nor for medical professionals. Finally, any comparison with practices during the last World War is inappropriate.

However, if the main message is that human connection and support are the first step in providing the best possible care for suffering patients, we fully agree. Nevertheless, when very old and fragile patients consider their lives are completed and they consequently request to die peacefully, surrounded by their loved ones, this request cannot and should not be ignored but listened to, professionally explored and, after meeting the due diligence criteria, should be respected. Although we agree to disagree on some points, we thank Meier for her contribution to the ongoing debate on this matter.

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In Reply The letters from Bollen et al and Florijn and Kaptein point to the reality of suffering among people, in this case frail older adults who choose death over continued life burdened by the limitations of old age. The authors argue that the right to self-determination is in moral conflict with respect for the sanctity of life and that moral conflict is inevitable. Of course, moral principles come into conflict and, of course, there are individuals who would choose to control the timing and circumstances of their own death. I am not arguing that such a desire is immoral or unethical. I am arguing that public policy in support of such action is quite likely to have unintended consequences. The authors insist that all of these Dutch cases of physician-assisted suicide are characterized by a vital patient-physician relationship and that all these requests are voluntary and well considered. Although we hope that this is true, there is growing evidence to the contrary. The reports of these cases are all post mortem when there is strong incentive by the involved physicians to report their adherence to the rules. Similarly, the Dutch review committees that, it is claimed, despite opposing evidence, always perform a thorough post hoc assessment, are themselves without regulatory oversight. The assertion that these instances of physician-assisted suicide always follow the letter of the law and never involve family, financial, or other pressures is only that—an assertion based on hope, not on research. Given the enormous caregiving and financial burdens of caring for vulnerable people, it is naive to believe that these pressures play no role in these decisions. In fact, in 2016, 201 euthanasia deaths were reported among Dutch people with mental illness or dementia, leading one of its strongest initial proponents, a psychiatrist, to say, “...it really went off the tracks when the review committee concealed that incapacitated people were surreptitiously killed. I don’t see how we can get the genie back in the bottle. It would already mean a lot if we’d acknowledge he’s out.”

Finally, I am admonished that “comparison with practices [of euthanasia] during the last World War is inappropriate.” Perhaps the authors feel that acting on the belief that some lives are unworthy of life was a time-only human event. History (and the present, for that matter) teaches otherwise. Extreme caution is necessary when we empower physicians to take life.

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Tocilizumab in Treatment for Patients With COVID-19

To the Editor Interleukin-6 (IL-6)-related cytokine storm has been proposed as a major target for the treatment of COVID-19. Retrospective studies have shown an association between tocilizumab (an IL-6 receptor antibody) administration and reduced hospital mortality in patients with COVID-19. This has triggered more than 100 clinical trials worldwide (as reported in ClinicalTrials.gov and the EU Clinical Trials Register). Randomized clinical trials are considered the gold-standard study design for comparative effectiveness research. However, several recently published randomized trials did not show the beneficial effects of tocilizumab in patients with COVID-19. For example, Salvareni et al did not demonstrate the therapeutic effect of tocilizumab at 8 mg/kg up to a maximum of 800 mg for 126 patients hospitalized with COVID-19 pneumonia. This

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high dose has been used in these reported randomized trials and most other ongoing clinical trials. So far, the lack of beneficial effects brings into question the application of tocilizumab in the treatment of COVID-19.

Here, we suggest lowering the doses of tocilizumab to at least half, to properly regulate IL-6-related biological responses and exert the therapeutic effects of tocilizumab for COVID-19. First, in some observational studies, lower doses of tocilizumab were associated with positive outcomes. For example, Biran and colleagues² reported that 400 mg of tocilizumab was associated with reduced mortality in 764 patients with severe COVID-19 in a multicenter observational study. This dose has been reported by others with positive outcomes. Second, the serum level of IL-6 has been identified as a cytokine signature to predict COVID-19 severity and survival; however, it is significantly lower than that of cytokine release syndrome observed in patients with cancer treated with chimeric antigen receptor-modified T cells.³ Therefore, for COVID-19 treatment, it may not be necessary to use the same high dose of tocilizumab as that used for those patients. Third, IL-6 is a pleiotropic cytokine with both pro-inflammatory and anti-inflammatory properties and is also involved in antiviral responses.⁴ According to pharmacokinetic studies, lower-dose tocilizumab blocks IL-6 binding to its soluble receptor, and thus inhibits pro-inflammatory response, while high-dose tocilizumab may bind to both soluble and membrane-bound IL-6 receptors and inhibit both pro-inflammatory and anti-inflammatory pathways.⁵ Taken together, low-dose tocilizumab may be a better option to reduce IL-6-related cytokine storm and mortality in patients with COVID-19.

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To the Editor Two randomized clinical trials recently published in JAMA Internal Medicine have reported no benefit of tocilizumab treatment for patients with COVID-19.¹,² An additional weakness to the results of these trials is the lack of data documenting the efficacy of tocilizumab to fully block interleukin-6 (IL-6) signaling. C-reactive protein (CRP), with its 18-hour half-life, is an easy biomarker of IL-6 inhibitor efficacy. Unfortunately, data about CRP inhibition are lacking in the study by Salvareni et al,³ and mean values of CRP inhibition are shown for only half of the patients in eFigure 5 in the Supplement of the study by Hermine et al,⁴ indicating partial inhibition of CRP production in the control group, likely due to anti-inflammatory treatments. We have documented⁵ that the whole body IL-6 production could be high in patients with cytokine storm (>7 mg/day), that is, 500-fold higher than in cancer (median 17 μg/day, range 0.5 to >358 μg/day), which could make IL-6 signaling inhibition difficult, especially in high-risk patients with COVID-19. A mandatory requisite to accurately evaluate anti-IL-6 therapy in COVID-19 should be monitoring CRP levels every 2 days and to provide data for each patient. This is a mandatory requisite, eventually not a sufficient one. The concentration of IL-6 in the liver (inducing CRP) could be lower than that observed at the site of production. In addition, no data are available about the diffusion and concentration of tocilizumab in the lungs. A recent study⁶ points out that IL-6 concentration in bronchoalveolar lavage fluid (BALF) of patients with COVID-19 may rise until it reaches 10 ng/mL, with a ratio of BALF:plasma of IL-6 significantly higher in nonsurviving patients having acute respiratory distress syndrome than in survivors. Such huge local IL-6 concentrations could be hardly inhibited by tocilizumab since 100 μg/mL tocilizumab (usual concentrations in treated patients) cannot block IL-6 concentration higher than 1 ng/mL in vitro.⁷ Tocilizumab treatment could induce a 20-fold increase of IL-6 concentration due to lack of IL-6 consumption by cells. We also documented circulating IL-6 increase during anti-IL-6 antibody therapy.⁸ How to increase the efficacy of anti-IL-6 therapy using currently clinically available inhibitors? A mathematical modeling shows that the association of an anti-IL-6R antibody (with tocilizumab affinity) and an anti-IL-6 antibody (with siltuximab affinity) could fully block the huge IL-6 concentrations documented in patients with COVID-19, unlike a single antibody. The explanation is that targeting different steps in IL-6 signaling provides synergistic inhibition.

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To the Editor The reports from Hermine et al1 and Salvarani et al2 join other randomized clinical trials in showing little clinical benefit from interleukin-6 (IL-6) blockade with tocilizumab in the treatment of COVID-19. At first sight, these studies challenge the notion that severe COVID-19 is mediated by IL-6-driven hyperinflammation. However, we propose that before dismissing this hypothesis, there is an urgent requirement to dissect these negative results at the mechanistic level.

Despite immunomodulating the IL-6 signaling cascade, no study systematically characterized activity of the IL-6 pathway before or after tocilizumab administration, akin to measurements made of viral titres when investigating antiviral drugs. Although IL-6 and C-reactive protein levels are reported, individual cytokine measurements do not reflect complex inflammatory cascades, and circulating IL-6 is paradoxically elevated following tocilizumab administration.3 Therefore, it is imperative that we apply novel immunophenotyping approaches to measure changes in IL-6 functional activity induced by tocilizumab in COVID-19, verifying adequate pathway suppression, and enabling correlation between clinical outcomes and levels of IL-6 activity.4,5 Only by understanding tocilizumab’s mechanistic correlates of clinical activity can we more confidently determine its therapeutic role in treating COVID-19.

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Conflict of Interest Disclosures: None reported.


5. Mihara M, Kasutani K, Okazaki M, et al. Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. Int Immunopharmacol. 2005;5(12):1731-1740. doi:10.1016/j.intimp.2005.05.010

In Reply Our randomized clinical trial,1 along with several other studies as detailed by Parr,2 has demonstrated no differences in mortality at days 28 or 30 when tocilizumab was used in treatment for patients with COVID-19. Benefits of this drug in specific subpopulations of patients, particularly those more seriously ill and inflamed, cannot be excluded. Recently, early results released from the Randomised, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) international platform trial showed that tocilizumab was effective in critically ill patients.3 In an observational study4 in the Reggio Emilia area, considering 172 patients consecutively treated with tocilizumab, the percentage of patients who died after tocilizumab therapy was similar to that of patients with COVID-19 hospitalized in the same time period and not treated with tocilizumab after a follow-up of more than 1 month. However, when some of our researchers considered the subgroup of patients undergoing non-invasive ventilation, tocilizumab reduced the risk of being intubated or dying.5 Randomized clinical trials are needed to confirm these results.

We completely agree with Rossi et al that C-reactive protein (CRP) is an easy biomarker of interleukin-6 (IL-6) inhibitor efficacy and that CRP serial determinations are useful in evaluating clinical response to tocilizumab. Using general linear model analyses for repeated measures, some of our group observed that CRP serial measurements after tocilizumab therapy are useful in identifying patients developing poor outcomes.4 A similar marked reduction in CRP levels at day 3 was observed between patients intubated or who died and those with a favorable outcome at the end of follow-up.4 However, at day 7, a significant and steady decrease continued to be observed only in patients with a favorable outcome, whereas in patients who died or were intubated CRP levels increased again. The proposed association between an anti-IL-6R antibody and an anti-IL-6 antibody to provide synergistic inhibition of IL-6 signaling is intriguing, because in autoimmune conditions the increased level of free IL-6 during tocilizumab treatment closely reflects the disease activity.

We also completely agree with Bell and Pollara that there is the urgent need to elucidate the mechanism and the immu-
In Reply We thank the authors of these letters for their interest in the important topic of patients hospitalized with pneumonia and COVID-19. First, in all letters, the authors claim that tocilizumab (TCZ) is not effective or is poorly effective in patients hospitalized with COVID-19. Among the 4 published randomized clinical trials of TCZ in patients hospitalized and not requiring assisted ventilation, 2 are positive and 2 are negative. These apparent contrasting results may be explained by differences in study populations. In the trials by Stone et al3 and Salvarani et al4 (the negative trials), numbers of patients received no supplemental oxygen at baseline and the 28-day mortality rate was low (4.9%2 and 2.4%), vs 11.5% and 9.8% in our trial1 and that of Salama et al5 (the positive trials), respectively. In addition, in the study by Salvarani et al,23% of the patients in the usual care arm received TCZ as a rescue. Of note, the 2 positive randomized clinical trials included identical patients (with oxygen requirement) and showed similar results on their primary end points (ventilation or death), with hazard ratios of 0.58 (95% CI, 0.33-1.00)2 and 0.55 (95% CI, 0.33-0.93),3 respectively. Although not yet peer reviewed, the REMAP-CAP randomized clinical trial5 showed that TCZ reduced organ support-free days and decreased mortality from 35.8% to 28% (odds ratio = 1.64; 95% CI, 1.25-2.14) in patients who were critically ill. Taken together, these data suggest that TCZ could be beneficial to prevent ventilation or death in the population of patients with more severe cases of COVID-19.

Second, in their comments, Yang and Liu to lower at least half the doses of intravenous tocilizumab from 8 mg/kg to 4 mg/kg to improve its efficacy in hyperinflammation in patients with COVID-19. When intravenous tocilizumab was not available at our hospital, we used subcutaneous tocilizumab at the dose of two 162-mg vials administered simultaneously. Pharmacokinetically, this dosage is similar to 4 mg/kg intravenously. We did not observe any difference in terms of efficacy and safety between intravenous and subcutaneous tocilizumab and we also showed a similar effect on inflammatory markers. Therefore, the dosages of 8 mg/kg and 4 mg/kg intravenously could be equally effective.

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In conclusion, we agree that the question of the dose is an important issue and could be solved by a more precise monitoring of serum C-reactive protein, interleukin-6, and interleukin-6 receptor levels. The 2 other important issues for defining the role of TCZ in treatment of COVID-19 are the type of patients who may benefit from this drug (probably patients worsening on oxygen or just entering an intensive care unit) and the evaluation of longer-term survival. Ongoing meta-analyses should respond to these questions.

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CORRECTION

Addition of Group Members Supplement: The Original Investigation titled “Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy,” published in October 2020, has been corrected to include the names of the COVID-19 Lombardy ICU Network members in a supplement.


Errors in Group Information Supplement: In the article titled “Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial,” published online on October 20, 2020, there were errors in the group information Supplement. There were 2 names misspelled in the Supplement. Samy Figueiredo has been corrected from the previous spelling of Samy Figueredo, and Marie-Aude Penet has been corrected from the previous Marie-Aude Pennet. This article Supplement was corrected online.


Error in Sample Size: In the article titled “Socioeconomic Inequality in Respiratory Health in the US From 1959 to 2018” published online May 28 in JAMA Internal Medicine, the sample size was presented incorrectly. Where it previously indicated that there were 215,399 participants, it now correctly says 160,495. This article was corrected online.