Drug Corner

Baricitinib : Delineating a New Treatment Option in COVID-19

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The later phase of COVID-19 in humans is characterized by declining viral duplication and may be associated with an boisterous hyperinflammatory response in a minority of subjects. This occurs due to dysregulated systemic immune over-activation, which is described as Cytokine Release Storm (CRS). CRS is one of the causative factors leading to development of Acute Respiratory Distress Syndrome (ARDS) and it also leads to organ failure in severe COVID-19 patients. Thus, it is of utmost importance to halt the progression of CRS rapidly and effectively. One of the channels involved in the inflammatory cascade is the Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) signalling pathway. This makes JAK inhibitors (JAK-i) a potential and powerful therapeutic approach in COVID-19 patients[1]. Baricitinib (C16H17N7O2S) is a reversible Janus-Associated Kinase (JAK) inhibitor (JAK1/JAK2) and is a tiny molecule. More than 65 nations have licenced it for the treatment of individuals with moderate to severe Rheumatoid Arthritis (RA) and the USFDA and DCGI have now approved it for emergency use in COVID-19 patients. It exerts its benefits as an immunomodulatory drug by interrupting the signalling of multiple cytokines. It might exhibit an antiviral effect by targeting the factors of the human cell that help in the endocytosis of the virus. However, Baricitinib can lead to reoccurrence of acute infections and might increase the chance of thromboembolic events in patients of COVID-19. Furthermore, one needs to be vigilant with the renal functions (measured with the eGFR), Absolute Lymphocyte Count (ALC), Absolute Neutrophil Count (ANC) and platelet count while administering Baricitinib[2]. This article reviews the available data on Baricitinib with a keen focus on anti-cytokine and anti-viral action, pharmacological profile and current clinical evidence in COVID-19.

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Key words **: Baricitinib, JAKi, COVID-19, severe acute respiratory syndrome, cytokine release syndrome.**

Introduction and Current Global COVID-19 Scenario :

In December of 2019, a seafood wholesale market in Wuhan, China, discovered a group of patients who developed idiopathic pneumonia. Later, by sample sequencing of these patients, a hitherto undescribed beta-corona virus was discovered. Human airway epithelial cells were used to isolate a Novel Coronavirus, which was later designated as SARS-CoV-2. On 11 March, 2020, the World Health Organization declared the disease as pandemic and it continues to create havoc across many countries. It has affected more than 170 million people in the world, with nearly 30 lakhs dying of the disease till date[5]. In India, the total number of cases have spiked up to 2.9 million. Mortality is also rapidly rising with the second wave and nearly 3.5 lakhs people in the country have lost their life to COVID-19[6]. The rapid increase of the cases in India and worldwide has been linked to rapid mutation and emergence of variants of the virus. The recently named variant of SARS-CoV-2 "Delta variant" which had initially impacted India, is now present in 60 countries and rapidly spreading everywhere[7].

Current treatment strategies and therapeutic gaps

Despite the fact that the COVID-19 vaccine programme continues in India and around the world, the disease burden is steadily increasing. It is critical to find effective medicines, especially in nations where vaccination rates are low. Because of the pandemic's sudden outbreak, timebound discovery of new medications is challenging. As a result, repurposing of current medications to manage COVID-19 is an appealing concept, especially the drugs which are already approved for other indications, since they have well-established safety profiles. The central data repository, called the CORONA project, which was launched in the year 2020, has the data of 443

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medications tested on 34,000 patients. There are only four drugs in the database (Baricitinib, Remdesivir, Tocilizumab and Dexamethasone) ranked as grade A (shown to be effective)[8]. Baricitinib is one such repurposed drug that is effective in combination with Remdesivir in hospitalized COVID-19 patients requiring additional oxygen, invasive mechanical ventilation or extracorporeal membrane oxygenation[4] and deserves special mention as one of the newest addition to the COVID-19 tool kit.

Baricitinib – basic pharmacology

In COVID-19 patients, there are three phases of the disease: early infection phase, inflammatory phase and the hyperinflammatory phase[9]. In the later phase, when the virus titres start declining, vigorous immune response predominates, which may lead to release of proinflammatory cytokines and chemokines. Despite the lack of clear evidence that they are involved in the pathogenesis of COVID-19, elevated serum cytokines and chemokines have been linked to ARDS and multiorgan failure in COVID-19 patients.Serum levels of proinflammatory cytokines were found to be increased in severe COVID-19 patients, including IL-2, IL-4, IL-6, IL-7,IL-10, TNF-α, and IFNγ. Amongst these, many cytokines employ one distinctive intercellular signalling pathway mediated by JAKs (Fig 1). Thus, inhibiting the cytokine storm by blocking the JAK-STAT pathway, constitutes an attractive therapeutic target in the treatment of COVID-19[12].

Baricitinib is a small reversible JAK1/JAK2 inhibitor that was first licenced for the treatment of adult patients with moderate to severe rheumatoid arthritis in over 65 countries[2]. In November, 2020, the US FDA granted an emergency use approval for Baricitinib in combination with Remdesivir to treat adults and pediatric patients aged 2 years and older requiring supplemental oxygen or invasive mechanical ventilation or Extracorporeal Membrane Oxygenation (ECM)[3]. On 1st May 2021, CDSCO also gave similar approval to use Baricitinib in suspected or laboratory confirmed COVID-19 with similar clinical profiles[4]. As illustrated in Fig 2, Baricitinib's anti-inflammatory actions are mediated via reversible JAK inhibition. It may possibly have antiviral properties since it prevents virus entry into the host cell by inhibiting AP2-associated protein kinase 1 (AAK1) and to a lesser extent, cyclin G187 associated kinase (GAK), which are responsible for virus endocytosis.

Oral formulation of Baricitinib is available. Baricitinib has an oral bioavailability of approximately 80%. Food has no significant clinical impact on the drug's bioavailability. About 50% of the drug is plasma protein bound. Around 75% of the administered amount was excreted out through urine, whereas about 20% was eliminated in the faeces[3]. Healthy volunteers have a half-life of 6 - 9 hours but rheumatoid arthritis patients have a half-life of 12 hours and those with severe renal impairment or end-stage renal disease have a half-life of 19 hours[2].

Clinical studies on Baricitinib :

The ACTT-2 (Adaptive COVID-19 Treatment Trial - 2) trial was a double-blind, randomized, placebo-controlled clinical trial conducted in hospitalized individuals with confirmed SARS-CoV-2 infection. It compared treatment with Baricitinib plus Remdesivir (n=515) to placebo plus Remdesivir (placebo group; n=518).All of the patients were given Remdesivir for 10 days and either Baricitinib or placebo for 14 days. The primary outcome was the length of time to disease recovery. Clinical state at day 15 was rated on an 8-point ordinal scale as the secondary outcome. Remdesivir was given intravenously on day 1 at a loading dose of 200 mg, then 100 mg every day until the patient was discharged from the hospital or died. Baricitinib was administered orally or via a nasogastric tube at a dose of 4 mg/day, or 2 mg/day if renal function was impaired (eGFR, 60 ml/min/1.73m^2).

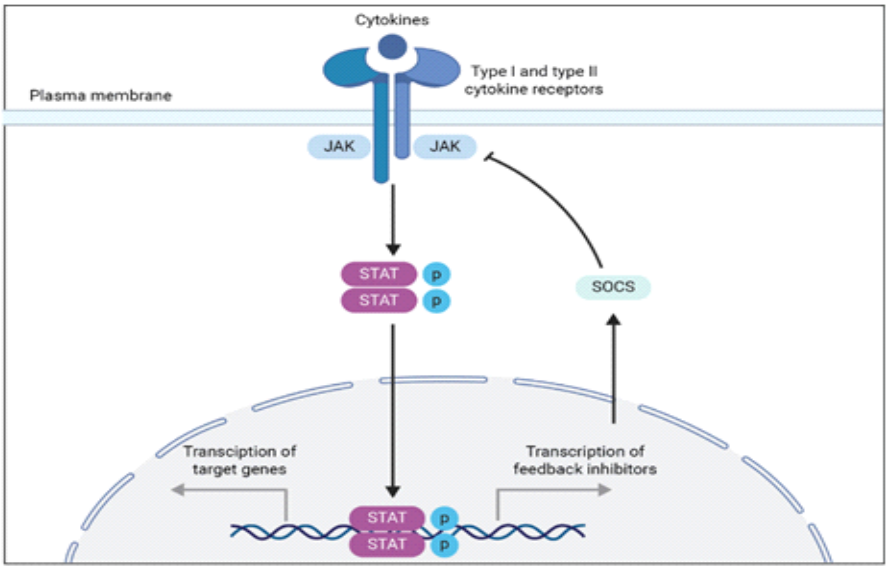


Fig 1 — JAK-STAT pathway

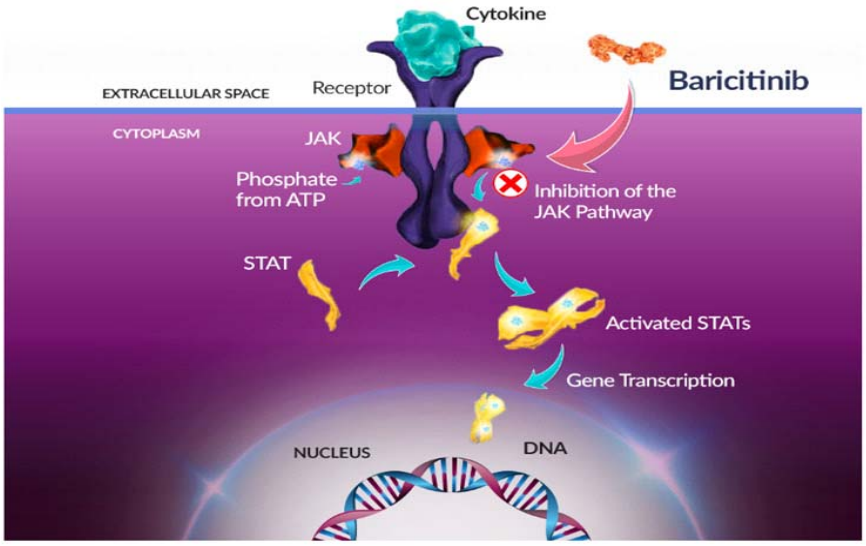


Fig 2 — Inhibition of JAK -STAT Pathway

When compared to Remdesivir alone, patients who received the combination therapy experienced substantial reduction in median time to recovery from 8 to 7 days (12.5% improvement)[p=0.047] (Fig 3). In the treatment arm, individuals on high-flow oxygen and non-invasive ventilation recovered 44 percent faster than those in the control arm (Fig 3). Patients who received Baricitinib in combination with Remdesivir had a better clinical state at Day 15 than patients who received Remdesivir alone [p=0.044]. When compared to Remdesivir alone, the proportion of patients who progressed to ventilation (non-invasive or invasive) or died by day 29 was lower in Baricitinib plus Remdesivir (23% *versus* 28%) [p=0.039]. By Day 29, the proportion of patients who died was 4.7 percent for Baricitinib in conjunction with Remdesivir *versus* 7.1 percent for Remdesivir, a 35 percent drop in the proportion of patients who died. As indicated in Fig 5, adverse events and serious adverse events were reported in 41% and 15% of patients treated with Baricitinib in combination with Remdesivir, respectively, compared to 48 percent and 20% of patients treated with Remdesivir. Infections and venous thromboembolism occurred in 6% and 4% of patients in the treatment arm, respectively, compared to 10% and 3% of individuals receiving Remdesivir. For Baricitinib-treated patients, no new safety signals have been detected[10].

In the phase 3 COV-BARRIER tiral, add on Baricitinib to Standard of Care (SoC) was compared to placebo (plus SoC) in hospitalized COVID-19 patients. The standard of treatment (SoC) at the time of study included corticosteroids, antimalarials, antivirals, and/or Azithromycin COV-BARRIER was a Global, randomized, double-blind, placebo-controlled trial which included 1525 people who did not require supplementary oxygen or high-flow oxygen. The primary endpoint was the proportion of patients who progressed to the first occurrence of noninvasive ventilation (including high flow oxygen) or invasive mechanical ventilation or death by day 28.

The primary endpoint of the study was not statistically significant but relevant only by numbers,

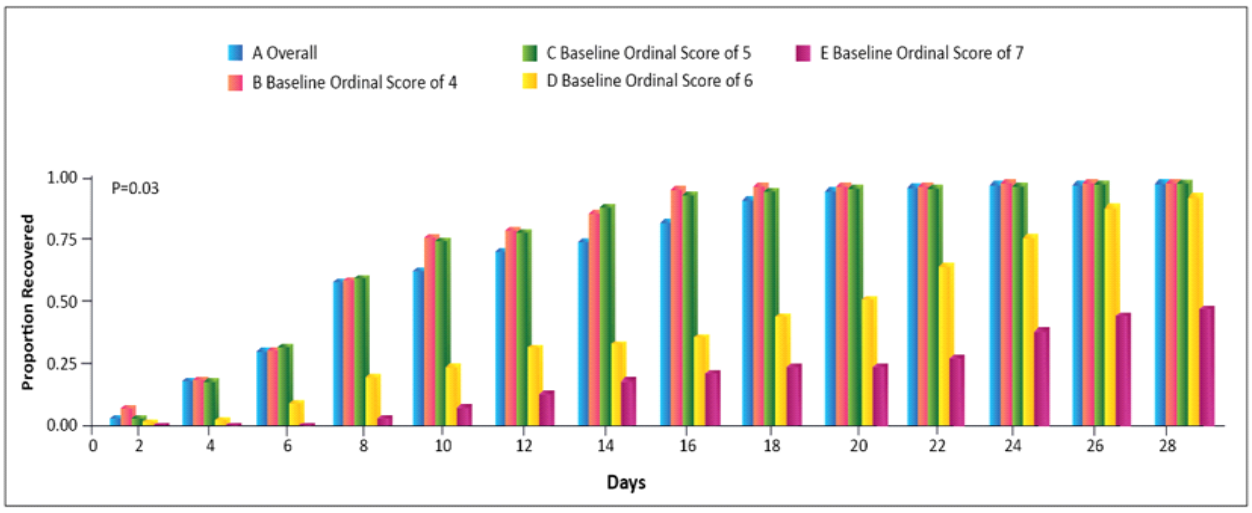
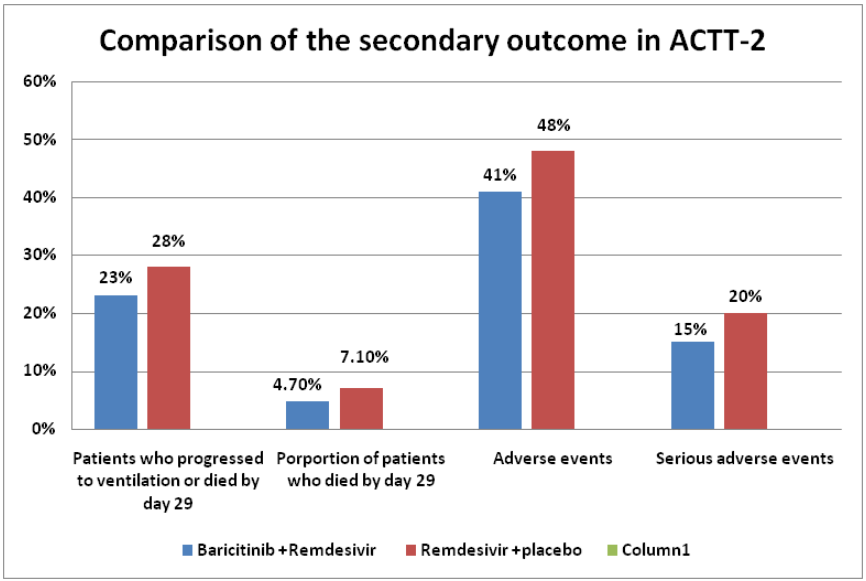


Fig 3 — Primary outcome in ACTT-2 trial (as per the ordinal score)



as seen in the results. Baricitinib-treated patients were 2.7 percent less likely than placebo to advance to ventilation or death (p=0.18). When compared to placebo, patients treated with Baricitinib had a 38 percent lower risk of death from any cause by day 28(p=0.0018). Furthermore, all baseline severity subgroups demonstrated a numerical reduction in mortality in the Baricitinib therapy arm with the highest reduction in individuals receiving noninvasive mechanical breathing at baseline (17.5% for baricitinib *versus* 29.4% for placebo; p =0.0065).There was also a decrease in mortality in the predetermined subgroups who were treated with or without corticosteroids at the start. Both of these trials were a significant step forward for Baricitinib in the treatment of COVID-19. Various further studies would be conducted to determine the molecule's safety and efficacy[11].

In an observational study, patients with moderate to severe SARS-CoV-2 pneumonia were given Lopinavir/ritonavir, HCQ, and Corticosteroids (CS group, n=50) or Corticosteroids and Baricitinib (BCT-CS group, n=62).The change in levels of oxygen saturation determined by pulse oximetry (SpO2)/FiO2 from hospitalisation to discharge was the primary end point. The percent of patients requiring supplementary oxygen at discharge and one month later were secondary end goals[14].

The results of the observational study showed that the BCT-CS group had a larger improvement in the oxygen saturation levels from hospitalisation to discharge than the CS group (p<0.001). When compared to the CS group, a much smaller proportion of patients in the BCT-CS group required supplemental oxygen at discharge (P<0.001) and at one month follow up (P=0.024). The study concluded that in moderate to severe COVID-19 pneumonia patients the combination of baricitinib plus corticosteroids was associated with significant improvement in the pulmonary function[14].

Uncertainties in knowledge :

Baricitinib is being used in rheumatoid arthritis patients since 2014; however, the emergency approval to use in COVID-19 was granted based on the results of ACTT-2 trial[3,10]. As previously discussed this trial used Baricitinib as an add on therapy to Remdesivir and compared outcomes with Remdesivir therapy. The utility of Baricitinib as a monotherapy or its benefits with agents like steroids (Dexamethasone) is less well described. The combination with agents like tocilizumab also needs exploration. There is a substantial need to determine whether patients with profiles that differ from the ACTT 2 trial's inclusion criteria would benefit from JAK inhibitor medications. Venous thromboembolic phenomena is a concern with use of Baricitinib and a specific study to address the magnitude and consequences of this in patients at high risk of thrombotic events (coronary heart disease patients, subjects with a known history of CVA, documented previous DVT etc) may be worthwhile. Need to collect data on the real-world effectiveness of Baricitinib in hospitalised patients with COVID-19 outside a rigorous trial setting may also be considered. The safety parameters would also need to be analysed in post marketing studies, once physicians start using the drug in a larger number of patients.

Positioning in practice :

Till the time more high-quality evidence emerges, the optimum strategy would be to utilise Baricitinib as a combination therapy with Remdesivir in patients having a clinical profile similar to the ACTT 2 study subjects. Thus, the physicians can use Baricitinib in combination with Remdesivir in hospitalised patient with COVID-19 pneumonia who require supplemental oxygen, non-invasive ventilation or high flow oxygen and invasive or ECM.

It can be administered orally or through nasogastric tube depending on the patient's condition. It has an advantage of 4 mg or 2 mg once daily dosing depending on the renal function of the patient. Baricitinib would

help to tackle the cytokine storm in the hospitalised patient and would prevent further worsening of the condition[3].

Future directions :

The cytokines produced by the JAK-STAT pathway that contribute to CRS suggest that blocking the route could be important in the treatment of COVID-19 patients. Various additional JAK inhibitors, such as ruxolitinib, Tofacitinib, and Fedratinib, are now being studied in COVID-19 patients in clinical trials[1] and a comparison of their relative benefits and demerits may be demystified with the publication of these studies. The molecular pathways underlying the inflammatory cascade in COVID-19 may be better brought to light with further studies providing opportunities to target hitherto undescribed pathways and mediators.

Conclusions

This review critically appraises the mechanisms of benefit and published evidences of Baricitinib in COVID-19. It further gives recommendations for positioning of baricitinib in the treatment of COVID-19 in real world setting, pending emergence of further high quality evidence. From the available evidence, Baricitinib in combination with Remdesivir offers an attractive treatment option for patients with COVID-19 and affords multiple benefits in clinical practice. The adverse event profile is favourable and contraindications are few.

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(Answers : Mediquiz 07/2021)

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