



Treatment of severe covid-19 with interleukin 6 receptor inhibition

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Tocilizumab and sarilumab only offer benefit in severe covid-19 when combined with corticosteroids

The use of tocilizumab or sarilumab in combination with corticosteroids has been an important development in the treatment of severe covid-19. In contrast to monoclonal antibody treatments that target circulating interleukin 6, tocilizumab and sarilumab specifically block the binding of interleukin 6 to its receptor.¹ The National Institute for Health and Care Excellence first issued guidance on using these treatments for covid-19 in April 2021, following the release of data from the RECOVERY² and REMAP-CAP³ trials.

The RECOVERY trial randomised 4116 patients with hypoxia (oxygen saturations <92%) and systemic inflammation (C reactive protein >75 mg/L) to receive either tocilizumab plus usual care or usual care alone. It found that the addition of tocilizumab reduced mortality at 28 days (rate ratio 0.85, 95% confidence interval 0.76 to 0.94), increased discharge from hospital within 28 days (rate ratio 1.22, 1.12 to 1.33), and reduced a composite endpoint of invasive mechanical ventilation or death (risk ratio 0.84, 0.77 to 0.92).² The REMAP-CAP trial randomised 803 patients who had recently (within 24 hours) commenced organ support in the intensive care unit to receive either tocilizumab plus standard care, sarilumab plus standard care, or standard care alone. It showed that the addition of tocilizumab or sarilumab increased the number of organ support-free days (odds ratio 1.64 (95% credible interval 1.25 to 2.14) and 1.76 (1.17 to 2.91), respectively) and that interleukin 6 receptor antagonism through either drug increased 90 day survival (hazard ratio 1.61, 1.25 to 2.08).³

Despite the findings of these landmark trials, some important questions remain unanswered. Firstly, given that 82% of patients receiving tocilizumab in the RECOVERY trial were simultaneously receiving corticosteroids, do interleukin 6 receptor antagonists provide mortality benefit in the absence of concurrent corticosteroid administration? Secondly, are tocilizumab and sarilumab equally efficacious in severe covid-19? In a linked *BMJ Medicine* paper (doi:10.1136/bmjmed-2022-000144), Zeraatkar and colleagues conducted a systematic review and network meta-analysis including 36 trials and 19 350 patients to help answer these questions.⁴

In their network meta-analysis, Zeraatkar and colleagues combined both direct and indirect comparisons of corticosteroids, tocilizumab, and sarilumab use for severe or critical covid-19.⁴ The scope of this study serves to increase the breadth of randomised trial data considered, thus generating

more relevant effect estimates than conventional static, pairwise meta-analysis. The researchers found that, in combination with corticosteroids, tocilizumab probably reduces mortality (odds ratio 0.79, 95% credible interval 0.70 to 0.88, moderate certainty of evidence) and sarilumab could reduce mortality (0.73, 0.58 to 0.92, low certainty of evidence). They further estimated that the effect on mortality of tocilizumab versus sarilumab might be similar when used in combination with corticosteroids (1.07, 0.86 to 1.34, low certainty of evidence). Moreover, they found no clear evidence that tocilizumab or sarilumab provided clinical benefit in the absence of concurrent corticosteroid use.

The authors used a thorough search strategy incorporating key sources of grey literature, and adopted a systematic approach to study selection and data collection. Their inclusion of four preprint reports reduced the risk of publication bias and reflects the need to continuously integrate new evidence as it emerges through the course of a pandemic.⁵ However, a potential caveat to this approach is that the data considered have not been formally peer reviewed and could be refined when eventually published.⁶ Moreover, because patients were not randomised on the basis of receiving corticosteroids, the characteristics of those patients who received corticosteroids could vary from those who did not, and any such differences might confound pooled estimates.

The authors' application of the grading of recommendations assessment, development and evaluation (GRADE) approach allows these different limitations to be weighed up and combined into an outcome specific rating of the certainty of evidence.⁷ For instance, the comparative efficacy of giving sarilumab alone versus tocilizumab alone (odds ratio 0.95, 95% credible interval 0.68 to 1.35) relies heavily on one study, the REMAP-CAP trial, contributing to its very low certainty of evidence grading. This very low sample size should be interpreted with greater caution than the effect of combined tocilizumab and corticosteroids versus corticosteroids alone (0.79, 0.70 to 0.88, moderate certainty of evidence), which is derived from many studies.

These findings reinforce previous evidence that inhibition of interleukin 6 receptors provides therapeutic benefit only when used in addition to systemic corticosteroids.^{2 3 8} In the absence of broader down-regulation of inflammation by corticosteroids,⁹ this inhibition might have neutral effects or even be harmful in some individuals. Considerable heterogeneity in the effect of interleukin 6 receptor inhibition with or without corticosteroids was observed in

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the RECOVERY trial² and has since been confirmed in a subsequent meta-analysis.⁸ Genetic data also support this finding, with evidence of such inhibition increasing levels of many pro-inflammatory cytokines¹⁰ and pneumonia risk.¹¹ Additional mechanistic studies will allow us to better understand the immunomodulatory interaction between corticosteroids and interleukin 6 receptor antagonists. Moreover, a detailed understanding of interleukin 6 receptor signalling in the context of severe covid-19 will help ensure that interleukin 6 receptor antagonists are used as efficaciously as possible in different scenarios.

In their timely study, Zeraatkar and colleagues highlight the nuanced contribution of immunomodulation in reducing covid-19 mortality. Their findings have implications for clinical practice in three important respects. Firstly, inhibitors of interleukin 6 receptors should only be used in combination with corticosteroids for the treatment of severe covid-19. Secondly, tocilizumab and sarilumab are similarly efficacious in severe covid-19 and so the recommendation that sarilumab only be used when tocilizumab is unavailable might no longer be appropriate.¹² Thirdly, immunomodulatory agents interact with one another, which has implications for emerging immunomodulatory covid-19 treatments. These emerging treatments include Janus kinase inhibitors (eg, baricitinib), which have effects that might also vary with concurrent corticosteroid use.¹³ Such interaction of immunomodulatory agents has further relevance for patients on long term immunosuppressive treatments. Further work is now required to delineate the precise nature of such interactions and their clinical implications.

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