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Treatment Strategies for Deficiency of Adenosine Deaminase 2

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TO THE EDITOR:

The deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive disease caused by biallelic mutations in *ADA2* (formerly *CECRI*).^{1,2} Manifestations include fever, early-onset lacunar stroke, livedo racemosa, portal hypertension, nodular vasculitis, immunodeficiency, red-cell aplasia, and neutropenia. Adenosine deaminase 2 (ADA2) is a growth factor for endothelial cells and promotes the differentiation of M2 macrophages. Deficiency of this enzyme results in decreased vascular integrity, a predominance of proinflammatory M1 macrophages, and perivascular inflammation mediated by tumor necrosis factor (TNF). For some patients, stroke episodes begin early in childhood and may affect areas deep in the brain. No defined treatment strategies exist, but exogenous ADA2 replacement and immunomodulatory drugs such as TNF inhibitors have been considered.^{2,3} There are case reports of successful allogeneic hematopoietic stem-cell transplantation with myeloablative or reduced-intensity conditioning in patients with profound immunodeficiency or primary hematologic manifestations.^{4,5}

In an open-label study, we administered a weeklong series of five infusions of fresh-frozen plasma (FFP), which normally contains approximately 13.8 mU per milliliter (range, 4.8 to 27.2) of ADA2, to 3 patients between the ages of 5 and 7 years in whom DADA2 had been diagnosed. We found no major safety concerns but little evidence of any durable effect on serum ADA2 levels, with pharmacokinetic studies showing very rapid clearance of the exogenous ADA2 (Fig. 1A; and Fig. S1 in the Supplementary Appendix, available with the full text of this letter at [NEJM.org](https://www.nejm.org)).

In a separate study, we initiated adjunctive anti-TNF therapy in an attempt to reduce glucocorticoid use and prevent neurologic events in 15 consecutive patients with DADA2. All the patients, who ranged in age from 3 to 26 years, had a history of stroke, and 12 had had more than one stroke; of the latter patients, 10 had received other forms of immunomodulatory therapy to prevent recurrent stroke with unsuccessful results (Table S2 in the Supplementary Appendix). Each of the patients received etanercept (at a dose of 0.8 to

1.2 mg per kilogram of body weight to a maximum of 50 mg weekly), adalimumab (40 mg every 1 to 2 weeks), infliximab (4 to 5 mg per kilogram every 6 weeks), or golimumab (50 mg weekly). Additional details about the medication regimens are provided in the Supplementary Appendix.

During treatment, all 15 patients underwent at least one follow-up examination with magnetic resonance imaging of the brain, and 11 patients underwent two or more follow-up scans without the observation of any new infarcts (Tables S3 and S4 in the Supplementary Appendix). Before the initiation of anti-TNF therapy, the patients had a cumulative duration of DADA2 of 2077 patient-months (i.e., since birth) and a cumulative total of 55 strokes. After anti-TNF initiation, the patients had no strokes during 733 patient-months of follow-up, with a median duration of 47 months (range, 25 to 128) ($P<0.001$) (Fig. 1B). Using a binomial approach for matched follow-up time, we determined that during the 733 patient-months before the initiation of therapy, the patients had 37 strokes (Fig. 1C).

Before anti-TNF treatment, 10 of the 15 patients were receiving glucocorticoids at an average dose of 0.53 mg per kilogram of body weight per day of prednisone equivalent (range, 0.23 to 1.08) (Table S4 in the Supplementary Appendix). At the time of the data analysis, all the patients had been weaned from glucocorticoids.

In addition to the major reduction in stroke activity, anti-TNF treatment resulted in positive changes in several key laboratory and other measurements. Before treatment, 10 patients had elevated levels of acute-phase reactants (indicating increased inflammation), values that normalized after anti-TNF initiation. Before therapy, 4 patients had anemia that resolved after treatment, although anemia developed in 1 patient during anti-TNF therapy as part of evolving bone marrow failure. Among 5 patients with hepatomegaly, the size of the liver normalized on follow-up ultrasonography after anti-TNF treatment, although mild hepatomegaly developed in 2 other patients after anti-TNF initiation. Of the 12 patients who had undergone transient elastography to quantify liver fibrosis, all had levels of less than 7 kPa (the cutoff value indicating no increase in hepatic stiffness associated with underlying liver disease) after anti-TNF therapy, including 6 who had had levels of more than 7 kPa before therapy.

There were no serious adverse events associated with anti-TNF therapy. Infusion reactions to infliximab developed in 1 patient, which necessitated a change to adalimumab. Of the 15 patients, 14 continued to receive anti-TNF therapy at the most recent follow-up. One patient discontinued the anti-TNF agent after undergoing successful hematopoietic stem-cell transplantation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Zhou Q, Yang D, Ombrello AK, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. *N Engl J Med* 2014;370:911–20. [PubMed: 24552284]
2. Navon Elkan P, Pierce SB, Segel R, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. *N Engl J Med* 2014;370:921–31. [PubMed: 24552285]
3. Caorsi R, Penco F, Grossi A, et al. ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study. *Ann Rheum Dis* 2017;76: 1648–56. [PubMed: 28522451]
4. Nanthapisal S, Murphy C, Omoyinmi E, et al. Deficiency of adenosine deaminase type 2: a description of phenotype and genotype in fifteen cases. *Arthritis Rheumatol* 2016;68:2314–22. [PubMed: 27059682]
5. Hashem H, Kumar AR, Müller I, et al. Hematopoietic stem cell transplantation rescues the hematological, immunological, and vascular phenotype in DADA2. *Blood* 2017;130: 2682–8. [PubMed: 28974505]

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Figure 1. Effects of FFP Administration and Anti-TNF Initiation in Patients with ADA2 Deficiency.
Panel A shows the half-life of adenosine deaminase 2 (ADA2) in 3 patients with a deficiency of this enzyme after an infusion of 100 ml of fresh-frozen plasma (FFP). Blood samples were drawn immediately after completion of the infusion and at 2 hours, 4 hours, and 6 hours after infusion, with values plotted after correction for the patient’s baseline ADA2 value. The median half-life was approximately 6.4 hours (range, 5.0 to 9.0). Panel B shows the cumulative number of strokes and recurrence rate in 15 study patients before and after the inhibition of tumor necrosis factor (TNF), according to the number of patient-months observed ($P<0.001$ by the likelihood ratio test). Panel C shows the number of strokes in the same 15 patients on the basis of matched follow-up time (733 patient-months) before and after anti-TNF therapy ($P<0.001$ by the Blyth–Still–Casella method).