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LETTER TO THE EDITOR

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Tocilizumab administration in patients with SARS-CoV-2 infection: Subcutaneous injection vs intravenous infusion

Dear Editor,

Recent studies have revealed that cytokine storm syndrome, which is caused by the activation of inflammatory cytokines, is likely underlying pathophysiology in patients with severe COVID-19 that has been associated with a high mortality rate.[1] Interleukin-6 (IL-6) plays a predominant role in this cascade, and tocilizumab (a humanized monoclonal antibody against IL-6 receptors) can interfere with this cascade. Tocilizumab has shown promising results in recent clinical trials in severe COVID-19 cases. It was administered through an intravenous route using different doses in a specified range (median: 400 mg; interquartile range: 320-480 mg).[2]

Furthermore, rheumatology studies revealed similar efficacy and safety profiles between subcutaneous and intravenous tocilizumab. The subcutaneous form is readily available in some countries and has been approved in the United States, Switzerland, Canada, Japan, and the European Union. On the contrary, the intravenous form has limited storage in some countries.[3]

To date, the administration of subcutaneous tocilizumab in COVID-19 cases has not been fully investigated; therefore, the conversion of intravenous doses to subcutaneous doses may be confusing. Here, we propose a practical recommendation.

Zhang et al conducted a study in 2010 in which they evaluated the pharmacokinetics of subcutaneous administration of tocilizumab, following a single dose injection in healthy volunteers. They found that the area under the concentration-time curve in volunteers who received tocilizumab at a dose of 162 mg through the intravenous route was 4340 ± 1360 μg·h/mL and that in volunteers who received tocilizumab at a dose of 162 mg through the subcutaneous route was 2370 ± 1240 μg·h/mL (mean ± standard deviation). The time to maximum observed plasma concentration was 1.5 and 72 hours (median) in the intravenous and subcutaneous groups, respectively. Hence, a coefficient of 1.8 may be acceptable for converting the intravenous dose to a subcutaneous dose. However, they found that the pharmacodynamic properties of tocilizumab, which is responsible for its clinical effects, at a dose of 162 mg in both routes are similar. This suggests that there may be no need for dose conversion.[4]

Considering the abovementioned parameters, it can be concluded that the administration of tocilizumab at a dose of 400 mg through the intravenous route (desired dose) may be equivalent to 400 mg tocilizumab through the subcutaneous route, despite the pharmacokinetic differences. This suggested dosing should be interpreted with caution due to individual pharmacokinetic variation.[5] The mentioned study also was done on healthy people. For example, in critically ill patients, the absorption process may be altered due to edema, shock state, and so on.

Also, Mazzitelli et al reported three patients with COVID-19 pneumonia who were treated with tocilizumab through a subcutaneous route. In their study, tocilizumab was administered at a single dose of 162 mg through the subcutaneous route. They found that the efficacy and safety of subcutaneous tocilizumab at a single dose of 162 mg is comparable with the intravenous route (8 mg/kg with a second dose 12 hours after the first dose and a possible third dose after next 24-36 hours, based on the clinical response). Hence, according to the pharmacokinetics information and abovementioned study, lower doses of intravenous tocilizumab may be adequate to achieve an acceptable clinical response.[6]

Future pharmacokinetic studies, which should be performed by measuring drug level, IL-6 level, and clinical efficacy, can provide solutions to this challenge as well.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

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