Monoclonal antibodies for the treatment of COVID-19 in a patient with high-risk acute leukaemia

Adults and children with acute leukaemia are at high risk of serious illness and death from COVID-19, compared with the general population.[1,2] Furthermore, delayed or interrupted leukaemia treatment due to SARS-CoV-2 infection may also result in poor prognosis, especially in aggressive forms of leukaemia. Initial studies of the general population have suggested that anti-SARS-CoV-2 monoclonal antibodies (mAbs) may play a promising role in COVID-19 treatment.[3] However, drug safety and efficacy data in patients with leukaemia are lacking. In this report, we describe the favourable evolution of an eight-year-old female patient with ambiguous lineage acute leukaemia, who presented at diagnosis with an active SARS-CoV-2 infection and was treated with combined mAbs.

The patient presented with fever, bone pain and bleeding symptoms (petechiae and spontaneous ecchymosis). Blood counts showed marked hyperleukocytosis (107×10^9/l with 85% blasts), mild non-regenerative normocytic anaemia (105 g/l), moderate thrombocytopenia (86×10^9/l) and normal neutrophil counts. The patient was subsequently referred to a tertiary centre. Bone marrow aspirate analysis revealed massive infiltration by medium-sized blast cells with a high nucleocytoplasmic ratio and non-granular cytoplasm. Immunophenotype analysis revealed ambiguous lineage leukaemia with $CD19^+$, $cCD79a^+$, $CD22^+$ and $CD10^-$ cells, of which 10% co-expressed monocytic markers (MPO, CD14, CD64, CD33). Cytogenetic analysis revealed the complex karyotype 46,XX,-10,-12,-17,-21,+4mar[23]/46,XX[2]. Fluorescence *in-situ* hybridization analysis was negative for the *BCR-ABL1*, *ETV6-RUNX1*, *TCF3-PBX1* and *TCF3-HLF* fusions, *KMT2A* rearrangements and intra-chromosomal amplification of chromosome 21. Multiplex ligation-dependent probe amplification revealed an *AF15–ZNF384* fusion.

Upon admission, the patient also tested positive for SARS-CoV-2 B.1.1.7, via real-time polymerase chain reaction (RT-PCR; multiplex TaqPath COVID-19; ThermoFisher Scientific, Waltham, MA, USA). Although the patient had a fever, she did not present with COVID-19 respiratory symptoms. The computed tomography (CT) scan showed mild ground-glass opacity. The patient probably contracted COVID-19 via household transmission, as her sister and both parents also tested positive for SARS-CoV-2. The patient's mother was pregnant and was the first member of the family to develop COVID-19 symptoms.

To mitigate the risk of a severe form of COVID-19, the patient was treated with a combination of the anti-SARS-CoV-2 mAbs bamlanivimab and etesevimab (off-label). This therapeutic decision was made by a board of experts that included representatives of the French drug agency (ANSM) and the manufacturer (Eli Lilly). The day after admission, the patient received 700 mg (i.e., approx. 25 mg/kg) of bamlanivimab and 1,400 mg (i.e., approx. 50 mg/kg) of etesevimab (adult doses). The COVID-19 treatment was well tolerated, and anti-leukaemic corticosteroids were then administered starting three days after the mAbs infusion. The evolution of the clinical, haematological, immunological and viral parameters is shown in Fig 1. Nucleocapsid antibodies were not detected, thus indicating that the patient did not develop a natural immune response to SARS-CoV-2 (data not shown). After the infusion, we detected very high serum levels of neutralizing anti-spike antibodies (i.e., infused mAbs). Although mAbs levels gradually decreased over time, the antibody titers remained high and subsequent mAbs administration was not needed. Viral clearance was observed 10 days after mAbs administration, with no recurrence after a >10-week follow-up.

Induction chemotherapy was administered according to standard guidelines for acute lymphoblastic leukaemia, including corticosteroids, vincristine, daunorubicin, pegaspargase and triple intrathecal chemotherapy. The patient also received a single dose of rasburicase to treat mild tumour lysis syndrome with increased serum uric acid levels. Aplasia occurred from day 15 to day 42 (neutrophil count nadir of 50/mm^3). No severe complications occurred. Complete remission was observed at the end of induction chemotherapy. The patient received a consolidation course.

Patients with a haematological malignancy are at an increased risk of rapid viral evolution, impaired viral clearance, altered humoral response, exhausted T-cell phenotype and prolonged virus shedding.[4,5] Without effective anti-SARS-CoV-2 drugs to treat acute leukaemia patients with COVID-19, the clinician must decide to either delay/interrupt the anti-leukaemic treatment or continue the leukaemia treatment and thereby render the patient at an even greater risk of developing a severe form of COVID-19.

Overall, these observations suggest that mAbs may be well tolerated for the treatment of SARS-CoV-2 infection in a

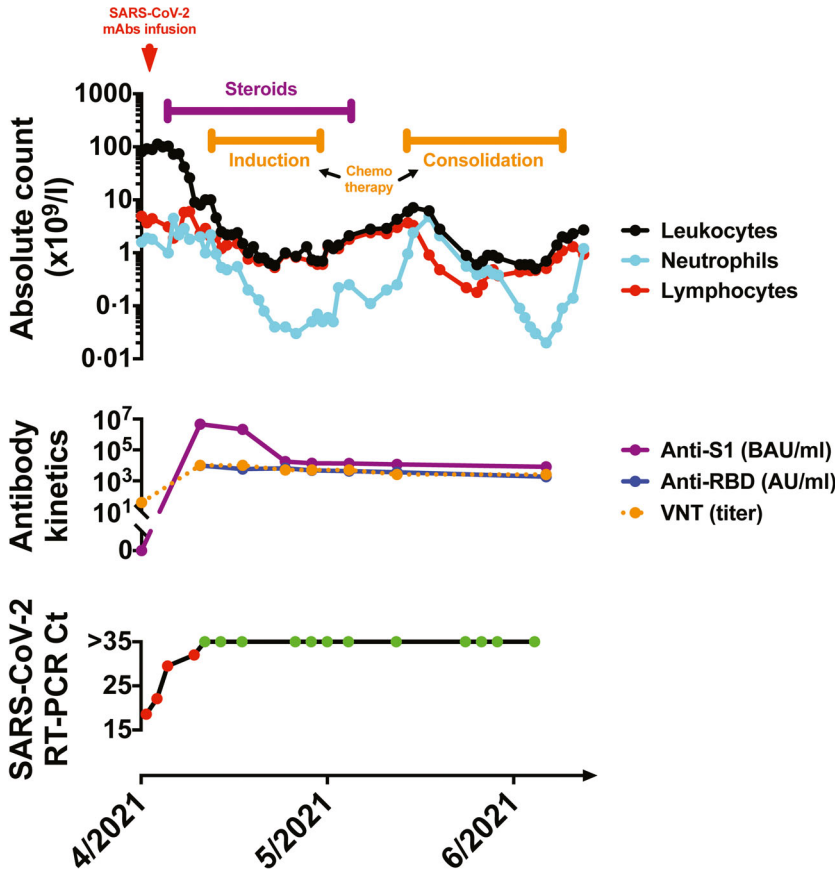

Fig 1. Evolution of the clinical, haematological, immunological and viral parameters over the course of the treatment. Top panel: Evolution of the leukocyte, neutrophil and lymphocyte levels over the course of the treatment. The timepoint of administering the monoclonal antibodies bamlanivimab and etesevimab is indicated by the red arrow. The timeframe of administering the anti-leukaemia treatment (steroids and chemotherapy) is shown in purple and orange, respectively. Middle panel: Anti-S1 antibodies were quantified using an ELISA kit: Anti-SARS-CoV-2 QuantiVac (IgG) [Euroimmun, Lübeck, Germany (binding antibody units per ml)]. Anti-RBD antibodies were quantified using an Access SARS-CoV-2 IgG II Reagent Kit [Beckman Coulter Brea, CA, USA (arbitrary units per ml)]. Viral neutralizing titers were quantified as previously described.[6] Bottom panel: SARS-CoV-2 RT-PCR results based on nasopharyngeal samples (multiplex TaqPath COVID-19; ThermoFisher Scientific, Waltham, MA, USA). The red and green dots indicate positive and negative tests, respectively. Ct, cycle threshold; ELISA, enzyme-linked immunosorbent assay; mAbs, monoclonal antibodies; RDB, receptor-binding domain; RT-PCR, real-time polymerase chain reaction; VNT, viral neutralizing titer.

patient undergoing therapy for high-risk leukaemia. The intensive anti-leukaemic treatment was administered without delay or interruption, and complete remission was observed at the end of induction therapy. Co-occurrence of COVID-19 and high-risk haematological malignancy may occur in regions with a high surge of COVID-19. Additional studies should be conducted to evaluate the safety and efficacy of mAbs in adult and paediatric patients with both an aggressive haematological malignancy and SARS-CoV-2 infection.

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Author contributions

PS wrote the paper; LN, PMSV, AA and ML performed the biological analyses; SS, MV, SV and VB acquired clinical data; XdL and HC coordinated the study; All authors edited and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of interest

The authors have no competing interests to disclose.

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Rivaroxaban for the treatment of superficial vein thrombosis, experience at King's College Hospital

The precise incidence of superficial vein thrombosis (SVT) is unknown. It is likely more prevalent than deep vein thrombosis (DVT), which is approximately 1 in 1 000 cases.[1] An annual incidence of 0·64% [95% confidence interval (CI) 0·55–0·74%] was reported in a community-based study of 265, 687 participants in France.[2] Historically, SVT was considered a self-limiting condition, however, a significant risk of progression to DVT or pulmonary embolism (PE) is now accepted.[3,4] Specifically, 6–14% of SVT cases have associated DVT, 20–33% have asymptomatic PE, and 2–13% have symptomatic PE.[1] Risk factors for developing lower-limb SVT are similar to those for DVT; these include varicose veins, thrombophilia, reduced mobility, pregnancy, active cancer, and a personal or family history of venous thromboembolism (VTE).[5]

The American College of Chest Physicians guidelines recommend SVT treatment with prophylactic fondaparinux or low-molecular-weight heparin (LMWH) over no anti-coagulation (Grade 2B evidence), and fondaparinux over LMWH (Grade 2C evidence).[6] Rivaroxaban has since been reported as non-inferior to fondaparinux in the SURPRISE study.[7] In 2019 we amended our protocol to recommend rivaroxaban 10 mg daily for six weeks for SVT > 5cm in length, and one of: above-knee involvement, severe symptoms, involvement of long saphenous vein, history of DVT or SVT or recent surgery in non-cancer patients, in line with the rivaroxaban treatment arm of the SURPRISE study. SVT within 3 cm of the saphenofemoral junction is managed as DVT with full-dose anti-coagulation. Additionally, patients with SVT < 5 cm or SVT > 5cm with no risk factors are treated conservatively with non-steroidal anti-inflammatory medications. At our centre, patients are reviewed at one week to assess symptomatic improvement and ensure tolerance to rivaroxaban, and again before the end of treatment, if required.

The efficacy and safety of rivaroxaban for the treatment of SVT in real-world clinical practice has not yet been described. We conducted a retrospective case note review to assess adherence to local guidance and the efficacy and safety of rivaroxaban for patients with SVT attending the anti-coagulation clinics at King's College Hospital and Princess Royal University Hospital, London.

Patients with an objective diagnosis of SVT were identified between June 2019 and December 2020. All patients had an isolated SVT confirmed by compression ultrasonography.[8] The primary efficacy outcome was SVT, DVT, or PE within 90 days of diagnosis. Primary safety outcomes were treatment-emergent major or clinically relevant non-major bleeding (CRNMB). Bleeding was defined using the International Society on Thrombosis and Haemostasis criteria.[9] Baseline characteristics and outcome data were extracted from the local hospital electronic patient record (EPR; Allscripts