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Case Report
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Monoclonal Antibodies for the Prevention and Treatment of COVID-19 Disease in Patients With Hematological Malignancies: Two Case Reports and a Literature Review

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The outbreak of coronavirus disease 2019 (COVID-19) pandemic has caused worldwide problems in the care of patients with hematological malignancies. Since the first reports on the new coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the Chinese city of Wuhan, many health systems have been pushed to their limits and beyond. In particular, the therapy of patients with hematological malignancies, both outpatient and inpatient, was substantially impacted by the major restrictions due to the isolation and hygiene measures. Not only the restriction of treatment under pandemic conditions but also a SARS-CoV-2 infection itself poses a risk for patients with malignancies. In fact, first studies have consistently shown increased mortality from COVID-19 infection in cancer patients.[1–3] Because of frequently compromised immune responses in cancer patients, vaccines have only limited effectiveness and, to date, only few antiviral agents are available.[4,5] Neutralizing antibodies might become an important pillar in the treatment of COVID-19 infection in immunocompromised patients. Monoclonal antibodies (MoAbs) against SARS-CoV-2 can be used in both settings, prevention and treatment. Most of the currently used MoAbs target the spike protein, which enables SARS-CoV-2 to penetrate the target cell via the angiotensin converting enzyme-2 receptor.[6]

Due to a long half-life of MoAbs of about 3 weeks for IgG1, a single antibody infusion appears to be sufficient. Limitations in therapy with neutralizing antibodies are mainly the unknown bioavailability in individual organs and possible resistances due to mutations in the spike protein.

Here, we report on 2 patients with hematological malignancies from our department, where we have used neutralizing antibodies for both the prevention and therapy of SARS-CoV-2 infection.

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Case 1: Bamlanivimab for prevention of SARS-CoV-2 infection

A 21-year-old woman with advanced-stage Hodgkin disease was receiving intensive chemotherapy according to the bleomcyin, etoposide, doxorubicin, cyclophospamide, vincristine, procarbazine, prednisone protocol. She was in good general condition (performance status 0) and at the time of contact with a COVID-19 positive individual, she received 4 of 6 cycles of planned chemotherapy. The contact person was patient's father, who presented with respiratory symptoms and tested positive for SARS-CoV-2 by a polymerase chain reaction (PCR) test. After a PCR test also her mother tested positive, while the patient remained negative. Sequencing results from patient´s mother showed the B.1.1.7 variant ("British variant") of SARS-CoV-2. Since 2 additional chemotherapy cycles of a strong immunosuppressive therapy were still intended for further treatment (only a partial remission in the interim positron emission tomography-computerized tomography after 2 cycles of chemotherapy), we decided to administer once the MoAb Bamlanivimab (LY-CoV555) intravenously at the recommended dose of 700 mg. The MoAb infusion was well tolerated. Subsequently, the patient did not develop any clinical symptoms and a PCR test carried out 1 week after the MoAb infusion was still negative for SARS-CoV-2. After being released from quarantine at home, the patient was able to continue the therapy in outpatient setting with a 10-day delay.

Case 2: Bamlanivimab for treatment of SARS-CoV-2 infection

A 52-year-old male patient admitted to our hospital due to pancytopenia was diagnosed with a *BCR-ABL1* positive (highest risk) acute lymphoblastic leukemia (ALL). The patient was in good general condition. In patient´s history, an immunoglobulin deficiency had been known for many years, but immunoglobulin substitution had never taken place before. A first SARS-CoV-2 PCR test was negative. Treatment was started with the administration of dexamethasone and cyclophosphamide. Given the detection of a *BCR-ABL1* fusion gene, targeted treatment with imatinib 600 mg qd was added to the therapy. However, in a routine PCR test, the patient tested positive 4 days after therapy with imatinib was initiated. At this time, the patient did not suffer from any symptoms that could be linked to a SARS-CoV-2 infection. The patient was transferred

to the isolation unit. The imatinib therapy was continued, but vincristine and pegylated asparaginase were not administered as foreseen in the induction phase of the initial treatment to prevent additional immunosuppression and also not to increase the thromboembolic risk by asparaginase. The B.1.1.7 SARS-CoV-2 variant was detected in the patient with no evidence for resistance mutations (E484K and L452R) against Bamlanivimab. Due to a deep immunosuppression and the higher risk of a severe and protracted course of SARS-CoV-2 infection in the patient, we decided—given lack of resistance mutations—to administer immediately—48 hours after the detection of the SARS-CoV-2 infection—the MoAb Bamlanivimab once at the dose of 700 mg. As the patient developed fever, intravenous antibiotics and oral antimycotic therapy with voriconazole were started. Because of the known immunoglobulin deficiency, also polyclonal immunoglobulins (Pentaglobin 20 g IV) were administered. No severe symptoms occurred during the further course. The patient required nasal oxygen only for 24 hours. Thirteen days after the first positive PCR test, the patient was PCR negative again. However, the PCR test turned positive again in a subsequent routine PCR test, so that the treatment of leukemia had to be further delayed. The phenomenon in immunocompromised/immunosuppressed SARS-CoV-2 infected patients to require longer time in order to ultimately turn negative by PCR is known as "shedding." The detailed course of the PCR results during the first treatment period of the ALL therapy is shown in Figure 1. The patient was discharged from the hospital after the induction treatment was completed. During the further treatment course, the patient experienced a neutropenic infection requiring admission and treatment at the intensive care unit, but he finally did recover.

Both patients have so far not been vaccinated. They have not been tested for the presence of COVID-19 antibodies before and directly after Bamlanivimab infusion.

Cancer and immunocompromised patients are at a higher risk of SARS-CoV-2 infection. Several studies also indicate that patients with active cancer have a significantly higher mortality rate than those without active tumor disease.[2,7,8] However, to date, it is not clear whether this is due to the malignant disease itself or the advanced age of cancer patients as well as concomitant diseases. The tumor therapy itself does not seem to be an independent risk factor for a severe course of SARS-CoV-2 infection.[9] There are indications that there is prolonged viral shedding in tumor patients, which might contribute to an increased mortality. A Spanish study showed that prolonged positivity for SARS-CoV-2 by PCR after 6 weeks was associated with a significantly increased mortality compared with patients who became negative (54.4% versus 1.4%; $P < 0.001$).[7,10]

In patients with cancer, not only a higher mortality but also reduced responses to the currently available vaccines are suspected. Patients with hematological neoplasms seem to have an even lower responses following a vaccination than those with solid tumors. In several studies, lower seroconversion rates of anti-spike IgG antibodies after COVID-19 vaccination were observed in tumor patients compared with a healthy comparison group.[11–13] Less effective immune responses in patients receiving immunosuppression due to a rheumatic condition to a vaccination were reported not only for vaccines against SARS-CoV-2 but also for other as, for example, influenza or pneumococcal vaccine.[14] Currently, there are no evidence-based recommendations for a modified vaccination schedule in cancer patients.

MoAbs act directly as antiviral agents. All currently available antibodies are directed against different epitopes of the SARS-CoV-2 spike protein, but studies with Middle East respiratory syndrome coronavirus show that other epitopes are also feasible.[15]

All currently commercially MoAbs (LY-CoV555 = Bamlanivimab, LY-CoV016 = Etesevimab and REGN-COV2

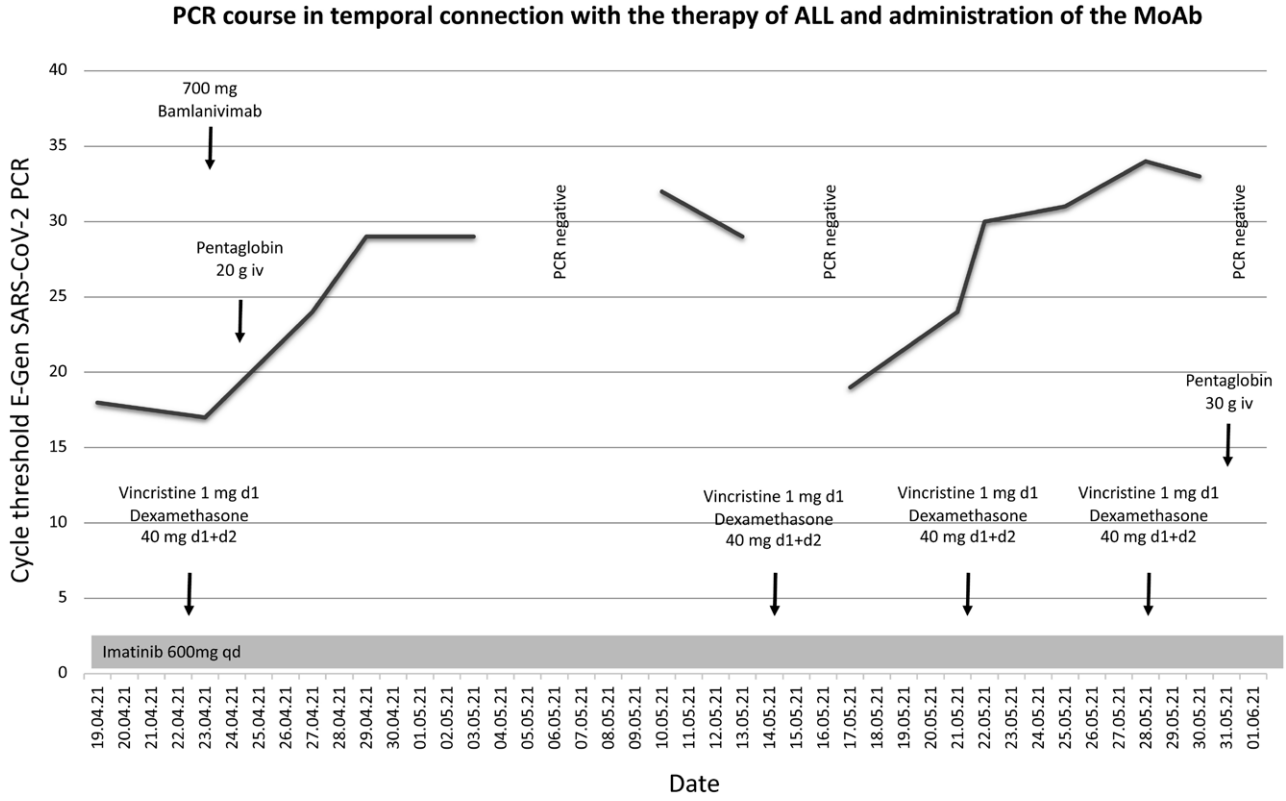

Figure 1. PCR course of the E gene of SARS-CoV-2 in the nasal swab together with the therapy of ALL. ALL = acute lymphoblastic leukemia; MoAb = monoclonal antibody; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

= Casirivimab + Imdevimab) have been shown to reduce viral load and hospitalization rates, but so far, no benefit on survival has been demonstrated.[16,17]

MoAbs are likely to have the greatest effect in the early, oligosymptomatic phase of the infection, where virus replication plays a major role. This is indicated by the data from the approval studies and the lack of effect of Bamlanivimab in hospitalized patients from the pivotal ACTIV-3 study (ClinicalTrials.gov Identifier: NCT04501978). A beneficial effect might also be expected in seronegative patients as postexposure prophylaxis. This is suggested by the first results from studies using either the antibody mix of Casirivimab + Imdevimab or Bamlanivimab as single agent (BLAZE-2 study); ClinicalTrials.gov Identifier: NCT04497987.[16,17] The beneficial impact of MoAbs in the early phase of the disease is also supported by one recent retrospective study in 616 high-risk patients with COVID-19.[16] In this study, the early use (within 5 days of diagnosis) of MoAbs not only significantly reduced the hospitalization rate (1.7% versus 24%; $P < 0.005$) but also appeared to be associated with a lower mortality rate (0% versus 2.7%).[18]

There is only very limited experience with the use of MoAbs in a preventive setting. A recently published study suggests a positive protective effect on contact in one's own household for Casirivimab and Imdevimab. SARS-CoV-2 negative persons who received Casirivimab and Imdevimab SC within 96 hours after contact with SARS-CoV-2 not only seemed to have a lower risk of developing COVID-19 (1.5% versus 7.8%; $P < 0.001$), but in those developing COVID-19, the duration of the symptomatic infection was 2 weeks shorter than in those who received placebo.[19] Although such data are not specifically available for Bamlanivimab, these first encouraging results provide some rationale to further explore the preventive use of moAbs.

All currently available MoAbs are directed against the "receptor-binding domain" of the SARS-CoV-2 virus. The antibody design was based on the first virus isolates from the patients in Wuhan. However, there is currently a significant increase of variant mutations such as B.1.1.7 ("British variant"), B.1.135 ("South African variant"), or P.1 ("Brazilian variant"). Since the B.1.135 and P1 variants in particular have developed resistance to the available MoAbs, the result of the sequencing needs to be available before the use of the antibodies. If this is not the case, the local epidemiological situation should be taken into account.[20]

Pre-eliminary data from a recent single center study suggest that in immunocompromised patients with COVID-19 treated with Bamlanivimab, the occurrence of an E484k mutation might confer resistance to Bamlanivimab resulting in a viral rebound.[21] In the light of these results, a combination of MoAbs might be a potential treatment option for immunocompromised patients. This concept is supported by the data form a phase 2/3 study including patients presenting with a mild to moderate COVID-19 course and suffering from a cancer or undergoing immunosuppressive therapy.[22] In this study, a combination of Bamlanivimab and Etesevimab was tested against placebo. In fact, patients receiving the antibody combination had a lower hospitalization rate (2.1% versus 7.0%; $P < 0.001$) and a significantly greater reduction in viral load on day 7 after administration of the study medication compared with the placebo group.[22]

Patients with hematological neoplasms frequently require urgent and intensive treatment, even in the context of a concomitant SARS-CoV-2 infection. Specific MoAbs might prevent a severe clinical course of a SARS-CoV-2 infection allowing a timely treatment of a potentially life-threatening hematologic disease. Our case reports show favorable clinical outcomes in patients with hematologic malignancies requiring intensive treatment after administration of Bamlanivimab for both prevention and treatment of a SARS-CoV-2 infection and emphasize the need for prospective studies using MoAbs for the treatment of SARS-CoV-2 infection as well as in preventive setting in patients with hematologic malignancies.

Disclosures

The authors have no conflicts of interest to disclose.

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