Gene Therapy Approaches to Immunodeficiency

Sujal Ghosh, MD[a,b], H. Bobby Gaspar, MBBS, PhD[a,*]

KEYWORDS

• Gene therapy • Primary immunodeficiency • Adenosine deaminase deficiency
• X-linked severe combined immunodeficiency • Chronic granulomatous disease
• Wiskott-Aldrich syndrome

KEY POINTS

- Ex vivo gene transfer can be used in different primary immune disorders.
- Initial results were tempered by genotoxicity associated with the gammaretroviral design.
- New "safer" vector designs combined with nonmyeloablative or fully myeloablative conditioning regimens allow enhanced engraftment and efficient transgene expression, while maintaining a robust safety profile.

INTRODUCTION

More than 300 gene defects have been associated with primary immunodeficiency syndromes (PID).[1] Treatment strategies encompass anti-infective prophylaxis and immunoglobulin substitution. However, hematopoietic stem cell transplantation has been the only option for definitive correction and functional reconstitution. Transplant-related mortality due to toxicity and infections is a major concern even in a fully matched setting. Despite emerging reduced-intensity conditioning regimens, a mismatched donor may lead to a fatal outcome in some patients.[2] Ex vivo gene transfer of autologous hematopoietic stem cells has been progressively developed in the past decades. Initial studies using gammaretroviral vectors showed success but also major safety issues because of insertional mutagenesis, which ultimately led to a range of newly developed safer vectors and promising current phase 1/phase 2 trials. In at least in one of the diseases, namely adenosine deaminase (ADA) deficiency, it seems gene therapy is an equal or even slightly superior treatment to current

Disclosure of Conflicts of Interest: H.B. Gaspar is a founder and advisory board member of Orchard Therapeutics and has financial interests in the company.

[a] Infection, Immunity, Inflammation, Molecular and Cellular Immunology Section, University College London, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK; [b] Department of Pediatric Oncology, Hematology and Clinical Immunology, Center of Child and Adolescent Health, Heinrich-Heine-University, Moorenstraße 5, 40225 Düsseldorf, Germany
* Corresponding author.
E-mail address: h.gaspar@ucl.ac.uk

Hematol Oncol Clin N Am 31 (2017) 823–834
http://dx.doi.org/10.1016/j.hoc.2017.05.003 **hemonc.theclinics.com**

standards of treatment with fully matched unrelated donors. Besides safety concerns, one major challenge of the future will certainly be the accessibility of gene therapy in other centers than the current few ones in high-resource countries.

ADENOSINE DEAMINASE DEFICIENCY

ADA is essential in the purine salvage pathway and catalyses the deamination of metabolites into deoxyinosine and inosine. Because it is ubiquitously expressed, mutations in *ADA* lead to accumulation of toxic deoxyadenosine triphosphate and adenosine triphosphate and subsequently to immunologic, pulmonary, gastrointestinal, skeletal, and neurologic abnormalities.[3] Affected infants present usually with a T-B-NK- severe combined immunodeficiency (SCID) phenotype in the first months of life with failure to thrive and severe infections. Weekly enzyme replacement therapy with pegylated bovine ADA allows partial numeric and functional T-cell reconstitution; however, long-term results show limited sustained efficacy. Hematopoietic stem cell transplant (HSCT) has been considered the only curative treatment for a long time, and success rates reach 90% in patients with a matched-sibling or matched-family donor without the need of any conditioning. However, the transplantation of matched unrelated donor (MUD) or haploidentical grafts is associated with inferior results (1-year survival: matched family donor [MFD] 90%, MUD 67%, haplo 43%).[4]

Gene correction of peripheral blood lymphocytes and later of hematopoietic progenitor cells has been attempted from the early 1990s. Initial studies at National Institutes of Health (NIH) Bethesda and San Raffaele in Milan with gammaretroviral vectors and concomitant enzyme replacement therapy (ERT) showed low toxicity, but lack of substantial immunologic and clinical benefit due to low levels of marked cells in the peripheral circulation.[5–8] The next generation of trials in Milan and London incorporated the idea of conferring a greater competitive advantage to transduced cells and so polyethylene glycol (PEG)-ADA was stopped before gene therapy; furthermore, a nonmyeloablative reduced intensity conditioning regimen with Busulfan or Melphalan was given to enhance engraftment. The trial at Children's Hospital Los Angeles and NIH amended its protocol after treating the first patients without conditioning.[4,9,10] Implementation of conditioning led to a more favorable outcome in all patients compared with the initial studies. Murine studies confirmed the findings of the positive effect of prior cytoreduction; however, it seems that cessation of ERT is of less importance, and ERT continuation showed significantly increased levels of gene-modified cells in the thymus in mice.[11] Based on that, current trials allow the continuation of ERT until day 30. Together the 3 gammaretroviral studies treated more than 40 patients with gammaretroviral vectors, and all patients are alive. Approximately 75% of patients are off ERT, and transduced cells engrafted permanently with partial reconstitution in all lineages 4 (Gaspar), 9 (Aiuti), 10 (Candotti). Notably, none of the patients have developed insertional mutagenesis, although in all studies, patients harbor integration events near protooncogenes, including LMO2 as a consequence of being treated with a gammaretroviral vector. The positive outcome and the excellent survival in ADA deficiency led to the market authorization of the Milan gammaretroviral vector by the European Medicines Agency (Strimvelis).[12]

Given the adverse events using gammaretroviral vectors in other gene therapy studies, the authors' group in London and the group at University of California, Los Angeles decided to proceed to further trials using a lentiviral vector. A codon-optimized human complementary DNA (cDNA) ADA gene under the control of the short form elongation factor-1 alpha promoter (EF1α) was shown to have efficacy in the murine model.[13] Furthermore, safety issues assessed through in vitro