EXCEPTIONAL CASE REPORT

blood advances

# Successful outcome of pre-engraftment COVID-19 in an HCT patient: impact of targeted therapies and cellular immunity

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**Key Points**

- We describe the clinical strategy implemented for successful treatment and outcome of pre-engraftment SARS-CoV2 infection in HCT recipient.
- Robust levels of SARS-CoV-2-specific and functional T cells rapidly expanded early post-HCT and may have contributed to viral clearance.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has emerged as a global pandemic that upended existing protocols and practices, including those for allogeneic hematopoietic stem cell transplantation (HCT). Here, we describe the successful clinical course and multiple key interventions administered to an acute lymphoblastic leukemia patient, who tested SARS-CoV-2 positive by reverse transcriptase polymerase chain reaction on day −1 of matched unrelated donor (SARS-CoV-2 immunoglobulin G negative) T-cell-replete HCT. This experience allowed for implementing a virologic and immunomonitoring panel to characterize the impact of SARS-CoV-2 on the recipient's nascent humoral and cellular immune response. The finding of robust, functional, and persistent levels of SARS-CoV-2-specific T cells, starting early after transplant was unexpected, and in combination with the clinical strategy, may have contributed to the favorable outcome. Additionally, it is plausible that preexisting cross-reactive endemic coronavirus immunity in the allogeneic graft reduced recipient susceptibility to COVID-19 disease. This case supports the critical role that T-cell responses may play in mitigating SARS-CoV-2 infection, even in the context of transplant immunosuppression, in which reconstitution of humoral response is commonly delayed. Interventional approaches to transfer SARS-CoV-2-specific cellular immunity such as HCT donor vaccination and adaptive cellular therapy could be of benefit.

## Introduction

Patients with immunocompromised hematology cancer who receive an allogeneic hematopoietic stem cell transplant (HCT) are at enhanced risk for serious complications from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] A comprehensive assessment of the impact of SARS-CoV-2 in transplant patients and transplant outcomes remains to be fully evaluated. Studies and single-center experiences chronicling coronavirus disease 2019 (COVID-19) outcomes in HCT recipients usually describe clinical management[1,3-6]; however, virological and immunological analyses are often missing or performed in patients who developed COVID-19 months after transplantation.[2] To our knowledge, there are no published reports detailing clinical management and immune response to COVID-19 in the HCT pre-engraftment phase.

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The full-text version of this article contains a data supplement.

Here, we report favorable HCT outcome of a patient who was transplanted during active COVID-19 infection.

## Case description

A 64-year-old Hispanic female with Philadelphia chromosome positive acute lymphoblastic leukemia in first remission was admitted for T-cell-replete HCT from matched unrelated donor (IgM/IgG negative for Spike [S] and Nucleocapsid [N] proteins, and S receptor-binding domain) using reduced intensity conditioning (fludarabine/melphalan) and graft-versus-host disease prophylaxis with tacrolimus/sirolimus.[7] According to City of Hope standard procedure during the COVID-19 pandemic, a nasopharyngeal swab (NPS) was performed within 72 to 96 hours before hospital admission and the patient tested negative for SARS-CoV-2 (Figure 1A), by reverse transcriptase polymerase chain reaction (RT-PCR; DiaSorin Molecular Simplexa COVID-19 direct assay).

### Infection with SARS-CoV-2

After completion of conditioning on day −1, NPS RT-PCR test returned positive. The patient was asymptomatic; however, a computed tomography scan of the chest showed 2 small foci of ground-glass density with new curvilinear atelectasis. She received her cryopreserved stem cell infusion as scheduled, and a 10-day course of remdesivir was promptly started. Additionally, a single unit of high-antibody-titer COVID-19 convalescent plasma was given on day +2 per US Food and Drug Administration emergency use authorization (https://www.fda.gov/media/141478/download). On day +19, she developed a 39.3°C fever, with computed tomography of the chest showing interval development of new multifocal ground-glass opacities bilaterally. An additional course of remdesivir for 10 days and empiric antibacterial and fungal coverage were instituted. Fever continued to day +21, when she achieved neutrophil engraftment.

### Engraftment syndrome

Because of the persistent fever and an episode of hypotension, associated with a rise in inflammatory clinical biomarkers (Figure 1B-C), 1 dose (8 mg/kg) of tocilizumab was administered. By day +24, she had developed a rash concerning for engraftment syndrome, for which she received a single dose of methylprednisolone sodium succinate 30 mg IV. Concurrently, she received infusion of SARS-CoV2-specific monoclonal antibody (casirivimab/imdevimab: Regeneron Pharmaceuticals) under emergency investigational new drug application.

### Immune reconstitution

Day +30 engraftment studies from peripheral blood showed successful donor-derived myeloid, T-cell, and natural killer cell engraftment (100% donor chimerism in all lineages). Discharge occurred on day +35, and on day +44, she tested negative for SARS-CoV2 by NPS RT-PCR. Day +100 bone marrow biopsy confirmed malignancy remission with no residual disease (detailed clinical time course in supplemental Table 1). Follow-up to day +365 was unremarkable, except for chronic graft-versus-host disease, which was resolved on prednisone and topical steroids; and hypogammaglobulinemia, requiring immunoglobulin infusions. She received both doses of BNT162b2 messenger RNA vaccine (on days +212 and +242) without adverse events. As of the writing of this report, the patient is alive and without evidence of malignancy or COVID-19, 1 year after HCT.

## Methods

Biospecimen collection and immunological analyses are detailed in supplemental Materials. Briefly, SARS-CoV-2 S and N humoral and cellular responses were characterized by performing SARS-CoV-2-specific neutralization assays based on lentiviral-pseudovirus, qualitative in-house-developed enzyme-linked immunosorbent assay, longitudinal ELISPOT for the detection of interferon-γ (IFN-γ)/IL-4 cytokines and multiparameter flow cytometry T-cell analyses. Patient specimens were also assessed for presence of SARS-CoV-2 S- and N-specific immunoglobulin G (IgG), IgM, mucosal humoral immunity (IgA), and functional cellular immunity, with T-cell memory immune phenotyping. Clinical and laboratory data were collected from electronic medical records.

## Results and discussion

To our knowledge, this is the first reported case of successful allogeneic HCT in a patient with active COVID-19 infection detected at day −1 of HCT. Prompt intervention with remdesivir (Figure 1A) did not appear to have an adverse effect on regimen-related organ toxicities. Neutrophil engraftment occurred at day +21 with clinical features of engraftment syndrome/cytokine release syndrome (CRS) associated with pulmonary infiltrates and high fevers (Figure 1A-C). It is possible that the active COVID-19 infection augmented the engraftment-associated CRS.[8] Nonetheless, our patient's engraftment syndrome/possible COVID-19 CRS resolved with corticosteroids and tocilizumab.[9] Full donor chimerism of myeloid and T cells was achieved by day +30, at which time longitudinal measurements of SARS-CoV-2-specific T cells started (Figure 2A; supplemental Figure 1). Immune monitoring showed elevated and steady levels of functional CD4 T cells specific for epitopes spanning the whole SARS-CoV-2 proteome and producing abundant IFN-γ in response to S and, to a lesser extent to N. Levels of SARS-CoV-2-specific functional T cells and IFN-γ measured in this patient were 5 to 10 times higher than in healthy adults who received COVID-19 vaccines (Chiuppesi et al, unpublished data), and exceeded those observed in a cohort of COVID-19 convalescent individuals.[10] There is accumulating evidence that early induction of SARS-CoV-2-specific T cells display a critical role in mitigating COVID-19, including modulating disease severity,[11] especially for immunocompromised hosts.[4,12] In the case of cytomegalovirus (CMV), which can cause significant morbidity and mortality in allogeneic HCT recipients, early reconstitution of polyfunctional CMV-specific T cells after T-cell-replete HCT (with tacrolimus/sirolimus prophylaxis) is associated with control of CMV viremia.[13] Moreover, recent studies have shown the presence of SARS-CoV-2 cross-reactive CD4 T cells in donors who were not exposed to SARS-CoV-2.[11,14] In our patient, it would be plausible that preexisting memory T cells in the donor graft, displaying cross-reactivity with SARS-CoV-2 and rapidly expanding in the viremic recipient early posttransplant, have contributed to viral control. Prolonged shedding of respiratory viruses in allogeneic HCT recipients is not uncommon as observed with rhinovirus,[15] endemic human coronaviruses,[16] and SARS-CoV-2.[17] The long-term shedding of viral RNA has been reported in COVID-19 immunocompetent individuals and more informative surrogates of viral transmission are often recommended.[18]

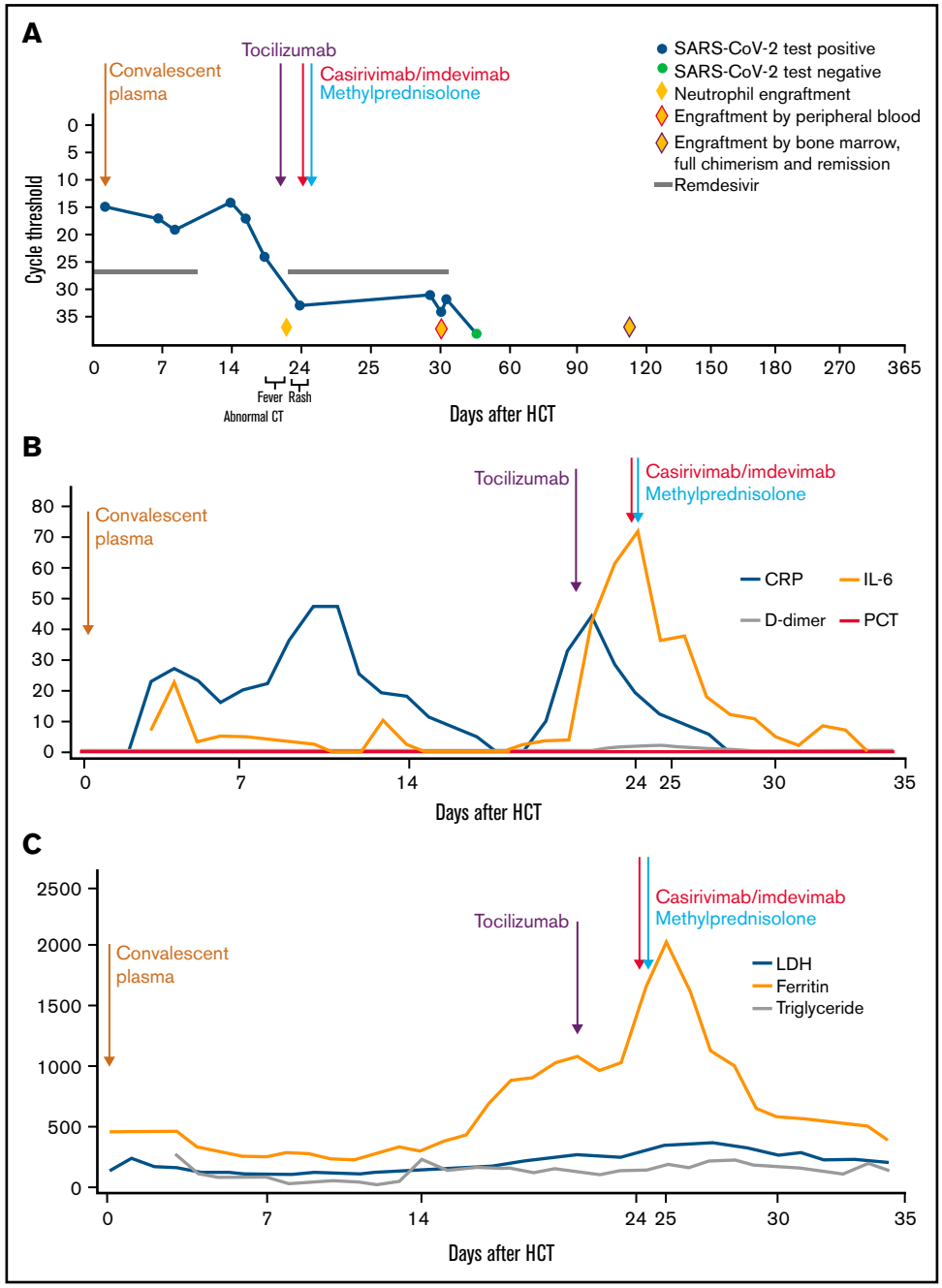


**Figure 1. Clinical course and days of interventions, from day −12 to day 100 post-HCT.** (A) The y-axis shows the SARS-CoV-2 Spike gene (S) cycle threshold (Ct) detected in the patient NPS. The S Ct measured by DiaSorin Molecular Simplexa COVID-19 direct assay real-time RT-PCR, for the qualitative detection of nucleic acid from SARS-CoV-2 coronavirus in NPS, are reported at the day post-HCT in which the NPS was performed. Ten-day courses of remdesivir (day 0 and +21) are indicated by the horizontal gray bars. Arrows show day of single dose administration of convalescent plasma (day +2), tocilizumab (day +21), methylprednisolone, and casirivimab/imdevimab (REGN-COV2) (both on day +24). (B-C) Clinical inflammatory biomarkers. (B) Longitudinal levels (x-axis, HCT day) of C-reactive protein (CRP, blue line; y-axis, mg/L), interleukin 6 (IL-6, orange line; y-axis, pg/mL), D-dimer (purple line; y-axis, mg/L), and procalcitonin (PCT, red line; y-axis, ng/mL) inflammatory markers; and HCT day of administration for tocilizumab (red arrow) and methylprednisolone (green arrow). (C) Longitudinal levels of lactic dehydrogenase (LDH, blue line; y-axis, U/L), ferritin (orange line; y-axis, ng/mL), and triglycerides (gray line; y-axis, mg/mL) inflammatory markers; and HCT day (x-axis, HCT day) of administration for tocilizumab (red arrow) and methylprednisolone (green arrow).

We observed no significant increase in detectable antibodies against SARS-CoV-2 antigens after COVID-19 convalescent plasma,[19] whereas casirivimab/imdevimab IgG1 monoclonal antibodies were detectable for prolonged duration (Figure 2B; supplemental Figure 2). The very high levels of S, S receptor-binding domain-IgG1, and neutralizing antibody,[20] and the concomitant absence of N-specific and of SARS-CoV-2-specific IgM/IgA/IgG3 suggest that SARS-CoV-2 seropositivity early posttransplant was due to casirivimab/imdevimab,[20]

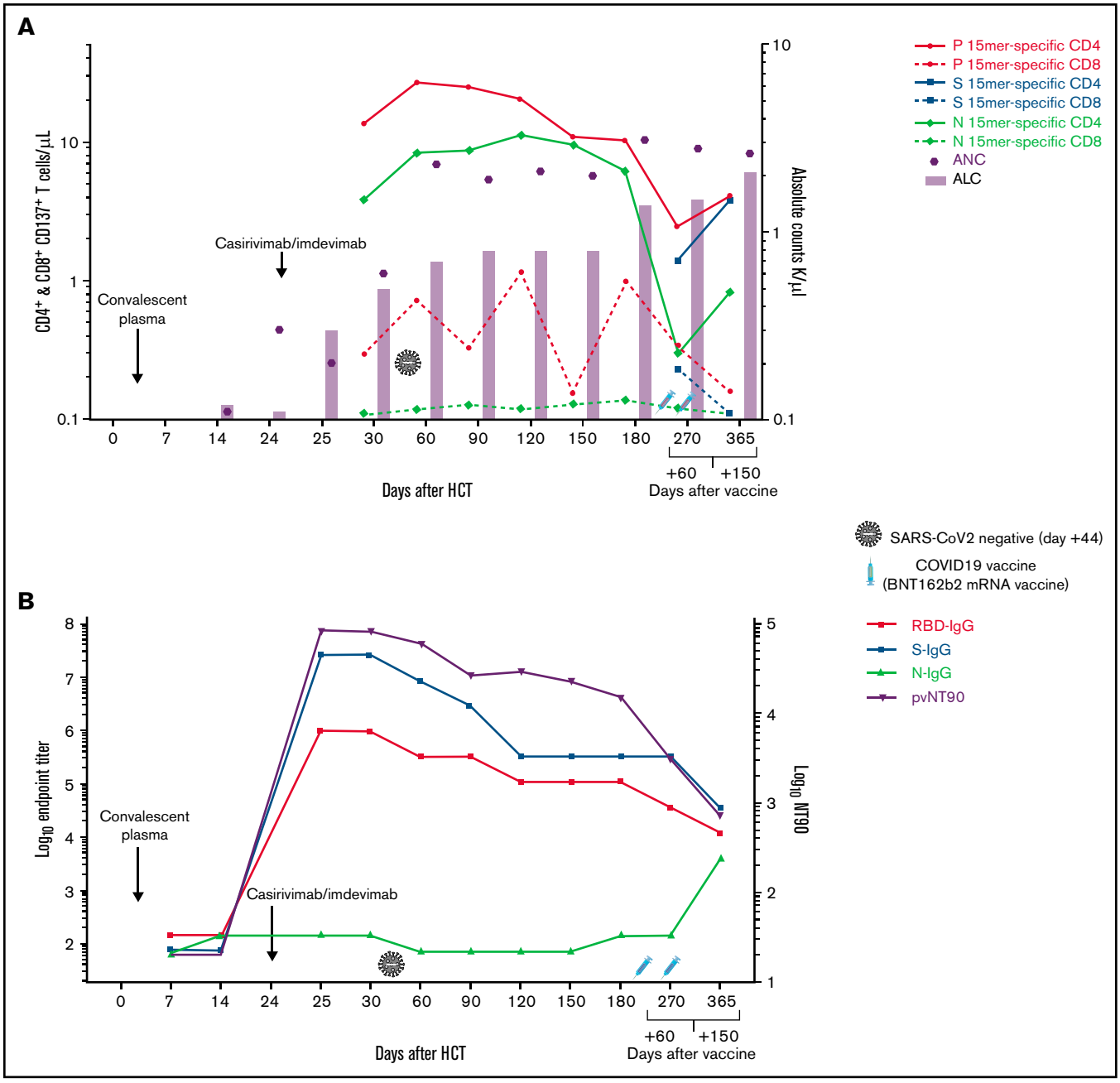


**Figure 2. Postengraftment levels of SARS-CoV2-specific cellular and humoral responses.** (A) In the plot, black circle symbols and lines indicate postengraftment (day +30 after HCT) longitudinal profiles of activated CD4 ($CD4^+CD137^+$, filled symbols and line) and CD8 T cells ($CD8^+CD137^+$, empty symbols and segmented line) specific for SARS-CoV-2 entire epitome (Proteome, P 15mer peptide library); red square symbols and lines activated CD4 (filled symbols and line) and CD8 T cells (empty symbols and segmented line) specific for SARS-CoV-2 Spike (S, S 15mer peptide library); blue diamond symbols and lines activated CD4 (filled symbols and line) and CD8 T cells (empty symbols and segmented line) specific for SARS-CoV-2 Nucleocapsid (N, N 15mer peptide library). NPS RT-PCR testing for SARS-CoV-2 and COVID-19 vaccine injections (BNT162b2 messenger RNA vaccine) are represented by icons. Scatter dots indicate absolute neutrophil counts (ANC, 2.0-7.3 K/µL normal range), and bars absolute lymphocyte counts (ALC, 0.8-3.1 K/µL normal range) measured after HCT. Percentage of lymphocytes started to be consistently within range by day 22 after HCT. (B) Binding antibodies to S, S receptor binding domain (RBD), and N were detected by enzyme-linked immunosorbent assay at the indicated time points. Neutralizing antibodies were measured using SARS-CoV-2 pseudovirus (pv) with S D614G mutation. Shown is the serum dilution that neutralized 90% of the pv (NT90). Approximate time of convalescent plasma and casirivimab/imdevimab (REGN-CoV2) infusions and COVID-19 vaccine injections are indicated.

rather than to de novo immunoglobulin production. However, low levels of S IgG3 and N-specific IgG started to be measurable after vaccination with BNT162b2. These findings are consistent with known delay in B-cell functional reconstitution and adaptive humoral immune recovery after HCT.[21] Injection of high doses of SARS-CoV-2 neutralizing monoclonal antibodies characterized by extended half-life had

relatively limited effects on COVID-19 in clinical trials.[20,22] As suggested by Sette and Crotty,[23] high concentrations of monoclonal antibodies are a key strategy to buy time before the development of an effective T-cell response (supplemental Figure 3). SARS-CoV-2-specific T cells measured in our patient were also durable, and after BNT162b2 messenger RNA vaccination the P- and S-specific functional CD4 T-cell levels increased (Figure 1A).

In summary, this case lends credence that successful allogeneic HCT in patients with active COVID-19 infection, treated with SARS-CoV-2-specifc targeted therapies, is possible and may suggest that early expansions of functional SARS-CoV-2-specific T cells can suppress viral replication. Nonetheless, in the current case, the causality of the favorable outcomes cannot be clearly identified. A multimodal intervention with early initiation of antiviral therapy and use of monoclonal antibodies is recommended. Approaches that may augment SARS-CoV-2-specifc immune recovery, such as adaptive cellular therapy[24] and COVID-19 donor vaccination,[25] to achieve transfer of SARS-CoV-2-specifc cellular immunity in the recipient could be considered for patient management.

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## Authorship

Contribution: I.A., S.D., H.P., and A.P. treated the patient; S.D., R.N., J.A.Z., C.L.R., M.A.M., D.J.D, and S.J.F. designed the study; F.C., Q.Z., V.K., K.F., Y.P., T.K., D.J., and S.O.F. performed specimen processing, reagent preparation, and immunological assays; C.L.R., F.C., and Y.P. analyzed the immune monitoring data; H.P., C.L.R., F.C., and A.P. wrote the initial manuscript; and all authors approved the final version.

Conflict-of-interest disclosure: C.L.R. received consulting fees and research funding from Helocyte Inc. D.J.D. received consulting fees, patent royalties, research funding, and fees for serving on the advisory board of Helocyte Inc and has 2 patents (8 580 276 and 9 675 689) that are licensed to Helocyte. D.J.D. and F.C. are co-inventors of the Patent Cooperation Treaty (PCT) application that covers the development of a COVID-19 vaccine (PCT/US2021/032821). R.N. is a consultant for Omeros, Bluebird, Viracor Eurofins, Magenta Therapeutics, Kadmon, and Napajen Pharma; received research funding from Helocyte and Miyarisan Pharmaceutical; and travel, accommodations, and expenses from Kyowa Hakko Kirin, Alexion Pharmaceuticals. S.D. is a consultant for Merck, Allovir, and Aseptiscope; on the advisory board for Merck; is an investigator for Allovir, Merck, Ansun, Gilead, Janssen, and Shire/Takeda; and is on speakers bureau of Merck and Astellas. The remaining authors declare no competing financial interests.

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