

A 24-Year Enzyme Replacement Therapy in an Adenosine-deaminase-Deficient Patient

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Severe combined immunodeficiency (SCID) is a fatal childhood disease unless immune reconstitution is performed early in life, with either hematopoietic stem cell transplantation or gene therapy. One of its subtypes is caused by adenosine deaminase (ADA) enzyme deficiency, which leads to the accumulation of toxic metabolites that impair lymphocyte development and function. With the development of polyethylene glycol-conjugated adenosine deaminase (PEG-ADA) enzyme replacement therapy, many ADA-deficient children with SCID who could not receive a hematopoietic stem cell transplantation or gene therapy survived and had longer and healthier lives. We report a 24-year course of treatment in a patient who was diagnosed with ADA deficiency at 4 months of age. The patient was treated with PEG-ADA, which was the only therapy available for him. The patient's plasma ADA level was regularly monitored and the PEG-ADA dose adjusted accordingly. This treatment has resulted in near-normalization of lymphocyte counts, and his clinical course has been associated with only minor to moderate infections. Thus far, he has had no manifestations of autoimmune or lymphoproliferative disorders. This patient is among the longest to be maintained on PEG-ADA enzyme replacement therapy.

The adenosine deaminase (ADA) enzyme is found in all cells, particularly the lymphocytes, and is essential for T-cell function. It deaminates adenosine (AXP) and 2'-deoxyadenosine. Mutations in the gene coding for ADA cause deficiency of this enzyme, which leads to elevated levels of deoxyadenosine triphosphate, which is cytotoxic and leads to cell apoptosis.^{1,2} ADA-deficient patients have dysfunction in all lymphocyte subtypes that results in severe combined immunodeficiency (SCID), a lethal disease during early childhood. ADA-deficient SCID patients comprise ~15% of all SCID cases³ and has the best prognosis with early immune reconstitution with stem cell transplantation or stem cell-targeted gene therapy (GT).

We report here the clinical course of a child, for whom immune reconstitution was not available, that we have been managing for 24 years on ADA enzyme replacement therapy. To our knowledge, this time frame is possibly the longest reported duration of such treatment.

CASE REPORT

Chief Complaint

Our patient presented at 3.5 months of age with fever and cough for a few days, diarrhea for 3 weeks, and oral thrush for 3 months. On physical examination, he had a temperature of 38.3°C, a respiratory rate of 25 breaths/min, a heart rate of 150 beats/min, and a weight of 8 lb 8 oz (<3rd percentile). The patient was

abstract

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Dr Tartibi provided clinical care of the patient, drafted the initial manuscript, and participated in preparing the final manuscript; Dr Hershfield provided expert special laboratory tests, offered guidance in patient management, and participated in preparing the final manuscript; Dr Bahna provided clinical care of the patient and participated in preparing the final manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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moderately dehydrated and appeared generally ill. He had severe oral thrush but no visible tonsils, palpable lymph nodes, or organomegaly. Chest auscultation showed clear lungs and normal heart sounds.

Birth History

Our patient was born term by cesarean delivery with a birth weight of 7 lb 12 oz to a 32-year-old G1 mother who received ampicillin-sulbactam before delivery because of fever. The amniotic fluid was meconium stained. The patient had poor Apgar scores of 4 and 6, bradycardia, and apnea requiring temporary intubation. Four hours' postdelivery, he became tachypneic, with partial pressure of oxygen of 65 mm Hg and a base deficit of 4.7 mEq/L. His chest radiograph showed bilateral mild patchy infiltrates. He improved on ampicillin and amikacin. At discharge from the hospital, the patient had a white blood cell count of 3100/ μ L with 82% polymorphonuclear cells, 1% bands, 3% monocytes, 14% eosinophils, and no lymphocytes.

Family History

The patient had no siblings, and there was no history of early deaths or immunodeficiency diseases in family members.

Laboratory Findings

At the initial presentation (3.5 months), the patient had severe hypogammaglobulinemia and lymphopenia (Table 1). Both his B- and T-cell numbers were very low, and his isohemagglutinin titers were undetectable. Mitogen lymphoproliferative tests could not be performed because of his severe lymphopenia. Both the infant and his mother were HIV negative. His red blood cell count-ADA activity was barely detectable, and dAXP (total 2'-deoxyadenosine nucleotides) was 20.6% of total adenine nucleotides (normal <1%), confirming ADA-deficient SCID. Molecular genetic analysis showed he is heterozygous

TABLE 1 Patient's Initial Immunologic Findings at 3.5 Months of Age

Laboratory Test	Finding	Normal Level
WBC, $10^3/\mu$ L	9.8	6–17.5
Lymphocytes, $10^3/\mu$ L	0	2.5–12
Neutrophils, $10^3/\mu$ L	7	1–8.5
Eosinophils, $10^3/\mu$ L	2	0–0.3
IgA, mg/dL	<7	2.9–125
IgG, mg/dL	<189	251–1069
IgM, mg/dL	<6	20–149
IgE, IU/mL	<9.2	<30
B cells/ μ L (CD19)	13	50–540
T cells/ μ L (CD3)	139	730–2790
T-helper cells/ μ L (CD4)	13	310–1920
T-suppressor cells/ μ L (CD8)	49	200–1320
T-helper/T-suppressor ratio (CD4/CD8)	0.3	>0.9
Natural killer cells/ μ L (CD16/56)	43	30–300
IL-2, U/mL (secretion from CD3)	4	3–30

Ig, immunoglobulin; IL, interleukin; WBC, white blood cell count.

for 2 missense mutations (A179D and R211H). Both mutations have been found in other patients, with R211H more frequent than A179D.

Clinical Course

The patient was started on prophylactic trimethoprim/sulfamethoxazole, intravenous immunoglobulin (IVIg), and polyethylene glycol-conjugated adenosine deaminase (PEG-ADA) therapy at 30 U/kg (of ideal body weight) intramuscularly twice a week. His oral thrush improved with oral ketoconazole and topical nystatin treatment. A bone marrow transplant was considered, but no HLA-matched donor was found. His CD4 count increased from 109 cells/ μ L to 418 cells/ μ L in 1 month. He developed a urinary tract infection caused by *Escherichia coli* and had a good response to cefuroxime.

At 9 months of age, the patient's T cells showed normal mitogen proliferation response, and prophylactic trimethoprim/sulfamethoxazole was discontinued; 1 month later, IVIg was discontinued. He showed a marked increase in B cells, and his hemoglobin levels and platelet counts continued to be within normal limits. During his first year of life, the patient's ADA levels were in the acceptable range, and he did not develop anti-ADA antibodies.

At 16 months of age (6 months after the IVIg was discontinued), the patient's immunoglobulin levels were within normal limits: immunoglobulin G, 475 mg/dL; immunoglobulin A, 19 mg/dL; and immunoglobulin M, 59 mg/dL. During his early childhood, he had a few upper respiratory tract infections. He had 2 accidental exposures to varicella; he was given varicella zoster immune globulin and did not develop any skin lesions.

Just before the patient turned 3 years old, he was hospitalized for 10 days for right middle lobe pneumonia and right otitis media that responded well to intravenous ceftriaxone. At that time, his PEG-ADA dose was 375 U once a week. At 3 years of age, he contracted meningoencephalitis of unknown etiology; his PEG-ADA dose was increased to 375 U twice a week. His major illnesses during the subsequent years were *Staphylococcus coagulase*-negative bacteremia at 4 years of age and membranous glomerulonephritis at 18 years of age.

The patient's PEG-ADA dose was periodically adjusted for weight, and he maintained plasma ADA levels in the range of 25 to 101 μ mol/h/mL during the first year; 27 to 211 μ mol/h/mL at 1 to 5 years of age; 63 to 152 μ mol/h/mL at 6 to 10 years of age; and 29 to 101 μ mol/h/mL at 11 to 24 years of age (Fig 1A). After the initiation

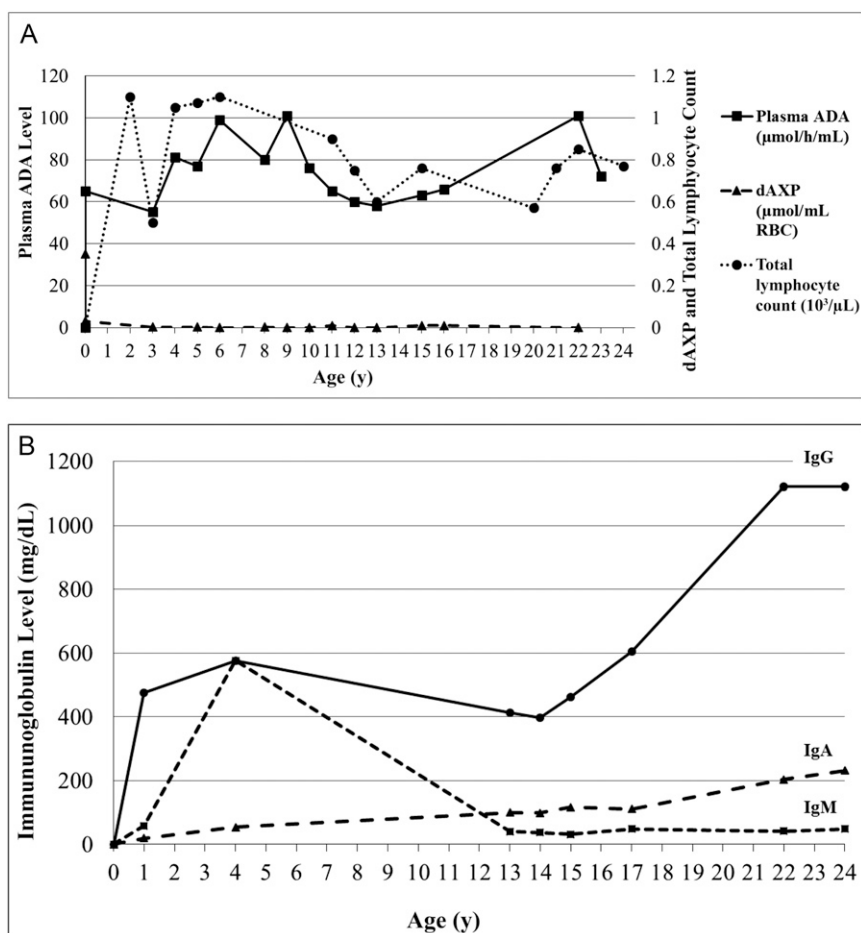


FIGURE 1
A, Plasma ADA level, red blood cell count (RBC) dAXP level, and total lymphocyte count according to age in a patient with ADA-deficient SCID receiving exclusive PEG-ADA enzyme replacement therapy for 24 years. B, Trend of immunoglobulin levels in our patient while receiving exclusive PEG-ADA enzyme replacement therapy for 24 years.

of PEG-ADA, there was a marked increase in his plasma ADA activity and lymphocyte count and a drop in red blood cell count–dAXP to barely detectable levels. His immunoglobulin levels have also been within normal range (Fig 1B). He currently continues to do well clinically, with no major infections. Table 2 displays the patient’s most recent immunologic evaluation at 24 years of age. His B- and T-cell proliferative responses to mitogens were good despite his mild lymphopenia and somewhat suboptimal lymphocyte viability (62.2%).

DISCUSSION

ADA-SCID, as with other types of SCID, is fatal unless diagnosed early

and treated appropriately. Although a cure requires hematopoietic stem cell transplantation (HSCT) or GT, exogenous enzyme replacement therapy has been successful in prolonging the life of ADA-deficient patients.⁴ With HSCT from an HLA-matched sibling or family member, the survival rate is >80% at 6 years.⁵ The survival rate is much lower with HSCT from matched unrelated donors (67%), mismatched related donors (43%), and mismatched unrelated donors (29%).^{4,6} Advances in GT using bone marrow CD34+ cells with a low-intensity nonmyeloablative conditioning regimen⁷ have markedly increased its efficacy, with a resulting high survival rate.⁸

Because neither HSCT nor GT was available for our patient at the time of his diagnosis, his treatment was based on ADA replacement therapy. PEG-ADA was first approved by the US Food and Drug Administration in 1990, shortly before our patient was diagnosed.⁹ Restoration of immune function usually occurs within 2 to 4 months of therapy.^{2,4} Because 2'-deoxyadenosine can rapidly equilibrate across the cell membrane and be deaminated by circulating PEG-ADA, enzyme replacement therapy results in elimination of elevated intracellular levels of deoxyadenosine triphosphate, permitting the recovery of effective (although not normal) immune function.² Dosing starts at 60 U/kg/week until the patient exhibits clinical improvement and an adequate plasma ADA level; it may then be reduced to 15 to 30 U/kg/week. In the first 8 to 10 years, PEG-ADA replacement therapy has been associated with less morbidity and mortality compared with haploidentical stem cell transplantations. Our patient maintained a good clinical course and immunologic status, including B-cell and T-cell functions despite a mild lymphopenia. His immunoglobulin levels have been within normal limits, which has not been the case for most patients treated solely with PEG-ADA.

PEG-ADA therapy requires monitoring of ADA and dAXP levels in erythrocytes to ensure adequate ADA activity.⁴ Low ADA levels and high erythrocyte dAXP levels should alert to the possibility of poor compliance, low dosage, improper storage (eg, PEG-ADA should not be frozen), or the development of neutralizing anti-ADA antibodies. A laboratory at Duke University Medical Center has performed this biochemical monitoring for most of the US patients being treated with PEG-ADA, and data accumulated between April 1986 and September 2008

TABLE 2 Immunologic Status of ADA-Deficient Patient at 24 Years of Age While on PEG-ADA

Laboratory Test	Finding	Normal Level
WBC, 10 ³ /μL	5.73	3.6–11.2
Lymphocytes, 10 ³ /μL	0.77	1–3
IgG, mg/dL	1120	700–1600
IgA, mg/dL	232	70–400
IgM, mg/dL	48	40–230
IgE, IU/mL	585	1.3–165
B cells/μL (CD19)	77	71–567
T cells/μL (CD3)	607	582–1992
T helper cells/μL (CD4)	207	401–1532
T suppressor cells/μL (CD8)	391	152–838
T helper/T suppressor ratio (CD4/CD8)	0.53	>0.9
NK cells/μL (CD16/56)	91	80–597
Diphtheria antibody, IU/mL	<0.10	>0.1
Tetanus antibody, IU/mL	1.05	>0.15
Lymphocyte proliferation ^a		
Viable lymphocytes, %	62.2%	≥75%
Proliferation to PWM as % CD45	11.8%	≥4.5%
Proliferation to PWM as % CD3	12.8%	≥3.5%
Proliferation to PWM as % CD19	16.6%	≥3.9%
Proliferation to PHA as % CD45	61.7%	≥50%
Proliferation to PHA as % CD3	65.5%	≥59%

Ig, immunoglobulin; IL, interleukin; PHA, phytohemagglutinin; PWM, pokeweed mitogen; WBC, white blood cell count.

^a Expressed as percent increase from baseline to maximum stimulation.

have been analyzed and published.⁴ Approximately 50% of patients started on PEG-ADA to that time had remained on it; ~20% had died while on therapy (mostly during the first 6 months), and ~30% underwent HSCT or GT. Of the patients being followed up on PEG-ADA therapy, 20% had been on therapy for 15 to 22 years. In general, after 10 to 15 years of therapy, the immune function declines²; however, our patient who has been on therapy for 24 years has exhibited relatively normal immune function, sufficient to prevent frequent or opportunistic infections.

The restoration of immune function on long-term PEG-ADA therapy varies. In 2 series^{10,11} including a total of 19 patients (aged 5–15 years) and receiving therapy for 5 to 12 years, immune restoration was only partial. Although there was an initial improvement in lymphocyte counts, later T-cell and B-cell cytopenia and dysfunction occurred, but the natural killer cell count showed inconsistent change. Nevertheless, those patients had good general health and did not experience opportunistic infections.

Initiating antimicrobial prophylaxis with trimethoprim/sulfamethoxazole and supportive immunoglobulin therapy is critical at the time of diagnosis, and it can usually be discontinued when immune restoration reaches a satisfactory level. In our patient, these treatments were discontinued at 9 months when he attained adequate levels of serum immunoglobulins and was maintaining a satisfactory clinical condition.

We previously reported a case of a 10-year-old boy treated with PEG-ADA for ~10 years, with normalization of his ADA and dAXP levels and a relatively healthy clinical course until he died of an Epstein-Barr virus–positive malignant brain lymphoma.¹² It seems that PEG-ADA therapy can provide adequate immune restoration, but the risk of developing lymphoproliferative disorders remains. ADA deficiency can cause pulmonary alveolar proteinosis and inflammatory liver disease, which may respond to PEG-ADA therapy.^{13–16} In addition to the high financial cost (\$100 000–\$300 000 per year, depending on the

dose), the aforementioned comorbid conditions make it important to consider potentially curative treatment with HSCT or GT whenever possible.^{7,8,17,18}

CONCLUSIONS

We describe a patient with ADA-SCID undergoing enzyme replacement therapy for 24 years, which is among the longest reported. Therapy was associated with a reduction in infections, particularly during his childhood, and no major infections through adulthood and without the development of autoimmune or lymphoproliferative disorders. Our report demonstrates the long-term efficacy of PEG-ADA in providing an adequate immune restoration and relatively good clinical well-being when curative HSCT or GT is not available.

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ABBREVIATIONS

ADA: adenosine deaminase
 AXP: adenosine
 dAXP: total 2'-deoxyadenosine nucleotides
 GT: gene therapy
 HSCT: hematopoietic stem cell transplantation
 IVIg: intravenous immunoglobulin
 PEG-ADA: polyethylene glycol–conjugated adenosine deaminase
 SCID: severe combined immunodeficiency

REFERENCES

- Blackburn MR, Kellems RE. Adenosine deaminase deficiency: metabolic basis of immune deficiency and pulmonary inflammation. *Adv Immunol*. 2005;86:1–41
- Hershfield M. Adenosine deaminase deficiency. GeneReviews. Available at: www.ncbi.nlm.nih.gov/books/NBK1483/. Accessed April 8, 2015
- Tasher D, Dalal I. The genetic basis of severe combined immunodeficiency and its variants. *Appl Clin Genet*. 2012;5:67–80
- Gaspar HB, Aiuti A, Porta F, Candotti F, Hershfield MS, Notarangelo LD. How I treat ADA deficiency. *Blood*. 2009;114(17):3524–3532
- Hassan A, Booth C, Brightwell A, et al; Inborn Errors Working Party of the European Group for Blood and Marrow Transplantation and European Society for Immunodeficiency. Outcome of hematopoietic stem cell transplantation for adenosine deaminase-deficient severe combined immunodeficiency. *Blood*. 2012;120(17):3615–3624, quiz 3626
- Booth C, Hershfield M, Notarangelo L, et al. Management options for adenosine deaminase deficiency; proceedings of the EBMT satellite workshop (Hamburg, March 2006). *Clin Immunol*. 2007;123(2):139–147
- Aiuti A, Slavin S, Aker M, et al. Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning. *Science*. 2002;296(5577):2410–2413
- Aiuti A, Cattaneo F, Galimberti S, et al. Gene therapy for immunodeficiency due to adenosine deaminase deficiency. *N Engl J Med*. 2009;360(5):447–458
- Hershfield MS, Buckley RH, Greenberg ML, et al. Treatment of adenosine deaminase deficiency with polyethylene glycol-modified adenosine deaminase. *N Engl J Med*. 1987;316(10):589–596
- Chan B, Wara D, Bastian J, et al. Long-term efficacy of enzyme replacement therapy for adenosine deaminase (ADA)-deficient severe combined immunodeficiency (SCID). *Clin Immunol*. 2005;117(2):133–143
- Malacarne F, Benicchi T, Notarangelo LD, et al. Reduced thymic output, increased spontaneous apoptosis and oligoclonal B cells in polyethylene glycol-adenosine deaminase-treated patients. *Eur J Immunol*. 2005;35(11):3376–3386
- Kaufman DA, Hershfield MS, Bocchini JA, Moissidis IJ, Jeroudi M, Bahna SL. Cerebral lymphoma in an adenosine deaminase-deficient patient with severe combined immunodeficiency receiving polyethylene glycol-conjugated adenosine deaminase. *Pediatrics*. 2005;116(6). Available at: www.pediatrics.org/cgi/content/full/116/6/e876
- Somech R, Lai YH, Grunebaum E, Le Saux N, Cutz E, Roifman CM. Polyethylene glycol-modified adenosine deaminase improved lung disease but not liver disease in partial adenosine deaminase deficiency. *J Allergy Clin Immunol*. 2009;124(4):848–850
- Grunebaum E, Cutz E, Roifman CM. Pulmonary alveolar proteinosis in patients with adenosine deaminase deficiency. *J Allergy Clin Immunol*. 2012;129(6):1588–1593
- Bollinger ME, Arredondo-Vega FX, Santisteban I, Schwarz K, Hershfield MS, Lederman HM. Brief report: hepatic dysfunction as a complication of adenosine deaminase deficiency. *N Engl J Med*. 1996;334(21):1367–1371
- Speckmann C, Neumann C, Borte S, et al. Delayed-onset adenosine deaminase deficiency: strategies for an early diagnosis. *J Allergy Clin Immunol*. 2012;130(4):991–994
- Sauer AV, Aiuti A. New insights into the pathogenesis of adenosine deaminase-severe combined immunodeficiency and progress in gene therapy. *Curr Opin Allergy Clin Immunol*. 2009;9(6):496–502
- Candotti F, Shaw KL, Muul L, et al. Gene therapy for adenosine deaminase-deficient severe combined immune deficiency: clinical comparison of retroviral vectors and treatment plans. *Blood*. 2012;120(18):3635–3646

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