Haploidentical CD3$^+$ TCR αβ/CD19$^+$–depleted HSCT for MHC class II deficiency and persistent SARS-CoV-2 pneumonitis

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leads to coronavirus disease 2019 (COVID-19), which can range from a mild illness to a severe phenotype characterized by acute respiratory distress needing mechanical ventilation. Children with combined immunodeficiencies might be unable to mount a sufficient cellular and humoral immune response against COVID-19 and have persistent disease.

Objective: Our aim was to describe a child with combined immunodeficiency and a favorable post–hematopoietic stem cell transplant (HSCT) course following a haploidentical HSCT in the presence of persistent SARS-CoV-2 infection.

Methods: A 13-month-old girl with MHC class II deficiency developed persistent pre-HSCT SARS-CoV-2 infection. Faced with a significant challenge of balancing the risk of progressive infection due to an incompetent immune system with the danger of inflammatory pneumonitis peri-immune reconstitution after HSCT, the patient's physicians performed a maternal (with a recent history of COVID-19 infection) haploidentical HSCT. The patient received regdanvimab (after stem cell infusion) and remdesivir (before and after stem cell infusion).

Results: The patient exhibited a gradual increase in her cycle threshold values, implying a reduction in viral RNA with concomitant expansion in the CD3 lymphocyte subset and clinical and radiologic improvement.

Conclusions: Combination of adoptive transfer of maternal CD45RO$^+$ memory addback T lymphocytes after haploidentical HSCT and use of regdanvimab (a SARS-CoV-2–neutralizing mAb) and remdesivir may have led to the successful outcome in our patient with severe immunodeficiency after she had undergone HSCT. This case highlights the role of novel antiviral strategies (mAbs and CD45RO$^+$ memory T lymphocytes) in contributing to viral clearance in a challenging clinical scenario. (J Allergy Clin Immunol Global 2023;2:101-4.)

Key words: *COVID-19, SARS-CoV-2, MHC class II deficiency, regdanvimab, CD3$^+$ TCR αβ/CD19$^+$–depleted haploidentical transplant*

INTRODUCTION

Children with inborn errors of immunity (IEIs) who are undergoing allogenic hematopoietic stem cell transplant (HSCT) represent a challenging cohort of patients who are at increased risk of serious complications due to common viral infections. This is partly due to the underlying disease and also to a post-HSCT immunodeficiency that ensues until engraftment and good immune reconstitution. Although probable prognostic factors influencing the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection occurring beyond engraftment have been described in recipients of HSCT, case reports describing outcomes of peri-HSCT SARS-CoV-2 infection in children are limited.[1] Novel antiviral strategies such as SARS-CoV-2–neutralizing antibodies, have become part of the treatment strategy aiming to improve viral clearance in such patients. Here, we report the successful outcome in a child with MHC class II deficiency and concurrent active SARS-CoV-2 pneumonitis who treated with haploidentical CD3$^+$ T cell receptor (TCR) αβ/CD19$^+$–depleted HSCT and received 2 courses of remdesivir and regdanvimab (Regkirona [Celltrion; South Korea]), a novel SARS-CoV-2 mAb.

The patient, a 13-month-old girl with MHC class II deficiency, was referred to our center for HSCT. Her growth and development were within normal range, and she was receiving antibiotic and subcutaneous immunoglobulin therapy. Preliminary blood results showed absent HLA-DR expression on her lymphocytes and monocytes. A genetic test identified a missense mutation, c.362A>T p.(Asp121Val), in the Regulatory Factor X Associated Ankyrin Containing Protein (*RFXANK)* gene, confirming autosomal recessive MHC class II deficiency.

Before the transplant, she developed human herpesvirus 6 viremia, which was treated with valganciclovir. Given the lack of a matched donor we prepared her for a CD3$^+$ TCR αβ/CD19$^+$–depleted haploidentical maternal HSCT. Unfortunately, both parents developed SARS-COV-2 infection. The patient subsequently

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Abbreviations used
COVID-19: Coronavirus disease 2019
HSCT: Hematopoietic stem cell transplant
IEI: Inborn error of immunity
RFXANK: Regulatory factor X associated ankyrin containing protein
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
TCR: T cell receptor

developed fever and tested positive for SARS-COV-2 (the sequencing-confirmed variant of concern VOC-21APR-02, DELTA variant). She remained well, without respiratory distress. In accordance with European Society of Bone Marrow Transplantation guidelines, the transplant was postponed for 3 months. During this time, she remained persistently positive for SARS-CoV-2 (Fig 1). As our patient was not eligible for the combination of casirivimab plus imdevimab combination (Ronapreve) as per the national guidelines, we sought Medicines and Healthcare Products Regulatory Agency approval for a novel mAb, regdanvimab (CT-P59 [Regkirona]) to attempt to reduce the viral load before HSCT. While awaiting approval, she was admitted with fever without signs of respiratory distress. A chest computed tomography scan showed widespread patchy air space opacification bilaterally that was consistent with coronavirus disease 2019 (COVID-19) pneumonia (Fig 1). She began receiving intravenous antibiotics and remdesivir (the first course consisted of a 200-mg loading dose followed by 100 mg intravenously once daily for 10 days). Because of a delay in delivery of regdanvimab, we were unable to give the drug before conditioning and stem cell infusion. She received fludarabine, thiotepa, and treosulfan with antithymocyte globulin and rituximab; underwent a maternal haploidentical HSCT; and received donor $CD45RO^+$ memory cells on day 1 after HSCT. The total $CD34^+$ and $CD45RO^+$ memory cell doses were 14.8×10^6 cells/kg and 1×10^6 cells/kg, respectively. Regdanvimab was administered at a dose of 40 mg/kg (324 mg in 50 mL of 0.9% saline) on day 2 after HSCT (Fig 1). A second course of remdesivir was started on day 2 after HSCT. Donor chimerism was 100% with good engraftment kinetics (neutrophil engraftment on day 12 after HSCT and platelet engraftment on day 15 after HSCT). Lymphocyte subset analysis on day 28 after HSCT showed 100% HLA-DR expression on lymphocytes and monocytes. Through the post-HSCT period, the patient's cycle threshold values (a surrogate for viral load) showed a gradual reduction in viral RNA (Fig 1). This coincided with expansion of the $CD3^+$ lymphocyte population and subsequent complete clearance of the viral RNA. She developed intermittent low-grade fever spikes between day 29 and day 64 after HSCT that was thought to be due to immune reconstitution, but she remained well. At last follow-up (6 months after HSCT), the patient was clinically well while undergoing immunoglobulin replacement without radiologic sequalae, with 100% donor chimerism, and recovering immune reconstitution (CD3 706 cells/μL, CD19 274 cells/μL, natural killer 265 cells/μL, CD4 276 cells/μL, and CD8 191 cells/μL). Written informed consent was obtained before the HSCT. Regkirona was provided on a compassionate use basis and procured and administered after Medicines and Healthcare Products Regulatory Agency approval.

RESULTS AND DISCUSSION

MHC class II deficiency is a rare autosomal recessive IEI resulting in a significant susceptibility to severe infections, predominantly of viral etiology.[2] Allogeneic HSCT in a young patient with good pre-HSCT organ function is associated with favorable outcomes.[3]

In a cohort of 94 patients with IEIs and SARS-Cov-2 infection, a substantial proportion of the cohort had mild disease, with the younger patients being at a higher risk of severe infection and need for intensive care unit stay.[4] None of the reported patients had MHC class II deficiency. The post-HSCT experience of 9 patients from the United Kingdom who had both malignant and benign conditions showed that although 1 patient (10%) had severe disease requiring remdesivir and tocilizumab, none of the patients died of COVID-19–related complications.[5]

The experience from a Spanish cohort of children after HSCT was similar. One patient had a severe course and received a combination of hydroxychloroquine, remdesivir, lopinavir/ritonavir, tocilizumab, anakinra, $CD45RA^-$ lymphocytes, and extracorporeal membrane oxygenation.[6] Before the availability of SARS-CoV-2–specific mAbs in the authors' institution, 1 patient with severe primary pulmonary SARS-CoV-2 infection after high-dose chemotherapy and autologous stem cell rescue required a combination of steroids, remdesivir, tocilizumab, baricitinib (a Janus kinase inhibitor), and extracorporeal membrane oxygenation.[7]

Although SARS-CoV-2 has been described in patients with many other IEIs, both before and after HSCT, we believe that this is the first report of SARS-CoV-2 infection before HSCT (or with active COVID-19 infection at transplant) in a child with MHC class II deficiency. Active SARS-CoV-2 pneumonitis in MHC class II deficiency represents a challenging clinical scenario, wherein the risk of progressive infection due to an incompetent immune system has to be balanced with the risk of development of florid infection while going through HSCT. Additionally, these patients incur the risk of inflammatory pneumonitis peri-immune reconstitution. Apart from experiencing the direct effects of chronic SARS-CoV-2 infection, patients with persistent SARS-CoV-2 infection may foster new variants.[8] Available treatments include antiviral drugs, convalescent plasma, and synthetic mAbs. Unfortunately, most of the well-conducted trials do not include patients with persistent SARS-Cov-2 or members of the extremely rare cohort of patients with IEIs who are undergoing HSCT.[9] As there have been concerns surrounding the efficacy of convalescent plasma, it has fallen out of favor.[10] It is well documented that remdesivir monotherapy is associated with frequent relapses or persistent PCR positivity, but mAb therapy combined with remdesivir has been associated with near-universal viral clearance and clinical recovery.[9] Although the results of a Cochrane review concluded that the available evidence was insufficient to draw meaningful conclusions regarding treatment with SARS-CoV-2–neutralizing mAbs,[11] the results of the RECOVERY trial were encouraging, with the mAB therapeutic REGEN-COV reducing 28-day mortality among patients who were seronegative at baseline.[12] Because our patient was not eligible for REGEN-COV or any other mAb at that time, we opted for regdanvimab (CT-P59) which was available on a compassionate use basis. In both preclinical and clinical trials, regdanvimab (CT-P59) has demonstrated efficacy in neutralizing the antibody-targeting receptor-binding domain of the SARS-CoV-2 virus and reducing viral titers.[13-15]

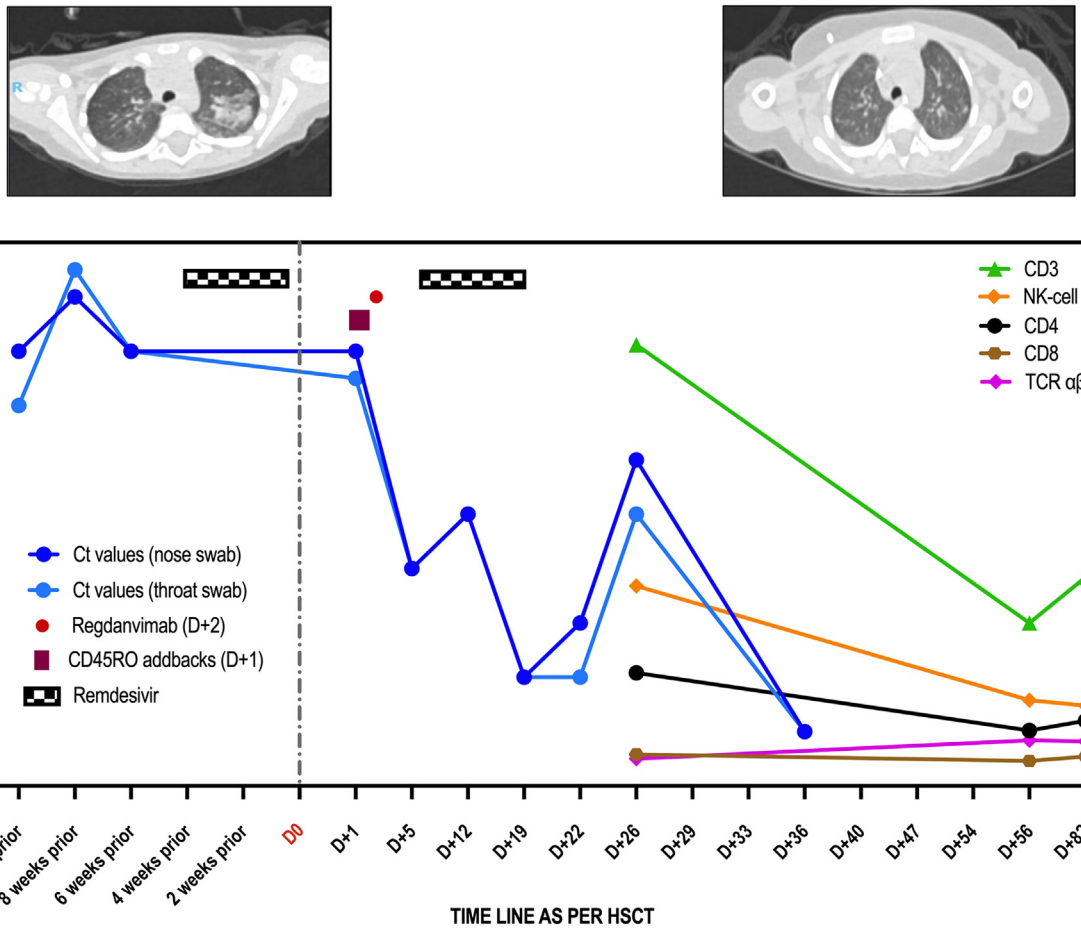

FIG 1. Temporal sequence depicting the preengraftment cycle threshold (Ct) values on nose and throat swabs, therapeutic interventions, radiologic changes, and lymphocyte subset kinetics. *NK,* Natural killer.

We were unable to quantify the relative expansion of SARS-CoV-2–specific T lymphocytes, but we observed an expansion of T lymphocytes with the decrease in viral load. In addition to the antiviral agent and the mAb, the maternal CD45RO$^+$ memory T lymphocytes could have also contributed to viral clearance. CD45RA-depleted haploidentical HSCT and low doses of CD45RA-depleted addbacks have been shown to preserve diverse donor memory T lymphocytes populations that may effectively protect against infections, predominantly viral.[16]

Despite the limitations of the inability to measure the serial numbers of SARS-CoV-2–specific T lymphocytes and single out the pivotal role of 1 treatment (among CD45RO$^+$ memory addbacks, mAbs, or remdesivir), this is the first report of successful a post-HSCT outcome in a patient with MHC class II deficiency with concurrent SARS-CoV-2 infection and pneumonitis. Our case highlights the role of novel antiviral strategies (mAbs and CD45RO$^+$ memory T lymphocytes) in contributing to viral clearance in a challenging clinical scenario. In countries in which restrictions are gradually being relaxed, leading to relative endemicity of the virus, concomitant SARS-CoV-2 infection in children embarking on HSCT or with significant immunosuppression is expected to become commonplace, highlighting the importance of novel strategies. It also highlights the significant role of multidisciplinary clinical teams to design the best management algorithm for complex patients.

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Key messages

- **The clinical course of a child with MHC class II deficiency with pretransplant SARS-CoV-2 infection and pneumonitis has been described.**
- **The combination of adoptive transfer of maternal CD45RO$^+$ memory addback T lymphocytes after haploidentical HSCT and use of regdanvimab (a SARS-CoV-2–neutralizing mAb) and remdesivir may have led to the successful outcome in our patient with severe immunodeficiency who was undergoing HSCT.**

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