# How We Manage Adenosine Deaminase-Deficient Severe Combined Immune Deficiency (ADA SCID)

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**Abstract**

Adenosine deaminase-deficient Severe Combined Immune Deficiency (ADA SCID) accounts for 10-15% of cases of human SCID. From what was once a uniformly fatal disease, the prognosis for infants with ADA SCID has improved greatly based on the development of multiple therapeutic options, coupled with more frequent early diagnosis due to implementation of newborn screening for SCID. We review the various treatment approaches for ADA SCID including allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA matched sibling or family member, or from a matched unrelated donor or a haplo-identical donor; autologous HSCT with gene correction of the hematopoietic stem cells (gene therapy – GT); and enzyme replacement therapy (ERT) with polyethylene glycol-conjugated adenosine deaminase. Based on growing evidence of safety and efficacy from GT, we propose a treatment algorithm for patients with ADA SCID that recommends HSCT from a matched family donor, when available, as a first choice, followed by GT as the next option, with allogeneic HSCT from an unrelated or haplo-identical donor or long-term ERT as other options.

**Introduction:**

Adenosine deaminase-deficient Severe Combined Immune Deficiency (ADA SCID) accounts for 10-15% of cases of human SCID [1]. Fortunately for affected patients, there are multiple treatment options, including allogeneic hematopoietic stem cell transplantation (HSCT), enzyme replacement therapy (ERT), and more recently autologous HSCT with gene therapy (GT). For the treating physician and patient's parents, the choice of which modality to use for immune restoration presents complex issues. In 2009, a group of experts on ADA SCID convened to amalgamate available data on outcomes from different treatment approaches and proposed a treatment algorithm [2]. In the interim, a more formal compilation and analysis of experience with outcomes using allogeneic HSCT for ADA SCID at multiple centers was published [3] and there has been a larger experience with positive outcomes from autologous HSCT GT (**Table 1**). These data and discussions led to the publication of specific recommendations for the treatment of ADA SCID [2] which were further modified on the basis of more center-specific experience [4]

**A. ADA SCID patients with matched family donor.**

HLA matched sibling donor (MSD), or in some cases matched family donor (MFD), transplantation without conditioning has been the *de facto* standard of care since first performed [5] for which there is essentially universal consensus among transplant physicians [6]. If possible, it is best to perform the transplant as soon as possible, before an infection may be acquired and to minimize other toxic effects from the high systemic levels of adenine metabolites. Even in cases where the SCID patient does have an active infection, there are few situations where proceeding to transplant as soon as possible is not indicated, if it is to be done without conditioning. The best potential for clearing the infection is immune restoration, which may in part occur from passively transferred donor T cells prior to *de novo* thymopoiesis.

Nevertheless, it may be recommended to start ERT prior to transplant to allow some endogenous immunity to develop to fight the infection (or if pulmonary alveolar proteinosis (PAP) is suspected, see below). Although the overall results of non-conditioned matched related donor transplant remain very good in terms of survival, our experience suggests that the efficacy may have some limitations. The lack of any cytoreductive conditioning means that in some cases there is a lack of engraftment and 2 of 17 treated at Great Ormond Street Hospital since 2000 required second procedures (Gaspar, personal communication). The immune recovery after a MSD/MFD unconditioned transplant is good and patients show evidence of effective T and B cell reconstitution [3]. While use of low dose busulfan in the setting of autologous gene therapy has been shown to increase the frequency of B cell reconstitution and decrease the need for ongoing immunoglobulin replacement therapy, there may be reluctance to use any conditioning for MSD/MFD transplants due to the long history of relative success without that risk.

**B. ADA SCID patients lacking a matched family member.**

If there is not an MSD or MFD, a choice must be made from among the different options: long-term ERT, allogeneic HSCT from an unrelated or haplo-identical donor, autologous HSCT with GT, or some combination of short-term ERT followed by a transplant.

**i. Enzyme Replacement Therapy (ERT).** Following the partial responses of immunity to repeated red blood cell transfusions as a source of exogenous ADA ERT, a pharmacologic formulation of purified bovine ADA conjugated to polyethylene glycol **(**PEG-ADA) was developed [7,8]. Since receiving FDA approval in the U.S. as an Orphan Drug, PEG-ADA ERT has been life-saving and sustaining for more than 100 patients, although long-term immune reconstitution may be sub-optimal [9]. ADA ERT remains an important therapeutic modality for

patients who do not have a transplant option, due to lack of a suitable donor or contraindications to transplant, as well as a bridge to allow immune restoration and recovery from infections prior to an allogeneic HSCT or autologous GT.

Use of ADA ERT may be limited by its high cost (approx. $200,000-400,000 per year) and variable availability, which currently is best in the U.S., where it is an FDA approved drug generally covered by third party payers, less so in other countries, where it may not be approved by the governing regulatory authority, or is simply not available. Additionally, ADA ERT is palliative and thus needs to be ongoing throughout life, which can pose a significant financial burden, as well as potential compliance issues with adolescence and transition to adult medical care. The advancement of a recombinant ADA ERT preparation (see NCT01420627 in ClinicalTrials.gov) may allow reduction of manufacturing costs compared to that needed to produce the naturally-sourced bovine-derived enzyme.

While there is not a great deal of information on dosing, the recommended dosing of ADA-GEN is 10 U/kg for the 1st dose, 15 U/kg for the second dose, 20 U/kg for the third with maximum dose not to exceed 30 U/kg. However, it is common practice to treat starting directly at the upper dose range of 30U/kg IM twice weekly for the first few months, until metabolic clearance of deoxyadenine metabolites is achieved. After that initial period, maintenance dosing can be somewhat lower, and due to the high cost of the single use vials, may be moderated to use whole vial increments. Typically, monitoring plasma ADA enzyme activity and red blood cell deoxyadenine metabolite levels is done quarterly, and this may signal when dosage increases are needed to account for increase in patient weight.

An important clinical consideration is how ERT therapy may affect subsequent HSCT. For allogeneic transplantation, the continued support of the host's immunity with ERT may act to increase risks for graft rejection, although Hassan et al [3] did not observe differences in

outcomes for patients who did or did not receive ERT prior to allogeneic HSCT. Some would advise stopping ERT for some time period prior to transplant to allow cellular immunity to wane. The optimal duration of the interval between stopping ERT and performing an allogeneic HSCT is not known. Lymphocyte counts decline over 1-3 months following ADA ERT withdrawal and so that may be the chosen time interval between cessation of ERT and performance of a transplant; however, the patient becomes increasingly more at risk for infection during this time. Alternatively, immune ablative conditioning with serotherapy (e.g. anti-thymocyte globulin) could be used to erase the allo-responsiveness induced by ADA ERT at the time of transplant, as may be done to eliminate engrafted maternal T cells in SCID or to ensure engraftment when transplanting for a non-SCID primary immune deficiency (e.g. Wiskott-Aldrich Syndrome {WAS} or Chronic Granulomatous Disease {CGD}).

For autologous GT transplants, the standard practice initiated by Aiuti et al [9], was to stop ERT for patients already receiving it, 1-2 weeks before the marrow harvest. In the autologous transplant setting, ERT is withdrawn, not to allow immunity to wane to decrease alloreactivity and rejection risks, but to produce a lymphopenic environment to drive *de novo* lymphocyte production from the gene-corrected graft. Indeed, we have observed that the serum IL-7 levels rise upon ERT withdrawal in the initial months after GT, inversely with the lymphocyte counts and then the IL-7 levels decline with T lymphocyte recovery from the gene-corrected transplant [11]. The current lentiviral vector trials in the U.S. and U.K. are continuing enzyme therapy through the first month post-GT, based on work in the murine model that demonstrated engraftment of gene-marked cells was the same or improved with 1 month of ERT post GT, compared to no ERT [12]. Continued ERT in the immediate period after transplantation of the gene-corrected cells may maintain a detoxified environment for improved engraftment. ERT is stopped after one month as the continued administration during T lymphocyte recovery over subsequent months may blunt the selective advantage of gene-corrected lymphocytes,

impeding maximal immune reconstitution with gene-corrected lymphocytes, although this has not been tested in patients. Based on our personal experience, in settings where a conditioning regimen is to be used either in the allogeneic or autologous setting, we would recommend that ERT is used at least until the time of the procedure (or 1 month after in autologous GT). This is based on the fact that we have not seen any resistance to engraftment with such protocols.

For patients who are diagnosed with either an identified infection or respiratory symptoms (tachypnea, hypoxemia, hazy pulmonary infiltrates on chest X-ray) that may represent Pulmonary Alveolar Proteinosis (PAP) [13,14], institution of ERT may allow improvement of infectious or pulmonary status prior to HSCT. For patients with severe infections, it may be possible to finesse the timing, e.g. start ERT and infuse donor bone marrow, allowing the ERT to provide systemic detoxification during the first month or so of engraftment, but stopping ERT before endogenous T cells start developing, after 2-3 months. There are minimal and only anecdotal data about this issue, but an organized study may be difficult to perform due to the rarity of such cases.

**ii. Alternative Donor Allogeneic HSCT.** While results with allogeneic HSCT from unrelated or haplo-identical donors in the prior era were less successful than with MSD/MFD, they still have provided life-saving treatments to the majority of treated SCID patients [2]. However, it is imperative to continually work to minimize and eliminate morbidity and mortality from transplant. It is hoped that newborn screening (NBS) to diagnose patients prior to the development of infectious or other complications of SCID, will improve outcomes. Although there is a possibility that delayed onset ADA individuals may be missed by NBS, it is likely that all true ADA SCIDs will be identified. Additionally, the multiple new approaches to allogeneic HSCT, such as improved methods for graft manipulation (e.g. selective T cell subset depletion)

and improved supportive measurescan be expected to contribute to improved outcomes. Although data for ADA SCID specifically does not exist, initial reports on approaches using haplo-identical transplants with α/β T cell depletion have shown impressive survival and immune recovery outcomes in SCID and other primary immune deficiency cohorts [15]. Thus, allogeneic HSCT for ADA SCID patients without a matched related donor remains an important modality for long-term disease correction. The choice between unrelated donor or haplo-identical donor is mainly one of center preference and expertise, and this is a continually evolving situation as new methods to facilitate engraftment and minimize graft versus host disease risks are implemented. Overall, our opinion is that it is generally preferable for SCID patients to be transplanted at centers with high levels of prior experience and standardized approaches for their clinical management, as well as state-of-the-art approaches to transplant, although this has not been formally demonstrated for PID.

**iii. Gene Therapy. Gene therapy (**GT) for ADA SCID has an excellent safety and efficacy record across trials and vectors over the past 15 years. There has been 100% survival and high rates of immune reconstitution from GT for ADA SCID, which provides protective immunity and responses to vaccination and no significant opportunistic infections [16-19]. The reduced cytoreductive conditioning used with low dose busulfan as a single agent allows a low acuity post-transplant clinical course compared to the combination of cytoreduction or myeloablative chemotherapy and pre- and post-transplant immune suppressive agents needed for some modes of allogeneic HSCT (e.g. unrelated donors). And, of course, the use of autologous transplant eliminates risks of GVHD and the need for immune suppression pre- and post-transplant. More recently, a lentiviral vector is being investigated in clinical trials of GT for ADA SCID with a potentially better safety profile, based on pre-clinical assessments [20].

Fortunately, there have been no cases of leukoproliferation from among more than 70 ADA SCID recipients of auto-grafts corrected with either gammaretroviral or lentiviral vectors. The

absence of this genotoxic complication in GT for ADA SCID with gammaretroviral vectors stands in sharp contrast to the occurrences of leukoproliferative complications in trials for other primary immune deficiencies (e.g. XSCID, WAS, CGD) [21-23]. The reason why it has not occurred in ADA SCID remains unknown; gammaretroviral vector integrations adjacent to the same proto-oncogenes implicated in leukoproliferation in other diseases have been seen in ADA SCID patients, but to date have not led to clinical complications [24].

Based on the excellent clinical outcomes at Hospital San Raffaele, the gammaretroviral vector-modified stem cell product for ADA SCID has been approved for licensure by the European Medicines Agency, the second EU-approved GT product (Strimvelis – GSK). Thus, this GT is now available on a regular basis with pharmaceutical-grade vector and cell manufacturing. Currently, receiving GT with Strimvelis does require being treated in Milan, as they are at present the only licensed cell manufacturing site. The fresh cell product must be delivered within a few hours from the laboratory to the patient, which practically means the patient needs to be nearby to the manufacturing site.

A lentiviral vector-modified stem cell product for ADA SCID under investigational study is also being brought forward to commercialization, having received Orphan Drug Designation in EU and US and Breakthrough Therapy Designation in the US. Efforts to develop a cryopreserved cell product would allow the patients to remain at their home hospital, with shipment of the stem cell source to a central pharmaceutical-level manufacturing facility, processing and freezing, and then shipping back to the home site for re-infusion.

With the advent of newborn screening for SCID in the majority of US states and other countries, ADA SCID patients are now routinely diagnosed in the first weeks of life. This presents a treatment dilemma about when to perform a transplant. With a matched sibling donor and no intent to use conditioning, the transplant can be done as soon as the donor is

available. For transplants that will give conditioning, delaying for some time may be considered to potentially reduce toxic effects to the infant. In this setting, it may be desirable to start PEG-ADA ERT as soon as possible upon confirmation of the ADA SCID diagnosis and absence of a matched family donor, and then to continue ERT until the allogeneic transplant or GT is done, ideally within the first year of life.

**Conclusion:** Happily, the prognosis for infants born with ADA SCID continues to improve, with early diagnosis and the multiple effective treatment options that are available. Outcomes with allogeneic HSCT and autologous GT continue to improve and a new formulation of ERT is under development. The optimal approach for any specific patient depends on a variety of factors, most importantly the presence or absence of a suitable HLA-matched sibling or family donor. For those lacking a matched family donor, the choice between unrelated or haplo-identical HSCT, or autologous GT depends on their availability and the perception of the responsible treating physician. From our experience of treating ADA SCID patients with both unrelated HSCT and autologous GT and the emerging data from the GT studies where the safety profile has been excellent, we would consider GT as an initial option before a MUD or haplo-identical HSCT. The low toxicity associated with the reduced intensity conditioning procedure means that if there is a failure of gene therapy, it is highly likely that patients will be able to undergo ether a second attempt at GT, a MUD HSCT if available or restart ERT. These suggestions are encapsulated in a further revised guideline recommendation (Fig 1). While the discussions here may provide some guidance for treatments, longer and more comprehensive follow-up on patients treated by these different modalities will be needed for confirm the optimal approaches, including on the effects on the neurodevelopmental abnormalities that may be seen in ADA SCID [25].

**Conflict of Interest:** The authors are both members of the Scientific Advisory Board for Orchard Therapeutics which is developing a lentiviral vector gene therapy for ADA SCID and has licensed it from their respective institutions, University College London and University of California, Los Angeles.

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**Figure legends:**

**Figure 1.** Algorithm for treatment of ADA SCID. NBS= newborn screening. FH= family history. ERT= enzyme replacement therapy. HSCT= hematopoietic stem cells. PAP= Pulmonary Alveolar Proteinosis.

**Table 1.** Historic outcomes from treatments for ADA SCID using different therapeutic modalities.

| Modality | Number of Patients | Overall Survival | Failure of treatment (need for HSCT/GT or restart ERT) | Patients able to stop IgRT (Immunoglobulin replacement) | References |
|---|---|---|---|---|---|
| **ERT** | 185 | 78% | 28% (mainly elective decision to undertake a definitive procedure) | ~50% | Gaspar et al., 2009 [2] |
| **MSD/MFD** | 56 | 82% | 7% | 95% | Hassan et al., 2012 [3] |
| **MUD inc UCB** | 15 | 67% | 7% | 81% | Hassan et al., 2012 [3] |
| **mMUD** | 7 | 29% | 0 | n/a | Hassan et al., 2012 [3] |
| **Haploidentical** | 30 | 43% | 27% | 100% | Hassan et al., 2012 [3] |
| **Gammaretroviral gene therapy** | 18 | 100% | 17% | 67% | Cicalese et al., 2016 [16] |
| | 8 | 100% | 50% | 50% | Gaspar et al., 2011 [17] (and unpublished data) |
| | 10 | 100% | 70% | 10% | Candotti et al., 2012 [11] |
| | 10 | 100% | 10% | 30% | Shaw et al., (2017) in press [18] |
| **Lentiviral vector mediated gene therapy** | 32 | 100% | 3% | 97% (due to decreased length of follow up this is based on patients who have stopped or are scheduled to stop Ig replacement) | (Gaspar and Kohn, unpublished data – data presented at ESID and ESGCT 2016) |

**HSCT** = hematopoietic stem cell transplant; **GT** = gene therapy; **ERT** = enzyme replacement therapy; **IgRT** = immunoglobulin replacement therapy; **MSD/MFD** = matched sibling donor/matched family donor; **MUD inc UCB** = matched unrelated donor including umbilical cord blood; **mMUD** = mismatched unrelated donor.