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Do remdesivir and plasma therapy favor long-term SARS-CoV-2 infection and mutations in immunocompromised patients?

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Supplementary Table: 1
SARS-CoV-2 variants may present mutations in the spike protein, which is the target of current vaccines and contains a very large number of epitopes eliciting immune responses.\(^1\) A possible source could be a Darwinian mechanism involving selection pressure by antibodies mainly directed against the spike and a mutagenesis stimulant such as remdesivir, which was recently confirmed.\(^2\)

We have been able to observe in our series that of 212 severely immunocompromised COVID-19 patients hospitalized who notably included 22 patients with lymphoma, only two had viral persistence beyond 70 days. One had received a course of remdesivir and a convalescent plasma outside our institute and his virus accumulated mutations in the spike (Supplementary Table S1). The literature also includes reports of seven immunocompromized patients with viral persistence associated with mutations in the spike protein in 6 cases. Of these seven patients, all received either remdesivir (5 cases) and/or convalescent plasma (6 cases). To our knowledge, these are currently the only observations of such changes in the spike protein during the course of infection. In addition, a recent in vitro study reported the selection on remdesivir of spike mutations present in the UK, South-African and Brazilian variants.\(^2\)

We therefore believe that both remdesivir and convalescent plasma therapy, alone and in combination, play a role in the promotion and selection of mutations in the spike protein. This means that in studies that reported cases of viral persistence in immunocompromised patients, it is essential to specify the therapy that has been used, which lacks for some patients,\(^3\) and to sequence genomes of persistent viruses, which lacks in a convalescent plasma therapy study.\(^4\)

In practice, it is essential in the context of this disease, as in other viral diseases, to bear in mind that the antivirals given in monotherapy to people who are chronic viral carriers, as in
the case of HIV or hepatitis C, easily select resistant viral mutants. Moreover, it was known
for remdesivir that it had mutagenic activity for Ebola virus in vitro and putatively for
coronaviruses, and the risk of occurrence of the mutations observed in case reports with this
drug was predictable. Furthermore, the combination of such a drug with an agent selecting for
serotherapy-resistant mutations constitutes a purely Darwinian model for selecting
serotherapy-resistant viruses, and raises the future problem of the risk of inefficacy of
vaccines targeting the spike protein.

References

1 Greaney AJ, Loes AN, Crawford KHD, et al. Comprehensive mapping of mutations to
the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human
serum antibodies. Cell Host Microbes 2021 Feb 8;S1931-3128(21)00082-2. doi:

2 Szemiel AM, et al. In vitro evolution of Remdesivir resistance reveals genome plasticity

three immunocompromised patients: from prolonged viral shedding to SARS-CoV-2
superinfection. J Infect Dis 2021 Feb 8;jiab075. doi: 10.1093/infdis/jiab075. Online
ahead of print.

4 Hueso T, Pouderoux C, Pére H, et al. Convalescent plasma therapy for B-cell-depleted

5 Lo MK, Albarino CG, Perry JK, et al. Remdesivir targets a structurally analogous
region of the Ebola virus and SARS-CoV-2 polymerases. Proc Natl Acad Sci U S A
2020; 117:26946-54.