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COVID-19 — deliberating beyond steroids in 2021

To the Editor

COVID-19 has caused huge morbidity and mortality in the second peak in India in 2021. The healthcare system is stretched to its limits trying to manage the huge burden of patients in disproportionate limited health care facilities. Triaging [1] has helped manage mild cases at home, moderate at health care centres so that tertiary hospitals are able to treat the severe cases requiring oxygenation or ventilatory support. However, severe cases of COVID-19 pneumonia despite oxygenation, ventilatory support and steroids [2] have poor outcome, which triggered various trials evaluating immunosuppressive drugs to improve prognosis by controlling the hyperinflammatory state. The evidence of use of these drugs is limited and based on available literature till date, the use of these drugs has been summarised in Table 1 [3–9] Although tocilizumab is an off-label drug described in Indian national guidelines, there are no official guidelines for the use of the other drugs in India leading to variability in usage. It is imperative to use these drugs under a trial mode to generate further evidence and regularise the usage. The use of these drugs should be judicious and after carefully ruling out contraindications following the concept of *primum non-nocere* i.e., first do no harm.

Conflict of interest

None declared.

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Table 1. Evidence for Immunosuppressants drugs beyond steroids for COVID-19

Name	Mechanism	When to give	When not to give	Major Trial	Remarks	Dose	Outcome	ADR
Baricitinib	TKI- JAK 1/2	Illness of any duration with $SpO_2 \leq 94\%$ or Supplemental O_2 or Mechanical ventilation	Pregnancy/lactation	ACTT-2 [3]	Most efficacious in patient on O_2 and above, receiving Remdesivir for 10 days	4 mg once a day (2 mg in deranged renal functions) for 14 days	Reduced day of recovery (10 days vs. 18 days)	Infections— respiratory and H. Zoster, Transaminitis, Prothrombotic (FDA black box warning), Hypersensitivity
Tofacitinib	TKI- JAK 1/3	No criteria specified	Underlying malignancy, lymphoproliferative disorders and active tuberculosis are usual contraindications of the drug. None have been mentioned in the trial	Hayek et al (retrospective observational study) [4]	Any admitted patient- requiring dexamethasone	5 mg twice a day	Mortality benefit	Hyperglycaemia, risk of carcinoma and prothrombotic state. However, trial found increased bleeding in tofacitinib group attributed to anticoagulation
Bevacizumab	MAB- VEGF A	$SpO_2 \leq 93\%$ or $RR \geq 30$ or P/F ratio 100–300 AND median duration- 10 days from symptom onset (maximum benefit)	Severe hepatic failure (CPS- C) Severe renal failure (GFR < 30/RTT) Uncontrolled HTN, Heart disease Coagulopathy/ active bleed Procoagulant state Major surgery/trauma in 28 days Active HIV/hepatitis Pregnancy/lactation	Pang et al. [5]		Single dose 500 mg	Rapid improvement in fever and PF ratio Vs. Standard care ($\pm$ steroids $\pm$ anticoagulants)	Hypertension, Haemorrhage, Cardiac failure, Posterior reversible encephalopathy syndrome, Thromboembolism, Infusion reaction
Itolizumab	MA-CD6 on T cell- Co-stimulation inhibition	$SpO_2 < 94\%$ or PF ratio < 200 With Ferritin > 400 or IL-6 > 4times ULN	Active/latent/inadequately treated TB Hep B/Hep C/HIV ANC < 1000 ALC < 500 Plt count < 50000	Islam et al. [6] Saavedra et al. [7]	Severe Covid-observational study- no control $SpO_2 < 94\%$ or PF ratio < 200 With Ferritin > 400 or IL6 > 4 times ULN	Three groups (Tocilizumab, Bevacizumab, Both) 1.6 mg/kg infusion after 1 week- 0.8 mg/kg	Survival benefit was found in patients receiving bevacizumab (92%) Mortality benefit	Diarrhoe, infusion related reactions

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Table 1. cont. Evidence for Immunosuppressants drugs beyond steroids for COVID-19

Name	Mechanism	When to give	When not to give	Major Trial	Remarks	Dose	Outcome	ADR
Tocilizumab	MAB -sIL-6 R	Among hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (Conditional recommendation, Low certainty of evidence)	Concern regarding interruption of treatment/relative contraindication GI symptoms suggestive of perforation Neutropenia/ thrombocytopenia Transaminitis — 5 times ULN Active infection Active malignancy	IDSA [8] and MOHFW, India [9]		8 mg/kg single dose	Infection and GI perforation Avoid if baricitinib is used	
		All criteria to be met. Severe disease Raised inflammatory markers. No response to steroids No active TB/ bacterial/fungal infection		MOHFW, India [9]		4–6 mg/kg		

ADR — adverse drug reaction; TKI — tyrosine kinase inhibitor; JAK — Janus kinase; FDA — Food and Drug Administration; MAB — monoclonal antibody; VEGF — Vascular endothelial growth factor; RR — respiratory rate; P/F — partial pressure of O₂/FIO₂; CPT — child Pugh score; GFR — glomerular filtration rate; RRT — renal replacement therapy; HTN — hypertension; HIV — human immunodeficiency virus; CD-6 — complement of differentiation; IL-6 — interleukin; ULN — upper limit of normal; TB — tuberculosis; Hep — hepatitis; ANC — absolute neutrophil count; ALC — absolute lymphocyte count; Plt — platelet; IDSA — Infectious Diseases Society of America; MOHFW — Ministry of Health and Family Welfare; GI — gastrointestinal