RECOVERY
Randomised Evaluation of COVID-19 Therapy

Intervention

Baricitinib 4mg once daily by mouth or nasogastric tube for 10 days or until discharge (whichever is sooner). Dose adjustment may be needed in renal impairment and for concomitant medications as below.

Summary of information on baricitinib in COVID-19

Baricitinib is an immunosuppressant that inhibits Janus kinase (JAK) 1/2 and is licensed for the treatment of rheumatoid arthritis and atopic dermatitis. JAK 1/2 inhibition prevents activation of the JAK-STAT pathway, which mediates the effect of several cytokines elevated in severe COVID-19, including interleukin-6[1]. Baricitinib also inhibits tyrosine kinase 2, another JAK that has been implicated as a mediator of inflammatory organ damage in a recent study of genetic susceptibility to severe COVID-19[2].

In the Adaptive COVID-19 Treatment Trial-2 (ACTT-2), baricitinib appeared to improve time to recovery among hospitalised patients with COVID-19[3]. However, the use of glucocorticoids was avoided in the trial, and it was not large enough to detect differences in mortality, so further randomised evidence is needed to establish the value of baricitinib in current clinical practice.

Potential harm

Baricitinib, like other JAK inhibitors, might increase the risk of venous thromboembolism (VTE)[4] when used as long-term therapy for rheumatoid arthritis, although no significant excess was seen among hospitalised COVID-19 patients in ACTT-2, with VTE occurring in 21/515 (4.1%) patients on baricitinib versus 16/518 (3.1%) on placebo. All participants in RECOVERY should receive VTE prophylaxis as clinically indicated, and the short duration of therapy (maximum 10 days) reduces any risk further. All VTE events are captured on the study Follow-up form.

Baricitinib moderately increases the risk of infection (primarily herpes zoster infection) so should be used with caution in patients with active serious infections other than COVID-19[5]. Diverticulitis has also been reported with baricitinib so should be considered in participants receiving baricitinib complaining of abdominal symptoms.

Frequently asked questions

1. ***What are the contraindications to baricitinib?***
   - eGFR <15 mL/min/1.73m^2 (including participants on dialysis/haemofiltration)
   - Neutrophil count <0.5 x 10^9/L
   - Active TB infection
   - Pregnancy or breastfeeding (a negative pregnancy test is required before randomising women of child-bearing potential)

2. ***Does baricitinib need dose adjustment with renal impairment?***
   Yes.
   - eGFR 30-59 mL/min/1.73m^2: 2 mg once daily
   - eGFR 15-29 mL/min/1.73m^2: 2 mg on alternate days

- eGFR <15 mL/min/1.73m^2: contraindicated

3. ***Are there any important drug interactions?***
   Only with probenecid, in which case the dose of baricitinib should be halved.

4. ***Can tocilizumab (or other IL-6 antagonists) be used in patients in the baricitinib arm of RECOVERY?***
   Yes. Tocilizumab provides high IL-6 receptor occupancy and therefore very effective inhibition of IL-6 signalling. The addition of baricitinib would likely provide little or no additional inhibition of IL-6 mediated inflammation. However, baricitinib inhibits the signalling of a much wider range of cytokines and might therefore provide additional benefits. Following the release of the RECOVERY tocilizumab results, the Steering Committee modified the trial protocol to allow these agents to be used together.

5. ***Is venous thromboembolism a contraindication to baricitinib?***
   No, it is left to the responsible clinician to balance the possible benefits and harm of baricitinib in this situation. The effect of baricitinib on VTE in COVID-19 is unknown. It could be detrimental, given the small excess risk of VTE seen in patients on long term treatment, but could also be beneficial, given that thrombosis in COVID-19 may be primarily driven by inflammation[6,7].

6. ***Is a pregnancy test required if a woman denies she could be pregnant?***
   A negative pregnancy test during the current admission is required for all women who are post-menarcheal and pre-menopausal and who are capable of becoming pregnant, including those using contraception.

7. **Can parenteral routes be used?**
   No.

References

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