



Letters

Outcomes of 3 patients with adenosine deaminase deficiency on long-term enzyme replacement therapy

Adenosine deaminase (ADA) deficiency is an autosomal recessive severe combined immunodeficiency that typically presents within the first year with severe infections. Other features of ADA deficiency include the following: autoimmunity, myeloid dysplasia, pulmonary disease, neurodevelopmental delay, skeletal dysplasia, hepatic dysfunction, and lymphoma.¹ Hematopoietic stem cell transplant (HSCT) and gene therapy (GT) have been successful in the treatment of ADA deficiency.^{2,3} Enzyme replacement therapy (ERT) has traditionally been used as a bridge to HSCT or GT and not as first-line, long-standing treatment. However, compliance is essential for long-term successful ERT.

ADA converts deoxyadenosine to deoxyinosine. In its absence, elevated deoxyadenosine triphosphate impairs lymphocyte survival. The enzymatic processing of purine toxic metabolites was initially accomplished by exchange transfusions with ADA-positive red blood cells. Bovine pegylated ADA (PEG-ADA) (pegademase bovine [ADAGEN {Leadiant Biosciences, Pomezia, Italy}]) was introduced in 1984 on a research basis, and the Food and Drug Administration approved it in 1990. Recombinant PEG-ADA (elappegademase [Revcovi {Leadiant Biosciences, Pomezia, Italy}]) was used on a research basis in 2015, and the Food and Drug Administration approved it in 2019. GT commenced in 1990.⁴

The outcome of ERT has been variable.⁵ There are 3 previously reported patients treated with PEG-ADA as ERT for more than 20 years. One patient who was treated with PEG-ADA for 27 years developed lymphoma.⁶ Another patient on PEG-ADA for 22 years had global developmental delay,² though neurologic defects are not expected to be corrected by ERT, HSCT, or GT. The third patient treated for 24 years remained clinically well.⁷ These 3 patients were never on exchange transfusion and had variable immune reconstitution with multiple severe infections on treatment. In addition, Kuo et al⁸ described 64 patients with ADA deficiency with 80% overall survival, whom 40% underwent HSCT and 70% were given ERT. However, the longest follow-up in this cohort was 26 years.

We present another cohort of 3 patients with ADA deficiency on PEG-ADA for 33, 36, and 25 years, respectively, 2 of whom were on ERT for 42 years, the longest PEG-ADA and ERT in the patients with ADA deficiency to our knowledge to date.

Patient A was diagnosed as having ADA deficiency at the age of 19 months.⁹ In early infancy, he had failure to thrive, oral candidiasis, absent tonsils, and *Pneumocystis* pneumonia. At the age of 22 months, he commenced partial exchange transfusions that continued until he was 9 years old when he started

intramuscular bovine PEG-ADA (ADAGEN). Although he had low B cells, he had normal serum immunoglobulins and never required immunoglobulin replacement therapy. Patient A had intermittent sinopulmonary infections when not compliant. He had extensive cutaneous verruca vulgaris throughout his body starting in his late 20s. Furthermore, he developed type I diabetes (T1DM) in his early 40s. He died at the age of 42 years secondary to noncompliant treatment of his T1DM leading to diabetic ketoacidosis.

Patient B is the younger brother of patient A and was diagnosed as having ADA deficiency by amniocentesis.^{9,10} At the age of 6 weeks, he underwent exchange transfusions. He transitioned to bovine PEG-ADA (ADAGEN) at the age of 6 years and to intramuscular recombinant PEG-ADA (Revcovi) at the age of 38 years. He had persistent hypogammaglobulinemia warranting replacement immunoglobulin at the age of 2 years. In childhood, he had chronic diarrhea that improved on PEG-ADA. He suffered recurrent skin abscesses and dental infections throughout adulthood regardless of compliance. He had primary varicella without recurrence. He was diagnosed as having hepatitis C at the age of 25 years secondary to intravenous drug abuse and underwent antiviral treatment with no detection of viremia. He had extensive cutaneous verruca vulgaris starting in his early 20s, which progressed to squamous cell carcinoma that still persists. When not compliant with therapy in his late 20s, he had pneumonia, bacteremia, and meningitis. He had ischemic strokes at ages 27 and 33 years. The patient is currently 42 years old and continues recombinant PEG-ADA and immunoglobulin (subcutaneous 500 mg/kg/month divided every 2 weeks with no related complications). His strokes left residual deficits, but he is ambulatory, high functioning, married with children, though not currently employed.

Patient C was diagnosed as having ADA deficiency at the age of 12 months after presenting with chronic diarrhea, pneumonia, otitis media, and oral candidiasis. He started bovine PEG-ADA (ADAGEN) and immunoglobulin. At the age of 18 months, he had mild idiopathic thrombocytopenia that self-resolved without complications. Replacement immunoglobulin was discontinued at the age of 10 years. He switched to recombinant PEG-ADA (Revcovi) at the age of 21 years. As a teenager, he was noncompliant with PEG-ADA and suffered chronic diarrhea, weight loss, recurrent localized varicella zoster, and pneumonia that resolved with compliance. The patient is currently 26 years old and continues recombinant PEG-ADA with no recent severe infections except persistent cutaneous bacterial abscesses throughout his body. He is high functioning, though with mild intellectual disability and not currently employed.

This ADA deficiency patient cohort is unique because all patients were diagnosed in infancy and treated throughout adulthood at the same center. All 3 patients presented with lymphopenia, poor

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Table 1
Trend of Laboratory Results From at Least 10 Years ago before Starting or while Not Compliant on ERT and Most Recent Laboratory Results Compliant on ERT (Left to Right)

Laboratory test	Patient A		Patient B		Patient C		Normal
Total lymphocytes (cells/ μ L)	500^a	838^b	740^c	2500 ^b	300^c	1300 ^b	1000–4800 ^b 3000–10,500 ^d
CD3+ (cells/ μ L, %)	UNK	106^b	1230 ^b	1938 ^b	187^b	989^b	1087–2198 ^b
CD4+ (cells/ μ L, %)	UNK	15^b	76 ^b	76 ^b	48^b	72 ^b	62–87 ^b
CD8+ (cells/ μ L, %)	UNK	270^b	570^b	570^b	124^b	553^b	677–1401 ^b
CD19+ (cells/ μ L, %)	UNK	17^b	23^b	32^b	40^b	40^b	38–55 ^b
CD16 + 56+ (cells/ μ L, %)	UNK	1088^b	1308 ^b	59^b	267^b	212–1007^b	212–1007 ^b
CD45RA+ (cells/ μ L, %)	UNK	69^b	52 ^b	15^b	19^b	15–38^b	15–38 ^b
CD45RO+ (cells/ μ L, %)	UNK	21^b	16^b	211 ^b	126^b	264^b	180–492 ^b
	UNK	3^b	1^b	8 ^b	17^b	19^b	8–23 ^b
	UNK	56^b	146 ^b	356 ^b	54^b	101^b	97–421 ^b
	UNK	8^b	9 ^b	14 ^b	7^b	7^b	5–17 ^b
	UNK	UNK	UNK	52^b	UNK	197 ^b	150–870 ^b
	UNK	UNK	UNK	10^b	UNK	33 ^b	28–71 ^b
	UNK	UNK	UNK	449 ^b	UNK	397 ^b	190–1050 ^b
	UNK	UNK	UNK	90^b	UNK	67 ^b	28–72
Mitogen-induced lymphocyte proliferation	Near absent	Near absent	Near absent	Suboptimal	Suboptimal	Near normal	Normal
Lymphocyte proliferation to anti-CD3/anti-CD25	UNK	UNK	UNK	Good	UNK	Good	Good
IgG (mg/dL)	100^a	1357 ^b	300^b	1160 ^{b,e}	1150 ^b	845 ^b	700–1600 ^b 424–1051 ^a
IgA (mg/dL)	410 ^a	217 ^b	0^b	42^{b,e}	134 ^b	84 ^b	60–400 ^b 14–123 ^a
IgM (mg/dL)	130 ^a	87 ^b	0^b	15^{b,e}	63 ^b	57 ^b	50–300 ^b 48–168 ^a
IgE (IU/mL)	UNK	UNK	822^b	57 ^{b,e}	UNK	1787^b	0–100 ^b
Tetanus titer protected postvaccination	Yes	Yes	Yes	Yes ^c	Yes	Yes	Yes
Strep pneumonia titer protected postvaccination	No	No	No	Yes ^c	No	Yes	Yes
ADA genetic defect	c.632G > A (p.Arg211His) p.986C > T (p.Ala329Val)		c.632G > A (p.Arg211His) p.986C > T (p.Ala329Val)		c.466C > T p.Arg156Cys Homozygous		None

Bolded values are out of range.

Abbreviations: ADA, adenosine deaminase; ERT, enzyme replacement therapy; Ig, immunoglobulin; UNK, unknown.

^aAge for laboratory value is 2 years old.

^bAge for laboratory value can be indicated as 18 years of age or above.

^cAge for laboratory value is 1 year old.

^dAge for laboratory value is 1 to 2 years old.

^eOn immunoglobulin.

mitogenic responses, absent ADA levels, and elevated deoxyadenosine nucleotide levels. Unfortunately, all patients had intermittent noncompliance associated with infections, in which immune parameters waned (particularly lymphocyte count) but improved with compliance. Antibodies to ADA were never checked owing to this improvement. Patients B and C have been compliant on recombinant PEG-ADA for the past 5 years, as the injections are administered in the office. Recombinant PEG-ADA is administered per manufacturer's instructions (0.2 mg/kg weekly). Serum ADA trough levels were maintained and deoxyadenosine nucleotide levels were undetectable on treatment. Plasma ADA activity trough levels were evaluated by biochemical assay (goal trough 20–25 μ mol/h/mL). All patients had immunologic improvement (Table 1). Most notably, patient B had low B cells, hypogammaglobulinemia, and poor specific antibodies, but now has normal B cells. All patients never had sinusitis or bronchiectasis, with patients B and C having recent computerized tomography scans. The only autoimmune complications are T1DM in patient A and idiopathic thrombocytopenia in patient B, though differential includes autoimmunity vs postviral.

All families refused HSCT at a young age. Patients A and B had an older brother with an ADA deficiency who died secondary to HSCT complications in infancy. HSCT and GT later in life were considered for all but were deferred owing to success on PEG-ADA. Patients B and C are alive but with considerable morbidities, which HSCT may have avoided. The degree of immune reconstitution with ERT is unclear. Our patient cohort reveals the relative efficacy of long-term ERT.

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