The trials testing the efficacy of tocilizumab in patients with Covid-19 pneumonia: are we missing something?

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January 30, 2024

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The new coronavirus infection (COVID19) is affecting societies and economies globally. Developing therapies for hospitalized patients is a global urgency to optimize the care and outcomes. . Investigators identify molecular targets with a potential role in the development and outcome of adult respiratory distress syndrome (ARDS) in Covid19, argue that a pragmatic, novel and rational target that should be seriously considered in efforts to mitigate the effects of COVID-19 infection. This is followed by rapidly designed randomized clinical trials (RCT) in patients with confirmed COVID-19 infection with subsequent plan to develop populational recomendations. The common end points are preventing intubation or death in hospitalized patients with COVID-19.

In this context, the efficacy of tocilizumab in patients with Covid-19 has been examined in several randomized trials (1-6). The trials differ significantly in the inclusion and exclusion criteria. The trials enrolled patients with a different disease severity at baseline. As evidence build up gradually in the current ecological crisis, the use of concomitant glucocorticoid or antiviral agents did not display most up-to-date standard of care in the trials. Commonly, the researchers report that the confidence intervals (CI) for efficacy comparisons are wide, so some benefit or harm is uncertain.

The trials did not show difference in mortality between the tocilizumab and control groups, but the other efficacy end point of survival without invasive or noninvasive mechanical ventilation by day 14 was acchieved in the CORIMUNO-TOCI-1 trial (3), without a mortality benefit at day 28. The results of the trials suggest that patient enrollment criteria determine the benefit from tocilizumab. Due to wide CIs, the conclusion is made in these trials that tocilizumab 'does not show efficacy' . CIs are helpful in determining not only statistical significance but also the clinical relevance of the findings. Hospitalized patients with Covid19 display wide physiological and biological heterogeneity (7). Wide CIs suggest how large the effect of a treatment could plausibly be. Thus, we can not rule out the possibility that tocilizimab would help in certain groups of patients. In fact, a systematic review and meta-analysis reports that addition of tocilizumab to the standard of care reduces mortality in severe COVID-19 (8).

The conventional RCT paradigm can test new therapeutic candidates in limited number of patients. For conditions with wide heterogeneity. the need exists to understand the mechanisms of vast heterogeneity in drug-related outcomes. Without further understanding the basis individual differences in drug safety and efficacy, we face the risk of early removal of a potentially useful companions from further development. As with any maturing field, conflicting observations should be expected. Global efforts are needed to inform the health care professionals about the interpretation of conflicting results and messages.

We wish to emphasize, however, avoiding premature clinical decisions in today's difficult conditions should be a centerpiece concept in clinical pharmacology and population health. With growing technological advances,

effective drugs are being developed and used in Covid19. Timely detection of population signals pertaining to efficacy and toxicity can be problematic.

The new coronavirus infection (COVID19) is a current and urgent matter globally. The medical communities could not anticipate the severity of the situation we are facing today. In the midst of pandemic we take the risks of visualizing the real effects of therapies either far too late and premature decisions about the safety. Exercising pharmacovigilance and the novel concept of pharmacogenovigilance thorough global centers can offer a mechanistic insight and firm causality assessment of Covid19 therapies (9,10).

In conclusion, Covid19 trials are in need of anticipatory systems that can detect early signals of safety and efficacy in the transition of health interventions to population scale applications. Early removal of a potentially useful therapies from further development can be a premature decision in today's difficult conditions.

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