



## Use of rituximab and the risk of adverse clinical outcomes in COVID-19 patients with systemic rheumatic disease

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We read with interest the descriptive study by Loarce-Martos et al. [1] to investigate the clinical characteristics and outcomes of patients with systemic rheumatic disease receiving rituximab who acquired coronavirus disease 2019 (COVID-19) or were presumed to acquire COVID-19 in a Spanish hospital. It was reported in the study that patients with systemic rheumatic disease receiving rituximab had unfavorable prognosis upon hospitalization with COVID-19, of which all experienced clinical worsening upon hospitalization and three out of eight hospitalized patients succumbed to death. In fact, the mortality rate among patients with systemic rheumatic disease receiving rituximab upon hospitalization with COVID-19 (37.5%) was higher than that reported in a retrospective observational, multicenter study [2] of 4035 Spanish hospitalized patients with COVID-19 (28.0%).

Nevertheless, such finding was in contrast to a single-center case–control study [3] from the Lombardy region of Italy, involving 1193 patients with psoriasis receiving either biologic agents or conventional small molecule drugs. A comparison of the cohort of psoriasis patients with the general population in the region did not detect an increased risk of admission to an intensive care unit or of death among patients receiving biological agents. Adding to the evidence is that an observational cohort study [4] which evaluated the effect of biological disease-modifying antirheumatic drugs on the clinical outcomes of patients with rheumatoid arthritis who developed serious infections (non-COVID-19) and reported that both subgroup of patients who received tumor

necrosis factor-alpha inhibitors and subgroup of patients who received biological agents other than tumor necrosis factor-alpha inhibitors had reduced odds for development of sepsis and reduced odds of mortality.

Although the study by Loarce-Martos et al. [1] was limited by its small sample size, it does however indicate a possibility for differential risk of adverse clinical outcomes among patients with systemic rheumatic disease based on the type of biological agents received. Particularly, rituximab causes B cell depletion that can be associated with decreased antibody production. This is best demonstrated in a pooled analysis of 2578 patients who received rituximab (along with methotrexate) in clinical trials for rheumatoid arthritis where the proportion of patients with low immunoglobulin (Ig)M 6 months after each course of treatment increased successively from 10% upon the first course to 40% upon the fifth course [5]. Although the proportion of patients with low IgG six months after each course of treatment remained stable, there were 5% of patients with a level of IgG below the lower limit of normal occurred at any point during follow-up.

Neutralizing antibody responses against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen responsible for COVID-19, are usually comprised of IgM and IgG, where the serum of patients with COVID-19 usually contains IgM and/or IgG antibodies to the spike protein of the SARS-CoV-2 envelope by day 14 after symptom onset [6–8]. Therefore, long-term administration of rituximab may impair the priming of antibody responses to neutralize viral replication, which explains the unfavorable clinical outcomes among COVID-19 patients with systemic rheumatic disease receiving rituximab.

On the other hand, the use of biologic cytokine inhibitors, such as tumor necrosis factor-alpha inhibitors may not carry the same risk for unfavorable clinical outcomes among COVID-19 patients with systemic rheumatic disease since these agents may dampen cytokine storm associated with COVID-19. The publication of this descriptive study by

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Loarce-Martos et al. should prompt more evaluation on the risk of COVID-19-related adverse clinical outcomes with different types of biological agents indicated for systemic rheumatic disease. Before emerging of more evidence, it is probably best that we take a prudent approach with routine monitoring of serum immunoglobulin levels and consideration for discontinuation of rituximab in patients who develop hypogammaglobulinemia amid the COVID-19 pandemic.

### Compliance with ethical standards

**Conflicts of interest** Chia Siang Kow and Syed Shahzad Hasan declare that they have no conflict of interest.

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