

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Influenza Immune Modulation Domain (IM Flu)



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CCCTG
Canadian Critical Care
Trials Group



GLOBAL COALITION
FOR ADAPTIVE RESEARCH™



REMAP-CAP
JAPAN



National University
Hospital

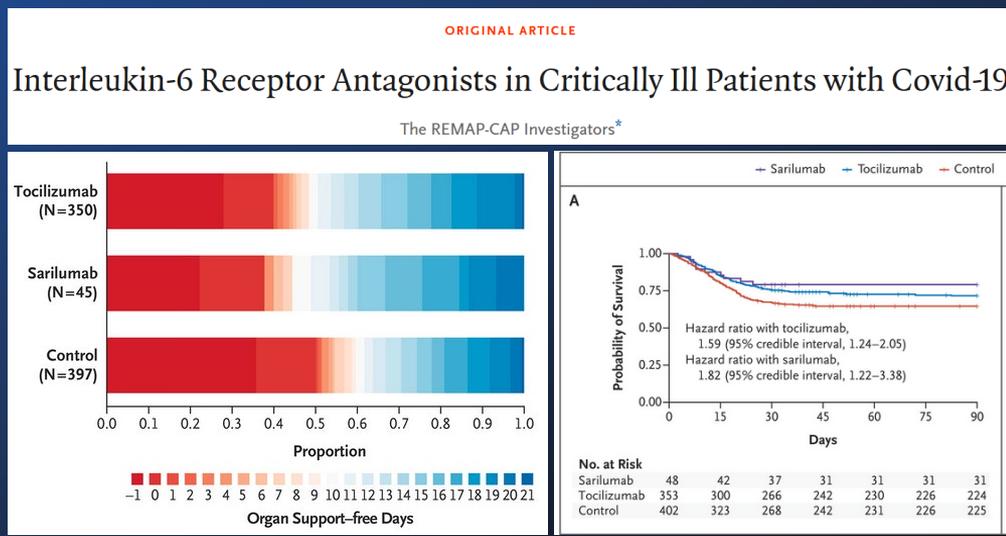
- Immune modulation with tocilizumab and baricitinib is effective in severe COVID-19
- There are similarities in the immune response in severe COVID-19 and severe influenza
- Interleukin-6 (IL-6) is a key cytokine and levels are elevated in both severe COVID-19 and severe influenza
- In influenza:
 - High IL-6 concentrations were associated with disease severity and mortality and inversely associated with arterial oxygen levels in hospitalized influenza patients

Available interventions:

- No Immune Modulation
- Tocilizumab
- Baricitinib

Background: Tocilizumab

- Interleukin-6 receptor antagonist
- Licensed for use in rheumatological conditions and for COVID-19
- Studied in REMAP-CAP ('IM1' COVID-19 Immune Modulation Domain) alongside another IL-6RA sarilumab

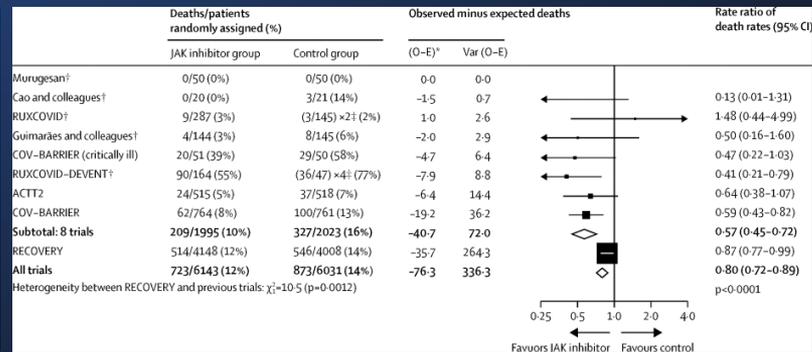
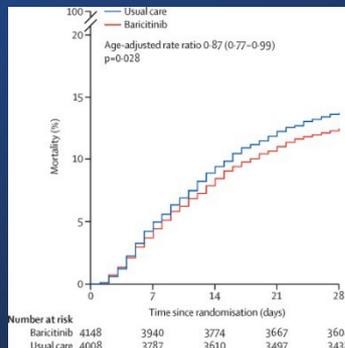


Background: Baricitinib

- Oral/enteral selective JAK1/JAK2 inhibitor
- Widely used for autoimmune and atopic diseases
- Inhibits the intracellular signaling of cytokines known to be elevated in severe influenza (including IL-6)
- Effective in severe COVID-19

Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis

RECOVERY Collaborative Group*



Does treatment with tocilizumab or baricitinib,
improve outcomes for critically ill adults with
severe influenza?

Inclusion Criteria:

- Platform eligible
- Severe state (receiving organ failure support)
- Influenza virus infection confirmed by microbiological testing.
- In the opinion of the treating clinician, the primary contributor to the patient's Severe Illness is a respiratory tract infection (e.g. not unwell with trauma and happen to have influenza)

Domain Exclusion Criteria:

- SARS-CoV-2 infection has been confirmed by microbiological testing
- Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization
- A neutrophil count $<1.0 \times 10^9 / L$
- Confirmed or strongly-suspected active mycobacterial infection or invasive fungal infection
- Patient has already received any dose of one or more of tocilizumab (or another IL-6 receptor antagonist) or baricitinib (or another JAK inhibitor) during this hospitalization or is on long-term therapy with any of these agents prior to this hospital admission.
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

Intervention Exclusion Criteria:

- Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent.
- Known or suspected pregnancy is an exclusion for Baricitinib.
 - Whether known or suspected pregnancy results in exclusion from the tocilizumab intervention depends on local approvals
- An ALT or an AST that is $>5x$ the upper limit of normal is an exclusion for tocilizumab
- A platelet count $< 50 \times 10^9 / L$ is an exclusion for tocilizumab
- A baseline eGFR $< 15 \text{ mL/min/1.73m}^2$ and/or receipt of renal replacement therapy (including long-term renal replacement therapy) at baseline is an exclusion from Baricitinib

Randomization with delayed reveal



- In patients with influenza test results pending, can randomize with 'Delayed Reveal' when test results are available.

No Influenza Immune Modulation Intervention



- Patients assigned to this intervention are not to receive any additional targeted immune modulation therapy until the end of study day 28
- Corticosteroids can be administered, either by enrolment in the Corticosteroid Domain of REMAP-CAP or as determined by the treating clinician

Adult dosing:

- Tocilizumab will be administered as a single dose of 8mg/kg based with the total dose not exceeding 800mg
- Given as an infusion via a central or peripheral line over a one-hour period

Pediatric dosing:

- For children weighing ≥ 30 kg adult dosing will be used (single dose of 8mg/kg based with the total dose not exceeding 800mg)
- For children weighing < 30 kg tocilizumab will be administered as a single dose of 12mg/kg
- Given as an infusion via a central or peripheral line over a one-hour period

Adult dosing:

- Baricitinib will be administered enterally at a dose of:
 - 4 mg once daily if the eGFR is ≥ 60
 - 2 mg once daily if the eGFR is ≥ 30 and < 60
 - 1 mg once daily if the eGFR is ≥ 15 and < 30
 - Dose withheld if the eGFR is < 15 mL/min or if the patient is receiving renal replacement therapy
- Cease baricitinib after 10 days or hospital discharge, whichever occurs first

Pediatric (≥ 9 years) dosing:

- Baricitinib will be administered enterally at a dose of:
 - 4 mg once daily if the eGFR is ≥ 60
 - 2 mg once daily if the eGFR is ≥ 30 and < 60
 - 1 mg once daily if the eGFR is ≥ 15 and < 30
 - Dose withheld if the eGFR is < 15 mL/min or if the patient is receiving renal replacement therapy
- Cease baricitinib after 10 days or hospital discharge, whichever occurs first

Pediatric (< 9 years) dosing:

- Baricitinib will be administered enterally at a dose of:
 - 2 mg once daily if the eGFR is ≥ 60
 - 1 mg once daily if the eGFR is ≥ 30 and < 60
 - Dose withheld if the eGFR is < 30 mL/min or if the patient is receiving renal replacement therapy
- Cease baricitinib after 10 days or hospital discharge, whichever occurs first

- Use hospital stock of tocilizumab and baricitinib
 - We are working with suppliers to investigate whether tocilizumab may be made available to participating sites

Primary endpoint

- The primary endpoint for this domain is the primary outcome specified in the version of the REMAP-CAP Core Protocol that is operative at the time of each adaptive analysis.

Secondary endpoints

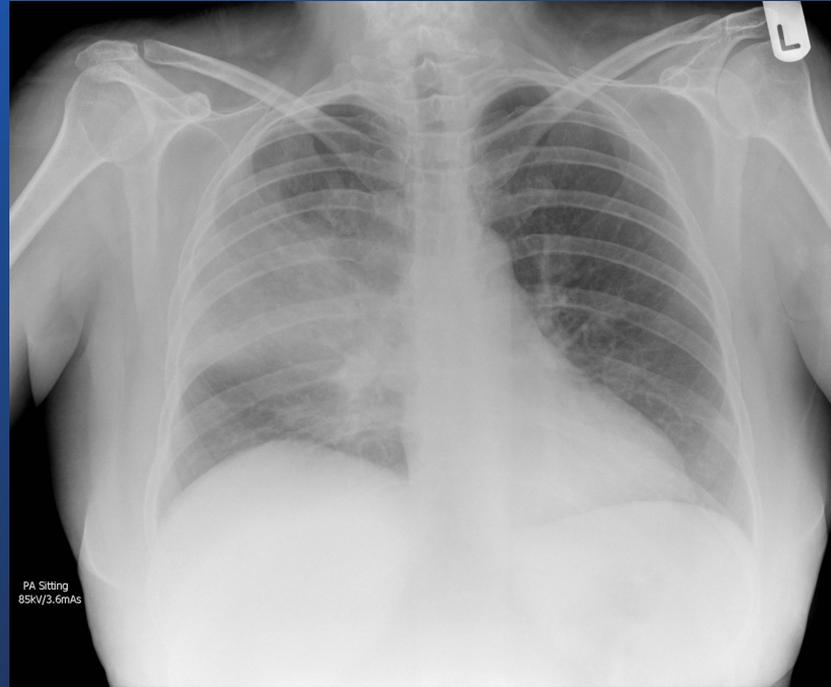
- As per core protocol with the following additional domain-specific secondary endpoints:
 - Positive blood culture for pathogenic bacteria and/or fungus during this hospitalization and more than 48 hours following randomization
 - Pulmonary aspergillosis, during this hospitalization and more than 48 hours following randomization

Domain specific adverse events



- Severe thrombocytopenia, out of keeping with clinical disease
- Severe neutropenia, out of keeping with clinical disease
- Increase in LFTs to 5x upper limit of normal
- Gastrointestinal perforation
- SAEs in the opinion of the site investigator reasonably have occurred as a consequence of study intervention or study participation

Questions?



Randomized, EMBEDDED, Multifactorial, AAdaptive PPlatform
For CCommunity-AAcquired PPneumonia