I read the article by Lainka et al. (12) with great interest. I want to make some comments on the case and the emerging role of stem cell gene therapy (SCGT) in adenosine deaminase (ADA) deficiency.

The treatment of choice is currently stem cell transplantation (SCT) from a histocompatible related donor. However, SCT from a haploidentical/unrelated donor has a higher failure rate (4), resembling this case (12).

An adjunct to SCGT, polyethylene glycol (PEG)-conjugated ADA replacement is an alternative for patients who either lack an HLA-identical donor or are at high risk for haploidentical SCT, like this patient (1, 9). Compatible with this report, PEG-ADA usually causes suboptimal and temporary immune reconstitution in the short term as well as even in the long term (6). A possible explanation for the incomplete restoration could be that enzymatic activity of ADA is found mostly in the plasma with very minimal amounts of tissues and may not fully lower intracellular levels in progenitor and/or mature lymphocytes (3).

Besides this method’s being expensive, 20% of patients fail to respond (1). Thrombocytosis, autoantibody development, and immune dysregulation were reported to be complications as seen in this patient (1, 3, 6, 10, 15). Development of anti-ADA autoantibody, a new type of antinuclear antibody with discrete speckled nuclear staining, may be part of autoimmune process during this therapy and recently also demonstrated in 4/100 lupus patients (13). Decreased thymic function, B-cell oligoclonality, and increased spontaneous apoptosis contributing this immune dysregulation and autoimmune phenomena were also found to be associated with PEG-ADA therapy (14). Additionally, increased TH2 cytokine profiles clarify eosinophilia, allergies, and/or TH2-pattern diseases e.g., atopic dermatitis, as seen in these patients (12, 16).

In the absence of enzyme replacement, recent SCGT results provide a new therapeutic option with/without nonmyeloablative conditioning, allowing full immunological/metabolic correction in four patients so far (1, 2, 17). Efficacy of SCGT is also confirmed in other SCID patients (1, 5). Thus, instead of PEG-ADA, can we think of SCGT primarily, such as in the case of haploidential- or unrelated-donor availability? Then, the question becomes whether SCGT is safe enough. Uncontrolled lymphoid proliferation in two SCID-XL patients was reported (8). However, for ADA deficiency, no case of leukemia has been reported, since SCGT does not confer a stimulatory signal but rather eliminates the toxic effects of irregular metabolites. Was this just a simple mishap or a problem with the integration site or the effect of metabolites. Was this just a simple mishap or a problem with the integration site or the effect of metabolites.

In conclusion, although it could be a life-saving therapy, in the long term, suboptimal immune function with PEG-ADA raises concern about declining immune function in time, with development of allergic (16) or autoimmune diseases (14) or malignancies (11). I believe that one should definitely consider SCGT providing optimal immune/metabolic reconstitution in light of new findings. I do not have any potential financial conflict of interest related to this study.

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Authors’ Reply

The letter by Dr. Öner Özdemir raises two important issues regarding the treatment of children with ADA deficiency. First, in response to our article describing temporary immune reconstitution, it discusses the efficacy of PEG-ADA replacement therapy, and second, it proposes the consideration of SCGT for optimal immune reconstitution.

Our report illustrates one risk of PEG-ADA therapy, the induction of neutralizing antibody. This complication must be taken into account when choosing therapy, but it has occurred in <10% of PEG-ADA-treated patients (4). Our patient may have been at higher risk than typical patients: she had a delayed presentation not only with immune deficiency but also with dysregulated humoral immunity and a high percentage of activated T lymphocytes. In this setting, a central-line staphylococcal infection, which began after about 5 weeks of treatment and later recurred, may have triggered neutralizing anti-ADA production, as well as reactivation of cytomegalovirus and autoimmune hemolysis, which had been present prior to treatment. As mentioned in our report, neutralizing antibody to PEG-ADA has also developed in another patient in association with nosocomial central catheter sepsis.

As Dr. Özdemir points out, two recent reports (2, 6) have highlighted declining lymphocyte counts and abnormal lymphocyte function during long-term PEG-ADA therapy. Although 13 of the 14 patients described in these reports have done well clinically, these abnormalities raised concern about how long this benefit could be sustained. Another recent report (5) of a fatal brain lymphoma in a patient after 10 years of PEG-ADA treatment further raises this serious concern. Rapidly increasing costs of health care also pose a barrier for pediatricians to prescribe long-term use of this very expensive noncurative treatment.

In spite of these reservations, for almost 20 years PEG-ADA has provided a generally well-tolerated and clinically effective alternative to haploidentical marrow transplantation. More than 140 patients have been treated to date worldwide, and about 60% of approximately 85 patients now receiving PEG-ADA have been treated for longer than 5 years and almost 40% for more than 10 years (4; M. S. Hershfield, unpublished data).

Dr. Özdemir suggests that it may be time to use SCGT rather than PEG-ADA for treating ADA-deficient children who lack a matched donor. This proposal is based on his view of the potential risks of SCGT and of its recently reported efficacy in two patients who had not received PEG-ADA therapy (1). However, currently open trials have to date accepted only a very small number of patients. Most patients received PEG-ADA therapy before and for some time after gene transfer. Evaluation of the response to gene therapy is problematic because of the concomitant treatment with PEG-ADA. In light of the cases of lymphoid leukemia that complicated SCGT for X-linked SCID (3), there clearly is a need for more in vitro and in vivo safety data. In our opinion, SCGT is still experimental and cannot yet be generally favored over other treatment modalities.

It would be ideal to have a clinical trial to compare the efficacy and safety of PEG-ADA, conventional stem cell transplantation (with an unrelated or haploidentical donor), and SCGT. However, because ADA deficiency is so rare, such a trial is not practical, and questions will remain as to which of the options would be best in individual patients. Eventually, as more reports of longer-term results of all treatment modalities appear, a meta-analysis may permit the development of a consensus protocol for treatment of ADA deficiency. Once this is implemented, analysis of systematically gathered clinical data will help to provide ADA-deficient children with the best therapy available.

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Author’s Reply

I am responding to Dr. Özdemir’s letter as a coauthor of reference 8. As acknowledged in reference 8, I have grant support from the manufacturer of PEG-ADA. Because of this conflict of interest, I am separating my response from that of Drs. Lainka and Niehues.

ADA deficiency is rare and phenotypically diverse and its therapies (and experience with them) continue to evolve; choosing treatment remains complex (5). Dr. Özdemir offers his views on the current roles of enzyme replacement and gene therapy, based on his reading of reference 8 and other articles. My own perspective on therapy, along with my reading of these papers, on several of which I am a coauthor, differs from Dr. Özdemir’s.

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In his fourth paragraph, Dr. Özdemir gives the impression that thrombocytosis, ADA autoantibodies, immune dysregulation, eosinophilia, and allergies are common complications of PEG-ADA therapy. A review by Aiuti (1), referred to by Dr. Özdemir, states that PEG-ADA “is limited by high costs and the risk of developing neutralizing antibodies or autoimmunity,” citing two other reviews in support. Both of these, my own 1998 review (4) and a 1999 chapter by Hirschhorn (6), mention expense and neutralizing ADA antibodies, but neither suggests that thrombocytosis or autoimmunity frequently complicates PEG-ADA therapy.

Dr. Özdemir attributes autoantibodies, immune dysregulation, eosinophilia, and atopic dermatitis to PEG-ADA therapy, citing references 8 and 12. In both cases, these problems occurred prior to diagnosis in single patients with a “delayed onset” phenotype, and the patients improved significantly after PEG-ADA was instituted. Immune dysregulation recurred in Lainka’s patient after neutralizing antibody caused the rapid clearance of PEG-ADA.

Dr. Özdemir cites recent reports of immunologic abnormalities in 14 patients on long-term PEG-ADA therapy, 13 of whom did well clinically (3, 10). Chan et al. (3) reported that 8 of 9 patients “have been free of significant infections or prolonged hospitalization after PEG-ADA was instituted” and “have attended regular schools without any protective isolation measures.” Their discussion further states, “This clinical course is far superior to the expected course: . . . demonstrating the ability of PEG-ADA therapy to be beneficial for at least a decade.” One of the nine patients lost protective immunity and eventually died of “multiorgan failure and disseminated adenovirus infection” after a haploidentical marrow transplant. The second report of five patients treated with PEG-ADA for 5 to 12 years states that “No major infections or other medical problems were observed in the patients since initiation of PEG-ADA therapy” (10).

Marwaha et al. (11) reported transient thrombocytosis soon after starting PEG-ADA in one patient, who had no clinical consequences (11). Transient thrombocytosis, also without consequences, has been observed in a few other patients (5), but not in the patient in the report by Lainka (8). This phenomenon may be an early hematopoietic response to release from metabolic toxicity.

Reference 2 (referred to by Dr. Özdemir) reports that PEG-ADA was life saving in ADA-deficient mice (2). It does not deal with autoimmunity, thrombocytosis, or immune dysregulation during PEG-ADA therapy either in these mice or in human patients. Reference 9 (referred to by Dr. Özdemir) provides no evidence that anti-ADA autoantibodies in 4/100 lupus patients caused lymphopenia or disease manifestations (9). The relevance to PEG-ADA therapy for SCID is not obvious.

Rather than being autoantibodies, the immunoglobulin G antibodies to ADA detectable in most PEG-ADA-treated patients are specific for bovine ADA and are without clinical consequence (5). They may reflect recovery of specific humoral immune function. Neutralizing antibodies to ADA do pose a risk, but these have occurred in fewer than 10% of more than 145 patients treated with PEG-ADA to date, mainly in some with delayed or late onset phenotypes. I know of no allergic reactions to PEG-ADA.

I agree with Dr. Özdemir that the recent report of a fatal brain lymphoma after 10 years of treatment with PEG-ADA (7) raises a concern about how long the clinical benefit of PEG-ADA can be sustained. The lymphocyte functional abnormalities reported by Chan et al. and Malacarne et al. do add to this concern (3, 10).

Everyone involved with treating ADA-deficient SCID has hoped for more than 15 years that safe and reliably effective curative gene therapy will soon become available. However, gene therapy remains experimental. It would be judicious to avoid drawing premature conclusions (as was done in the case of gene therapy trials of the 1990s). Just as with PEG-ADA, which received FDA approval in 1990, gene therapy trials will accrue patients slowly, and they will have to be followed over a long period of time before optimal methods and the range of responses to gene therapy are established.

When and whether gene therapy will be widely available are uncertain, but it seems unlikely that the majority of newly diagnosed patients with ADA-deficient SCID will have access to gene therapy for at least several years. Until then, PEG-ADA will remain a life-saving, though imperfect, therapeutic option. It will be important to continue to report on the long-term experience with PEG-ADA.

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