi filgotinib, peficitinib, upadacitinib, decernotinib, itacitinib and others have been developed to increase therapeutic efficacy [13].

The first generation ATP-competitive JAK inhibitors Baricitinib and tofacitinib target the JH1 (jak homology) tyrosine kinase domain by interacting with the active conformational site of the ATP-binding pocket. Next-generation JAKi have been developed in a way they have a selective affinity for one particular JAK enzyme, in order to reduce undesirable adverse effects with high clinical efficacy.

Some patients infected with COVID-19 would suddenly worsen and developed acute respiratory distress syndrome (ARDS), and then shock, tissue perfusion disorders in the later stage, eventually die from multiple organ failure, and this was mainly caused by cytokine storm [14]. High levels of cytokine signaling from clinically severe phase of COVID-19, signals through the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway [15]. To reduce the death rate of COVID-19, the cytokine storm needs to be blocked and anti-inflammation therapy should be initiated. cytokine storm was controlled by using large doses of glucocorticoid in Previous therapies [16]. However, this may result complications and slows down the clearance of the virus. Therefore, the use of drugs targeted at Janus Kinases will be effective in improving disease severity by limiting the hypercytokinemia (elevated level of various cytokines in the blood) and a systemic inflammatory response called cytokine release syndrome (CRS) seen in patients having COVID-19 [17].

Receptor-mediated endocytosis or also called clathrin-mediated endocytosis is the most common pathway for virus entry into the cells [18]. Recently, angiotensin-converting enzyme II (ACE2), which is an important cell surface protein has been identified for SARS-CoV-2 in humans as well as animals [19]. it has several regulators from which the two important regulators, AP2-associated protein kinase-1 (AAK1) and cyclin G-associated kinase (GAK), mediate clathrin-dependent endocytosis and the JAKi Baricitinib was expected to have a high binding affinity to AAK1 and GAK and interrupt the passage and intracellular assembly of SARS-CoV-2 into the target cell. Thus reduces the viral entry and the associated inflammation resulting in inhibition of several cytokines involved in the cytokine storm in severe cases of COVID-19 [20].

Pharmacokinetic factors and Pharmacodynamics:

Tetracycline is readily absorbed, such as doxycycline, and is bound to the plasma at various degrees. Doxycycline is completely absorbed by oral administration in the stomach and proximal small bowel. After administration, it forms complexes with the metal ion in food and free form of the drug [5, 8].

- Absorption: Doxycycline after oral administration is completely absorbed. It is highly lipid-soluble and has a poor calcium-binding affinity.
- Distribution volume: 0.7 L/kg
- Protein binding: greater than 90 %
- Metabolism: liver, bile-concentrated gastrointestinal tract.
- Elimination route: The active and unchanged drug primarily includes urine and feces. In 92 hours, between 40 percent and 60 percent of the dose administered can be accounted for in the urine, and about 30 percent can be accounted for in the feces.
- Half-life: 16.33 hr. (± 4.53 SD) [20].

Clinical development:

Various pharmacokinetic and pharmacodynamic models were developed to find out the concentration-time profiles and dose/exposure-response relationships for the key efficacy parameters of baricitinib [21]. This includes a proportion of patients achieving American College of Rheumatology 20% (ACR20), 50% (ACR50), or 70% (ACR70) response through 24 weeks of treatment with the drug. An ACR20/50/70 response is described as a reduction of ⩾20%, ⩾50%, and ⩾70%, respectively, in the number of tender and swollen joints and in at least three of the following ACR core measures: patient's pain assessment, physician's and patient's global assessment of disease, physical function as assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the level of acute-phase reactants: erythrocyte sedimentation rate or C-reactive protein (Felson DT).

A 24-weeks randomized phase IIb study was conducted with patients given daily doses of placebo or 1, 2, 4, or 8 mg baricitinib for 12 weeks. And an additional 12 weeks continued blinded treatment of 2, 4, and 8 mg baricitinib. Patients allotted to placebo or 1 mg baricitinib were re-allotted to 2 mg twice daily or 4 mg once daily between 12-24 weeks. The terminal point was the proportion of patients in the combined 4 and 8 mg groups achieving an American College of Rheumatology 20% (ACR20) response versus placebo at week 12. Notably, in the combined baricitinib 4 and 8 mg groups more patients achieved an ACR20 response at the 12th week compared to placebo. Significant differences versus placebo were also observed at 12th week, in patients achieving ACR50, ACR70 and remission as measured by Disease Activity Score for 28-joint counts, Clinical Disease Activity Index and Simplified Disease Activity Index. An improve in all measures through 24 weeks was observed in patients receiving 2, 4, or 8 mg of baricitinib. And the drug was well tolerated with no unexpected safety findings through week 24 [22].

In 52-week double-blind phase 3 placebo-controlled study, 290 patients with moderately to severely active RA and inadequate response to MTX were randomly assigned 1:1 to placebo or baricitinib 4-mg once daily. At week 12 more patients achieved ACR20 response with baricitinib compared to placebo. Similarly at week 12 Significant improvements were seen in Health Assessment Questionnaire-Disability Index (HAQ-DI), DAS28-hsCRP, morning joint stiffness, worst joint pain and tiredness in

the baricitinib group than with placebo. Through week 24, rates of adverse events emerged from treatment including infections were higher for baricitinib compared to placebo, while serious adverse event rates were similar between baricitinib and placebo. Therefore, in patients with RA who had an inadequate response to MTX, baricitinib was associated with significant clinical improvements as compared with placebo [23].

Current Commercialization Status:

Baricitinib an oral, selective JAK1&2 inhibitor with moderate activity against TYK2 and Tofacitinib which is a selective JAK1&3 inhibitor with less activity against JAK2 and TYK2 go through extensive phase III clinical trials in RA and exhibited satisfactory and continuous improvements in disease activity, function and patient-reported outcomes as well as disease treatment modification. Baricitinib has also been shown dominance against adalimumab in a cohort of MTX-IR patients, achieving a new milestone in drug development for RA [24]. Such features of baricitinib have led to the approval of the drug for RA in more than 40 countries, including by the European Medicines Agency (EMA) and NICE; however, FDA rejected its approval by requesting further clinical safety data due to concerns regarding the increased risk of venous thromboembolism at that time.

In February 2017, baricitinib was approved in the EU, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded adequately to, or in patients who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs) as a monotherapy or in combination with methotrexate, 4 mg, and 2 mg once daily [25]. On May 31, 2018, baricitinib (2 mg tablets) has been approved for treatment of rheumatoid arthritis by FDA. The drug is developed by the American pharmaceutical company Eli Lilly and Incyte Corporation under the brand name Olumiant [26].

Conclusion

Janus kinase (JAK) inhibitors (JAKinibs), a novel group of oral small molecule inhibitors, like baricitinb are not only used for the treatment of rheumatoid arthritis (RA) but also atopic dermatitis and active systemic lupus erythematosus as well as covid 19 with good efficacy and safety records. JAKinibs perform their function via competitive inhibition of the ATP binding site on JH1 (kinase domain). Nowadays a number of Jakinibs are in clinical trials and new compounds that are more selective for Janus kinase 1 or Janus kinase 3 are under investigation.

Considering the potential for increased lung injury with corticosteroid use in patients with COVID - 19, JAK - STAT inhibitors were theorized to have an effect on the hyper inflammatory state that occurs in COVID - 19. Baricitinib also prevents viral entry, assembly, and viral infection by inhibiting AAK1 activity. According to recent reports Baricitinib is being further studied as an ideal drug for COVID - 19, this is done using various invitro and *in-silico* studies.

Acknowledgements

Authors are thankful to the Principal, K L College of Pharmacy, KLEF, Guntur, India, for providing necessary facilities and actions towards the fruitful completion of this work.

Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

References

1. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nature Reviews Drug Discovery. 2017;17(1):78. doi:10.1038/nrd.2017.267
2. Taylor PC. Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis. Rheumatology (Oxford).2019 Feb 1;58(Suppl 1):i17-i26. doi: 10.1093/rheumatology/key225. PMID: 30806707; PMCID: PMC6390878.
3. Zhang X, Zhang Y, Qiao W, Zhang J, Qi Z. Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19. Int Immunopharmacol. 2020; 86: 106749. doi:10.1016/j.intimp.2020.106749
4. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. J Infect. 2020;81(2):318-356. doi:10.1016/j.jinf.2020.04.017
5. Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, Zerbini CA, Gurbuz S, Dickson C, de Bono S, Schlichting D, Beattie S, Kuo WL, Rooney T, Macias W, Takeuchi T. Baricitinib, Methotrexate, or Combination in Patients with Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. Arthritis Rheumatol. 2017 Mar;69(3):506-517. doi: 10.1002/art.39953. PMID: 27723271; PMCID: PMC5347954.
6. Shi JG, Chen X, Lee F, Emm T, Scherle PA, Lo Y, Punwani N, Williams WV, Yeleswaram S. The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. J Clin Pharmacol. 2014 Dec;54(12):1354-61. doi: 10.1002/jcph.354. PMID: 24965573.
7. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res. 2018;6:15. Published 2018 Apr 27. doi:10.1038/s41413-018-0016-9
8. Benjamin O, Bansal P, Goyal A, et al. Disease Modifying Anti-Rheumatic Drugs (DMARD) [Updated 2021 Jul 6].
9. Lin CM, Cooles FA, Isaacs JD. Basic Mechanisms of JAK Inhibition. Mediterr J Rheumatol. 2020;31(Suppl 1):100-104. Published 2020 Jun 11. doi:10.31138/mjr.31.1.100
10. Babon JJ, Lucet IS, Murphy JM, Nicola NA, Varghese LN. The molecular regulation of Janus kinase (JAK) activation. Biochem J. 2014;462(1):1-13. doi:10.1042/BJ20140712
11. Kiu H, Nicholson SE. Biology and significance of the JAK/STAT signalling pathways. Growth Factors. 2012;30(2):88-106. doi:10.3109/08977194.2012.660936
12. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT Signaling as a Target for Inflammatory and Autoimmune Diseases: Current and Future Prospects [published correction appears in Drugs. 2017 May;77(8):939] [published correction appears in Drugs. 2017 Jun 12:]. Drugs. 2017;77(5):521-546. doi:10.1007/s40265-017-0701-9
13. Angelini J, Talotta R, Roncato R, Fornasier G, Barbiero G, Dal Cin L, Brancati S, Scaglione F. JAK-Inhibitors for the Treatment of Rheumatoid Arthritis: A Focus on the Present and an Outlook

on the Future. Biomolecules. 2020 Jul 5;10(7):1002. doi: 10.3390/biom10071002. PMID: 32635659; PMCID: PMC7408575.

14. Basu-Ray I, Almaddah Nk, Adeboye A, et al. Cardiac Manifestations of Coronavirus (COVID-19) [Updated 2021 May 19].
15. Luo W, Li YX, Jiang LJ, Chen Q, Wang T, Ye DW. Targeting JAK-STAT Signaling to Control Cytokine Release Syndrome in COVID-19. Trends Pharmacol Sci. 2020;41(8):531-543. doi:10.1016/j.tips.2020.06.007
16. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin Immunol. 2020;214:108393. doi:10.1016/j.clim.2020.108393
17. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607-613. doi:10.1016/j.jinf.2020.03.037
18. Cossart P, Helenius A. Endocytosis of viruses and bacteria. Cold Spring Harb Perspect Biol. 2014;6(8):a016972. Published 2014 Aug 1. doi:10.1101/cshperspect.a016972
19. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. Circ Res. 2020;126(10):1456-1474. doi:10.1161/CIRCRESAHA.120.317015
20. Pillaiyar T, Laufer S. Kinases as Potential Therapeutic Targets for Anti-coronaviral Therapy [published online ahead of print, 2021 Jun 3]. J Med Chem. 2021;acs.jmedchem.1c00335. doi:10.1021/acs.jmedchem.1c00335
21. Zhang X, Chua L, Ernest C 2nd, Macias W, Rooney T, Tham LS. Dose/Exposure-Response Modeling to Support Dosing Recommendation for Phase III Development of Baricitinib in Patients with Rheumatoid Arthritis. CPT Pharmacometrics Syst Pharmacol. 2017;6(12):804-813. doi:10.1002/psp4.12251
22. Pope J, Sawant R, Tundia N, Du EX, Qi CZ, Song Y, Tang P, Betts KA. Comparative Efficacy of JAK Inhibitors for Moderate-To-Severe Rheumatoid Arthritis: A Network Meta-Analysis. Adv Ther. 2020 May;37(5):2356-2372. doi: 10.1007/s12325-020-01303-3. Epub 2020 Apr 15. PMID: 32297280; PMCID: PMC7467453.
23. Smolen JS, Xie L, Jia B, Taylor PC, Burmester G, Tanaka Y, Elias A, Cardoso A, Ortmann R, Walls C, Dougados M. Efficacy of baricitinib in patients with moderate-to-severe rheumatoid arthritis with 3 years of treatment: results from a long-term study. Rheumatology (Oxford). 2021 May 14;60(5):2256-2266. doi: 10.1093/rheumatology/keaa576. PMID: 33200220; PMCID: PMC8121442.
24. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, Yakushin S, Ishii T, Emoto K, Beattie S, Arora V, Gaich C, Rooney T, Schlichting D, Macias WL, de Bono S, Tanaka Y. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. N Engl J Med. 2017 Feb 16;376(7):652-662. doi: 10.1056/NEJMoa1608345. PMID: 28199814.
25. Wu ZP, Zhang P, Bai JZ, Liang Y, He JS, Wang JC. Efficacy and safety of baricitinib for active rheumatoid arthritis in patients with an inadequate response to conventional synthetic or biological disease-modifying anti-rheumatic drugs: A meta-analysis of randomized controlled trials. Exp Ther Med. 2018;16(3):2449-2459. doi:10.3892/etm.2018.6495
26. Markham A. Baricitinib: First Global Approval. Drugs. 2017 Apr;77(6):697-704. doi: 10.1007/s40265-017-0723-3. PMID: 28290136.