EDITORIAL

Interleukin-6 Receptor Inhibition in Covid-19 — Cooling the Inflammatory Soup

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Viruses cannot replicate by themselves. Instead, they rely on the host for almost all their replicative functions. Similarly, many viruses are unable to cause damage without the host immune system. Because of this, two strategies can often ameliorate disease — antivirals, which block replication, and antiinflammatories, which can limit the damage induced by infection. In the lung, this latter strategy is exemplified by the treatment of *Pneumocystis jiroveci*, in which treatment with glucocorticoids reduces the severity of disease and the risk of death.[1,2] However, because blocking inflammatory pathways raises the possibility of diminishing the host response and increasing replication of the pathogen, antibiotics or antivirals are used simultaneously.

With coronavirus disease 2019 (Covid-19), the role of localized inflammation was evident early on, because severe symptoms developed in many patients late after infection, when the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load was decreasing. One of the prime candidates for mediating inflammation in Covid-19 has been interleukin-6, a cytokine produced by macrophages that induces a proinflammatory response and is often elevated in patients with Covid-19. One of the attractions of interleukin-6 is that there are already approved agents that block either the cytokine or its receptor. In fact, enthusiasm for this therapy was so high that interleukin-6 blockade was being widely used in the United States before we had any evidence of its efficacy. However, in the absence of potent antivirals to block SARS-CoV-2 replication, it was unclear whether this strategy was safe. The results of two trials now appear in the *Journal*, with apparently contradictory results.

In the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP),[3] which had an adaptive design, approximately 800 patients in need of respiratory or blood-pressure support or both were randomly assigned to placebo or a single injection of an interleukin-6 receptor blocker, tocilizumab or sarilumab. The primary outcome was a composite of in-hospital death and days free of respiratory or blood-pressure support to day 21. The group receiving an interleukin-6 receptor blocker had an in-hospital mortality of 27%, as compared with 36% in the control group, and those receiving the receptor blocker had a median of 10 to 11 organ support–free days, as compared with 0 days for controls. In COVACTA,[4] a more traditional randomized, controlled trial, 452 patients with Covid-19 (oxygen saturation, ≤93%) were randomly assigned in a 2:1 ratio to receive one dose of tocilizumab or placebo. The primary outcome was clinical status at day 28; mortality was a secondary outcome. The group receiving tocilizumab had a median clinical status of 1 (discharged or ready for discharge), and the control group had a median clinical status of 2 (out of intensive care and not receiving supplemental oxygen). Mortality was 19.7% in the tocilizumab group and 19.4% in the control group. REMAP-CAP was positive and an open-label trial; the negative COVACTA study was double-blind and placebo-controlled. It is unclear whether the open-label nature of REMAP-CAP may have affected decision making related to clinical management.

These are the latest of several trials assessing the role of interleukin-6 inhibition. Most have not found an effect on mortality.[5-9] However, a recent preprint from the RECOVERY trial showed that,

as in REMAP-CAP, treatment with tocilizumab led to lower death rates across groups with differing disease severity.[10]

How can we make sense of these disparate results? Differences among the trials include enrollment criteria, the time at which anti–interleukin-6 therapy was initiated (relative both to the time of infection and to the severity of inflammation), the primary outcome, and background care. All inflammation may not be the same: patients with severe disease at initial presentation may have a different pathogenesis than those in whom inflammatory disease develops later, which suggests that the timing of treatment may be crucial in understanding responses. Perhaps the greatest variable, however, may be the periods of time over which the trials were conducted. The baseline therapy of Covid-19 has changed and mortality appears to have fallen since the beginning of the epidemic. One particularly notable change has been that patients with severe disease, the targets of therapy in most of these trials, now almost universally receive glucocorticoids, since these drugs were shown in July 2020 to reduce mortality.[11] Only a minority of patients in the COVACTA trial were treated with glucocorticoids. Fewer in the group that received tocilizumab (19.4%) than in the group that received placebo (28.5%) also received glucocorticoids. In contrast, 93% and 82% of all patients in REMAP-CAP and the RECOVERY trial, respectively, were receiving glucocorticoid therapy.[10] Subgroup analysis in the RECOVERY trial indicated that those receiving glucocorticoids had a survival advantage,[10] which suggests a treatment interaction with interleukin-6 inhibition. Interleukin-6 blockade plus glucocorticoids, acting in different ways, may be additive or synergistic. Alternatively, the use of glucocorticoids may simply be a marker for other changes in treatment that have occurred during the course of the epidemic.

These points raise thorny issues. Is the value of interleukin-6 inhibition dependent on the timing of treatment, being beneficial only if proximate to an acute late inflammatory decompensation event? We rely on clinical trials to either endorse or reject possible interventions. But what if the results of trials change as the underlying therapies improve, a particular problem with platform trials, which always need to include contemporaneous controls? For now, we are left with evidence of benefit from interleukin-6 inhibitors, at least under some circumstances, but how to best use them remains unclear.

Disclosure forms provided by the authors are available at NEJM.org.

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