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Sotrovimab-emergent resistance in SARS-CoV-2 Omicron: A series of three cases

Dear Editor,

The monoclonal antibody sotrovimab, which targets the Spike (S) protein of SARS-CoV-2, has been considered a valid therapeutic option during the Delta and Omicron BA.1 waves. Despite baseline sensitivity, the target of a single domain by a single mAb makes treatment-emergent resistance a serious concern, which has been extensively characterized *in vitro*[1]. Four cases of treatment-emergent S:E340K were previously detected among 45 outpatients at risk of progression in the COMET-ICE randomized controlled trial [2] run during the Alpha variant of concern (VOC) wave: of relevance, such trial excluded severely immunocompromised patients [3], which nowadays represent one of the more likely subsets to receive sotrovimab. Rockett et al. recently reported sotrovimab-emergent resistance (wither S:E340K/A/V or S:P337H/L/R/T) in 4 out of 100 outpatients infected with the Delta VOC of SARS-CoV-2 due to E340K mutations in the Spike protein [4]. Huygens et al. reported that, following treatment with sotrovimab, Spike mutations associated with reduced *in vitro* susceptibility were detected in 6 of 47 (13%) immunocompromised patients [5].

Among the first 16 outpatients affected by the Omicron BA.1 VOC receiving sotrovimab at the ASST Sette Laghi between January and March 2022, 9 had persistently positive PCR in nasopharyngeal swabs (NPS) at day 10: of them, 2 showed treatment-emergent E340D. Case 1 was a 51-years old HIV-positive female with cerebral toxoplasmosis, and Case 2 was a 43-years old male kidney transplant recipient. As per E340K/A/V, even E340D is exceedingly rare in the GISAID database (732 out of 2390,087 Omicron sequences as of June 26, 2022 [6]): while such entries mostly consist of pretreatment samples, low overall prevalence suggests minimal fitness of E340 mutants.

We later observed a third case in a 66-years old male recipient of allogeneic hematopoietic stem cell transplantation. He had received 3 doses of miRNA-1273 vaccine (last dose in April 2022), tested positive for SARS-CoV-2 in NPS on May 5, 2022, and was promptly treated with sotrovimab at the transplant center. After viral sequencing of the initial NPS confirmed BA.2 (against which sotrovimab has baseline resistance [7–11]), repeat sequencings since June 5 showed the emergence of S:Y508H (absent on June 3), and since June 13 the further emergence of S:A262S and S:P337S. The latter mutations is associated with a further mild (1.3-fold) reduction in sotrovimab neutralization [12]. Despite rescue therapy with remdesivir and baricitinib, the patient is still positive in both NPS and bronchoalveolar lavage fluid at the time of writing.

As previously seen with different individual anti-Spike monoclonal antibodies [1], the risk of immune escape in immunocompromised patients should encourage polyclonal formulations. Combining these concerns with the baseline resistance of the BA.2 sublineage to sotrovimab, we recommend follow-up monitoring in severely immunocompromised patients treated with sotrovimab, and reconsideration of polyclonal or combination therapies.

Declaration of Competing Interest

We declare we have no conflict of interest related to this manuscript.

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