stages of the trial, including funding acquisition and publication. Finally, we clearly state in the article that mycophenolate increases the risk of miscarriage and birth defects, and stringent contraceptive measures were required during the trial. In addition, we have been very careful to avoid the conclusion of recommending mycophenolate mofetil as a routine first-line option and have called for further research to clarify the role of this drug in treatment pathways.

In response to van Dijk and Schutgens: we selected the generic quality-of-life tools for their validity, reliability, and responsiveness in adult patients with ITP.[3] We chose to use the area under the curve (as is used in health economic analysis) to assess patients' quality of life during the entire follow-up period rather than at an individual time point. We acknowledge that the differences in quality-of-life scores could be chance findings after adjustment for multiple testing, and we agree that the clinical importance of this difference has not been proved and that combination therapy may be justified in some circumstances.

Charlotte A. Bradbury, M.D., Ph.D.
University of Bristol
Bristol, United Kingdom
c.bradbury@bristol.ac.uk

Quentin Hill, M.D.
Leeds Teaching Hospital NHS Trust
Leeds, United Kingdom

Rosemary Greenwood, M.Sc.
University Hospitals Bristol and Weston NHS Trust
Bristol, United Kingdom

Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc2115772

VITT after ChAdOx1 nCoV-19 Vaccination

TO THE EDITOR: The *Journal* recently published three studies involving a total of 39 persons in whom vaccine-induced immune thrombotic thrombocytopenia (VITT), a devastating syndrome characterized by thromboses in unusual sites, developed after they received the ChAdOx1 nCoV-19 vaccine. The articles by Schultz et al. and Greinacher et al. (June 3 issue)[1,2] and by Scully et al. (June 10 issue)[3] all conclude that it was highly unlikely that the patients had been previously infected with SARS-CoV-2, since they tested negative for antibodies to the SARS-CoV-2 nucleocapsid protein. I believe that this statement is questionable and probably erroneous.

Studies have shown that most SARS-CoV-2 infections are in asymptomatic persons and that up to 10% of mild-to-moderate confirmed cases of Covid-19 do not involve serologic conversion, so SARS-CoV-2 antibodies will not be detectable during or after infection.[4,5] Given that data on T-cell responses, which are highly sensitive (and more specific than antibodies for previous exposure to SARS-CoV-2), are missing, previous SARS-CoV-2 infection cannot be ruled out.[4,5] It is disappointing that none of the three studies reported in the *Journal* took advantage of the T-cell–receptor sequencing tests that have been approved by the Food and Drug Administration (FDA) (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-adaptive-biotechnologies-t-detect-covid-test) to rule out the presence of Covid-19–specific T lymphocytes. Confirmed exposure to SARS-CoV-2 might link the syndrome to persistent vascular inflammation in a small subgroup of persons,[6] allow for the implementation of risk-mitigation strategies, and explain why VITT is more frequent than had been found in an early trial of the ChAdOx1 nCoV-19 vaccine.[7]

Alessandro D. Santin, M.D.
Yale University School of Medicine
New Haven, CT
alessandro.santin@yale.edu

No potential conflict of interest relevant to this letter was reported.

This letter was published on November 3, 2021, at NEJM.org.

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DOI: 10.1056/NEJMc2111026

TO THE EDITOR: The occurrence of thrombocytopenia and thrombosis at unusual vascular sites after adenoviral vector–based vaccination against SARS-CoV-2 has alarmed the public. Laboratory findings from three independent case series indicate a pathomechanism similar to that of autoimmune heparin-induced thrombocytopenia (HIT) — namely, high titers of IgG antibodies to platelet factor 4 (PF4)–polyanion complexes that activated platelets by means of FcγIIA receptors. We note that the syndrome was termed VITT and that patients were treated with intravenous immune globulin. Nevertheless, the high mortality suggests the need for other, possibly more effective, treatment options.

Bruton's tyrosine kinase (BTK) inhibitors that have been approved for the treatment of B-cell cancers block the FcγIIA receptor–mediated platelet aggregation induced by serum obtained from patients with HIT and inhibit various prothrombotic pathways while also preserving hemostatic functions.[1,2] We found that low concentrations of the BTK inhibitors ibrutinib and fenebrutinib prevented platelet aggregation in-

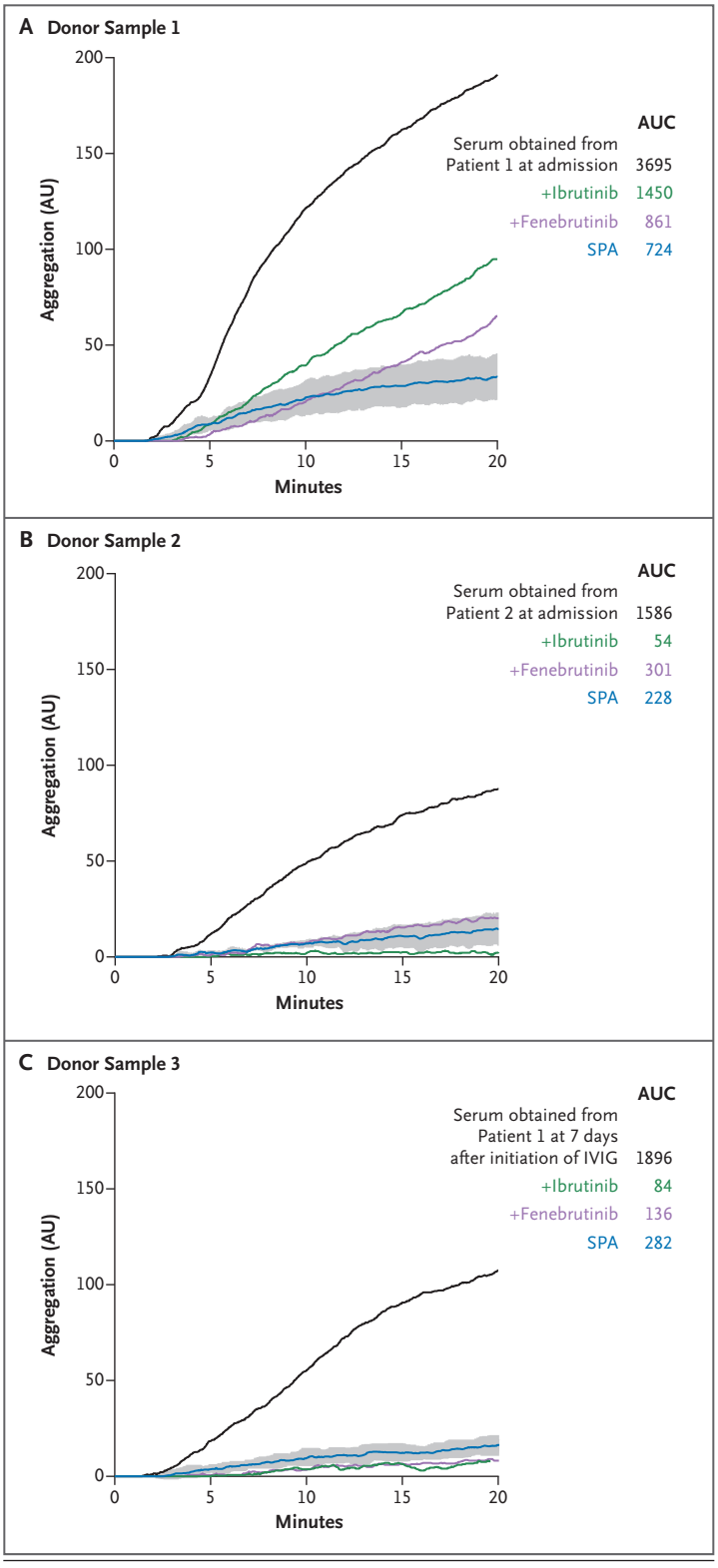

Figure 1. Platelet-Aggregating Activity in Donor Samples in Response to Serum Obtained from Patients with Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT).

Shown are results in blood samples obtained from healthy donors whose platelet-aggregating activity in response to serum obtained from patients with VITT was inhibited by a Bruton's tyrosine kinase inhibitor (ibrutinib or fenebrutinib). Serum samples from two patients with VITT were obtained at admission; an additional sample from Patient 1 was obtained 7 days after the initiation of intravenous immune globulin (IVIG) therapy. Also shown is the mean spontaneous platelet aggregation (SPA) without added serum (blue); the shaded area around the blue line in each panel indicates the standard deviation. Full experimental details are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org. AU denotes arbitrary units, and AUC the area under the curve.

duced by serum obtained from patients with VITT and that the drugs added to partial inhibition with intravenous immune globulin therapy or FcγIIA receptor blockade (Fig. 1). Therefore, we consider the oral application of low-dose BTK inhibitors for the early treatment of suspected VITT (on the basis of symptoms, elevated D-dimer level, and thrombocytopenia) to be a therapeutic option beyond intravenous immune globulin and direct oral anticoagulants that is worthy of testing.

Christian Weber, M.D.
Philipp von Hundelshausen, M.D.
Wolfgang Siess, M.D.

University Hospital at LMU Munich
Munich, Germany
chweber@med.lmu.de

No potential conflict of interest relevant to this letter was reported.

This letter was published on November 3, 2021, at NEJM.org.

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DOI: 10.1056/NEJMc2111026

DRS. GREINACHER AND THIELE AND A COLLEAGUE REPLY: Santin suggests an interesting approach for ruling out previous asymptomatic SARS-CoV-2 infection by means of a T-cell–receptor sequencing test. Unfortunately, this assay may not be able to confirm or rule out prevaccination SARS-CoV-2 infection. The FDA emergency use authorization for this assay indicates that pedigreed specimens with direct evidence of previous non–SARS-CoV-2 coronavirus (common cold) strains such as HCoV-HKU1, HCoV-NL63, HCoV-OC43, or HCoV-229E have not been evaluated.[1] Persons who had a common cold before testing might have a false positive result. Furthermore, vaccination induces a T-cell response mainly against the SARS-CoV-2 spike protein.[2] To our knowledge, it remains unclear whether the assay can differentiate between T-cell receptors that are specific for the spike protein and T-cell receptors that recognize epitopes on other proteins of SARS-CoV-2. The performance of this test has not been established in persons who have received a Covid-19 vaccine. We had the opportunity to interview 30 patients with VITT. Most patients were young and had been healthy before vaccination without any evidence of clinical symptoms associated with ongoing inflammation or persistent vascular inflammation.

Weber and colleagues build on their recent article,[3] the hypothesis of which is consistent with in vitro experiments that have been conducted by others.[4] Pharmacologic interference with the activation pathway of the FcγIIA receptor may be an attractive option in the treatment of patients with VITT. Such approaches include BTK inhibitors, Src and Syk inhibitors, and deglycosylation of IgG by a specific enzyme that abrogates the binding of IgG to the FcγIIA receptor.[5] However, no clinical data are available on the application of these strategies in patients with VITT or other FcγIIA receptor–mediated platelet-activating disorders, including HIT. Currently, most clinical experience involves the use of intravenous immune globulins for blocking FcγIIA receptor–mediated platelet activation in patients with VITT or autoimmune HIT. However, the proposed options might be of high interest in persons in whom VITT antibodies persist as autoantibodies causing platelet activation and recurrent thrombosis or in medical systems that have limited access to or an insufficient supply of pharmacologic intravenous immune globulins.

Andreas Greinacher, M.D.
Linda Schönborn, M.D.
Thomas Thiele, M.D.

Universitätsmedizin Greifswald
Greifswald, Germany
andreas.greinacher@med.uni-greifswald.de

Dr. Schönborn reports no potential conflict of interest relevant to this letter. Since publication of their article, Drs. Greinacher and Thiele report no further potential conflict of interest.

This letter was published on November 3, 2021, at NEJM.org.

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DOI: 10.1056/NEJMc2111026

DR. SCULLY REPLIES: Patients in the three cohorts presented with this new clinical syndrome of VITT after receiving their first dose of the ChAdOx1 nCoV-19 vaccine, and they met the diagnostic criteria for VITT, including the presence of anti-PF4 antibodies. Important considerations included the role of SARS-CoV-2 infection and the presence of antibodies, both to SARS-CoV-2 and to the vaccine. In our cohort, we conducted extensive SARS-CoV-2 antibody testing with a flow cytometer (CytoFLEX, Beckman Coulter). SARS-CoV-2 spike, receptor-binding domain, and nucleocapsid IgG serum angiotensin-converting–enzyme 2–receptor binding inhibition and spike antibodies to seasonal coronaviruses HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E were measured by a multiplexed electrochemiluminescent assay (Meso Scale Discovery), as previously described.[1] These confirmed antibody levels were compatible with the receipt of one dose of vaccine only and were not suggestive of antibodies to SARS-CoV-2.

Persons may have asymptomatic SARS-CoV-2 infection, and the antibodies may not be detectable by current assays. A plausible hypothesis is SARS-CoV-2 antibodies could be stimulated in relation to an acute event, such as VITT. SARS-CoV-2 was not detected in any patient on polymerase-chain-reaction (PCR) testing.

Santin asks why T-cell–receptor sequencing tests were not also used. The assay was approved by the FDA only under emergency use authorization, and we rely on evaluated PCR-based tests. As documented by the FDA,[2] it is unknown how long the T-cell immune response remains after infection and how long protection is provided by the T-cell immune response. Finally, the importance of the three *Journal* articles describing VITT cases was to highlight this life-threatening condition that may occur after ChAdOx1 nCoV-19 vaccination. Further work is necessary to understand the pathogenesis, and T-cell–receptor sequencing tests may be a focal assay to help elucidate the cause.

Weber and colleagues present their hypothesis and laboratory data on the use of BTK inhibitors in patients with VITT. Their data make perfect biologic sense. Companies that produce these compounds have been contacted but were unable to participate in a clinical study involving patients with VITT. The initial treatment was based on the extrapolation of HIT treatment for this new syndrome. The treatment and outcomes have been presented for a large cohort of cases,[3] but this study did not include BTK inhibitors.

Marie Scully, M.D.

University College London Hospitals NHS Foundation Trust
London, United Kingdom
m.scully@ucl.ac.uk

Since publication of her article, the author reports no further potential conflict of interest.

This letter was published on November 3, 2021, at NEJM.org.

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DOI: 10.1056/NEJMc2111026

Convalescent Plasma for Outpatients with Covid-19

TO THE EDITOR: In the Covid-19 Convalescent Plasma in Outpatients (C3PO) trial,[1] Korley et al., members of the Strategies to Innovate Emergency Care Clinical Trials Network (SIREN), administered convalescent plasma to high-risk outpatients within 1 week after the onset of symptoms of Covid-19. It is unclear why the authors selected 1 week instead of a shorter time frame, since it has been shown that the 30-day and 60-day mortality benefits of convalescent plasma have been observed when it is administered within 3 days after diagnosis and that the benefit dissipates after this point.[2,3]

The aim of their trial was to determine whether convalescent plasma prevents progression to severe Covid-19. However, severe Covid-19 was not defined, and the authors instead assessed disease progression, which relies on surrogate