Editorial

Baricitinib set to join the Covid-19 therapeutic arsenal?

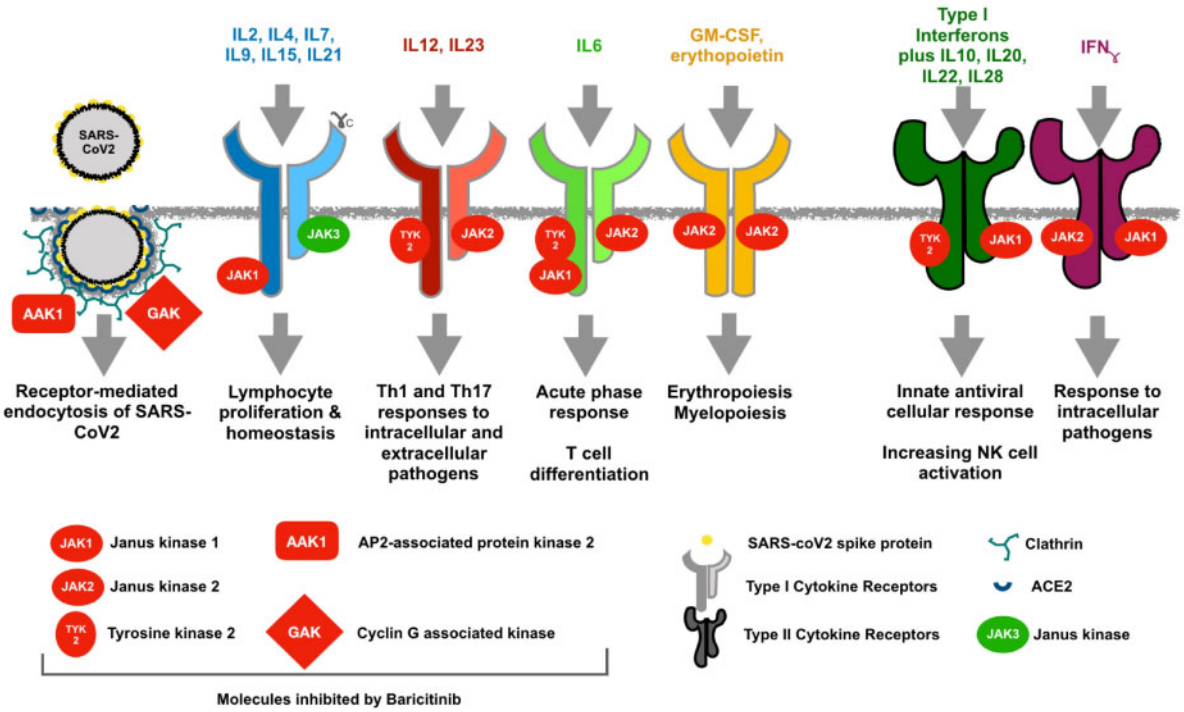
Although coronavirus disease 2019 (Covid-19) is triggered by an infectious agent, SARS-CoV2, the severe organ dysfunction, which occurs in ~15% of cases, appears to be a consequence of acute multisystem inflammatory disease. Several innate immune components exhibit exaggerated activity in severe Covid-19 [1]. Dysregulation has been reported in cytokine networks and associated acute phase and cellular anti-viral responses, the complement cascade and endothelial cell activation [2]. Despite the viral aetiology of Covid-19, immunomodulation has been explored as a therapeutic approach, supported by the evidence of benefit seen with dexamethasone in hospitalized patients [3]. Dexamethasone reduced the incidence of death by 29% in patients requiring invasive mechanical ventilation (IMV) and by 11% in patients receiving oxygen without IMV; however, mortality increased by 27% in patients not requiring respiratory support at randomization. Mortality of hospitalized patients remains high despite use of remdesivir and dexamethasone as standard. Since corticosteroids appear to be beneficial relatively late in the Covid-19 trajectory, it is important to identify the molecular pathways responsible for triggering and amplifying earlier pathological responses. Cytokine networks present several putative targets, but the hierarchy of cytokine responses in Covid-19 remains poorly understood. Trials using monoclonal antibodies that target single cytokines or their receptors have been disappointing in Covid-19, so drugs such as the Janus kinase inhibitors (JAKi), which inhibit multiple cytokine signalling pathways, offer an attractive strategy. Following the recent report of efficacy of baricitinib in a phase 3 trial [4], we examine the rationale of adding baricitinib to standard of care (SoC) in Covid-19.

JAKi interfere with the JAK–signal transducer and activator of transcription (STAT) pathways as communication highways in the immune system, transducing signals through >50 cytokine and growth factor receptors [2] (Fig. 1). Baricitinib is relatively JAK1,2-selective, and also has a direct anti-viral effect by inhibiting AP2-associated protein kinase 1 (AAK1) and cyclin G associated kinase (GAK). AAK1 and GAK are involved in triggering clathrin coating of membrane pits during endocytosis—the mechanism by which SARS-CoV2 is internalized following binding of its spike protein to angiotensin-converting enzyme 2 (ACE2) on the cell surface [5]. Given the broad range of cytokine signals transduced via JAK1/2 (Fig. 1), baricitinib could accelerate viral replication or increase risk of bacterial infection. However, a meta-analysis examining 66 159 patients with immune mediated inflammatory disease (IMID) who had long-term exposure to JAKi, revealed an increased relative risk of herpes zoster (relative risk, 1.57) but serious infection events were not increased [6]. JAKi may paradoxically enhance the anti-viral response through various mechanisms, e.g. reduction of IFN-mediated upregulation of ACE2 (cellular target for SARS-CoV2), or limitation of lymphopaenia arising from over-dominance of myelopoiesis in an excessive acute phase response [1]. Reducing activated T lymphocytes and NK cells could also limit cytotoxic tissue damage. The window of therapeutic efficacy of JAKi is likely to be during the immunopathological stage 2 of Covid-19, although some efficacy with baricitinib is possible in stage 1, due to its anti-viral activity.

The recently published phase 3 trial (ACTT2) ($n = 1033$) reported that baricitinib + remdesivir (*vs* remdesivir alone) reduced median time to recovery in all patients hospitalized with Covid-19 from 8 to 7 days (12.5% improvement; 95% CI: 6, 8; $P = 0.04$). The more clinically meaningful effect, however, was reported in the patients receiving high-flow oxygen or non-invasive ventilation at enrolment with a reduction in time to recovery from 18 to 10 days [rate ratio 1.51 (95% CI: 1.10, 2.08)] [4]. Patients in ACTT2 with milder disease at baseline (hospitalized but not requiring oxygen) did not appear to benefit from addition of baricitinib. In contrast, the RUXCOVID study ($n = 432$) failed to meet its primary end point in a similar group of patients hospitalized with Covid-19 randomized to receive ruxolitinib (also a JAK1/2 inhibitor) or placebo [7]. Important differences between RUXCOVID and ACTT2 are the direct anti-viral effects of baricitinib itself, and the use of remdesivir in ACTT2. A trial exploring efficacy of tofacitinib (a JAK1/2/3 inhibitor) is underway in Brazil.

The risks of using any pleiotropic immunomodulator, such as a JAKi, demand careful consideration of its risk–benefit balance. Reports of increased venous thromboembolism (VTE) in RA patients treated with JAKi raise a specific concern about the use of baricitinib in Covid-19. The incidence of pulmonary embolism in severe Covid-19 is ~2-fold higher than in historical cohorts of patients requiring critical care for influenza. Although an excess of VTE events has been suggested with JAKi in patients with RA, meta-analyses of randomized-controlled trial (RCT) data using JAKi in IMID showed that the pooled incidence rate ratio for VTE was not increased [8]. Overall, it appears excess risk of VTE

Fig. 1 Molecular targets of baricitinib



Baricitinib inhibits several molecules, shown in the figure in red. These include Janus kinase proteins (JAK1 and JAK2) and closely related tyrosine kinase 2 (TYK2), which transduce signals through a range of type I and type II cytokine receptors. Baricitinib thereby has a broad suppressive effect across innate and adaptive immune pathways, including the acute phase response, antiviral response to interferons and lymphocyte proliferation and differentiation. Baricitinib also has a direct antiviral effect via inhibition of angiotensin-converting enzyme 2 (ACE2)-mediated enocytosis in clarthrin-coated pits.

events is low, and the immunosuppressive effects of baricitinib might be expected to reduce immune-mediated prothrombotic signals in Covid-19. Data from the ACTT2 study showed a similar incidence of VTE in baricitinib (4.1%) and control (3.1%) groups, with a non-significant difference of 1.0 percentage point [4]. Currently all patients in the UK with Covid-19 receive enhanced thromboprophylaxis as SoC. In the ongoing phase 4 drug repurposing trial: TACTIC-R (baricitinib *vs* UK SoC), thromboembolic events are being captured as adverse events of special interest [9] and, in the baricitinib arm, are a trigger for cessation of therapy. Further data are anticipated from a phase 3 trial: COV-BARRIER (baricitinib *vs* placebo).

The theoretical benefits of baricitinib in Covid-19 are supported by emerging trial data and no new safety signal has emerged. The window of greatest benefit appears to be in patients requiring hospitalization but not critical care. This contrasts with the window of benefit for dexamethasone, which appears maximal in patients requiring IMV. Addition of baricitinib to the UK SoC is likely to reduce the length of stay of patients and to reduce pressure on ICUs. Ongoing trials should clarify the efficacy of baricitinib alone (COV-BARRIER) or added to dexamethasone as SoC (TACTIC-R). Design of future studies to determine the optimal use baricitinib, dexamethasone and other immunomodulators in Covid-19 will depend on improved patient risk stratification (including genotyping) [10], the impact of the international vaccine roll-out and the longer-term burden of Covid-19.

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