Hematopoietic Stem Cell Transplantation for Progressive Combined Immunodeficiency and Lymphoproliferation in Patients With Activated Phosphatidylinositol-3–OH Kinase δ Syndrome Type 1


PURPOSE OF THE STUDY: To examine clinical features, laboratory findings, treatment, and outcomes of patients with activated phosphatidylinositol-OH-3 kinase δ syndrome type 1 (APDS1) and evaluate hematopoietic stem cell transplant (HSCT) as a potential treatment option.

STUDY POPULATION: This study included 23 patients with confirmed PIK3CD mutations. Nine of these patients underwent HSCT.

METHODS: This was a retrospective study to characterize clinical characteristics, laboratory findings, treatment, and outcomes of patients with APDS1. Patients were identified by patient registry, physician referral, or having been previously reported in literature. Data were obtained by review of medical records and physician questionnaires.

RESULTS: Common clinical features of patients with APDS1 included recurrent infections, lymphoproliferation, and enteropathy, with a median age at symptoms onset of 11 years old. The majority (65%) of patients received immunoglobulin replacement, and some additionally had prophylactic antimicrobial agents. Eleven transplantations were performed for recurrent infections or treatment refractory disease among 9 total patients. Fludarabine-based reduced-intensity conditioning regimens were used in all transplants (90–180 mg/m²), and 55% used human leukocyte antigen–mismatched donors. All but 1 patient ultimately achieved engraftment, but 36.4% had initial graft failure and required retransplantation, boosts of peripheral blood stem cells, or growth hormone administration for delayed T lymphocyte recovery. More than 90% of transplanted patients had an adverse complication, most commonly mild graft-versus-host disease. Despite this, most symptoms were improved post-HSCT, and no patients required ongoing immunoglobulin replacement by day 100 post-HSCT. The 30-year overall survival was 86.1%, and event-free survival was 39.6%.

CONCLUSIONS: HSCT should be considered in patients with APDS1 and recurrent infections and/or treatment refractory lymphoproliferation. Clinical symptoms improved posttransplantation, although adverse complications and graft failure were frequent.

REVIEWER COMMENTS: Patients with APDS1 are at increased risk for recurrent infections, bronchiectasis, lymphoproliferation, chronic viral infections, and lymphoma. This article highlights the role that HSCT may play in the future management of patients with APDS1. Although not without its own risks, early HSCT can improve clinical symptoms and reduce the lifetime risk for potentially fatal complications in this disease. Investigators in this study closely examine HSCT regimens for APDS1 patients among various international medical centers, which serves as the first critical step toward improving event-free and overall survival for these patients.

Jakinibs for the Treatment of Immune Dysregulation in Patients With Gain-of-Function Signal Transducer and Activator of Transcription 1 (STAT1) or STAT3 Mutations


PURPOSE OF THE STUDY: To investigate the efficacy of jakinib therapy in patients with gain-of-function (GOF) signal transducer and activator of transcription 1 (STAT1) or signal transducer and activator of transcription 3 (STAT3) mutations.

STUDY POPULATION: The study included 17 total patients with either a STAT1 GOF (n = 11) or STAT3 GOF (n = 6) mutation who were treated with jakinibs (ruxolitinib or tofacitinib). Patients came from 11 international centers.

METHODS: This was a retrospective study to describe disease-related clinical manifestations and determine indication for treatment, dosage, length of treatment, treatment response, and treatment-associated complications. All subjects underwent thorough pre- and posttreatment
clinical and laboratory evaluations and follow-up (follow-up period: 1–34 months).

RESULTS: Fourteen patients (82%) responded favorably with clinical improvement to jakinib treatment. Observed clinical improvements included resolution of enteropathy leading to total parenteral nutrition independence, better lung function, improved autoimmune cytopenias, decreased arthritis symptoms, and remission of hemophagocytic lymphohistiocytosis. All patients with STAT1 GOF had resolved chronic mucocutaneous candidiasis with treatment. Most patients tolerated the jakinib well with minimal or transient adverse effects. An increase in herpes zoster infections (none systemic and all cleared with antiviral agents) was observed in some patients. Four patients died despite treatment with a jakinib. The majority of these patients were critically ill with severe invasive infection or progressive lung disease. One patient died due to posttransplant complications.

CONCLUSIONS: Jakinibs are both safe and effective in the treatment of patients with STAT1 or STAT3 GOF mutations with clinical manifestations of autoimmunity and/or immune dysregulation.

REVIEWER COMMENTS: Patients with STAT1 and STAT3 GOF mutations often present in early childhood with severe and/or refractory infections, lymphoproliferation, auto-inflammation, and autoimmunity. Jakinibs allow for a targeted therapeutic approach to block the cytokine-induced JAK activation in STAT1 and STAT3 GOF diseases. This is the first study to evaluate the use and clinical impact of jakinibs in STAT1 and STAT3 GOF. The results are overwhelmingly encouraging, with the majority of patients having clinical improvement and reduction or resolution of autoimmune manifestations after treatment with a jakinib. Use of jakinibs late in disease progression or when critically ill was associated with mortality, suggesting early initiation may improve efficacy. This study has significant clinical impact in the treatment of STAT1 and STAT3 GOF and reinforces the notion that early genetic diagnosis of primary immunodeficiency diseases may lead to targeted therapeutic options and improved clinical outcomes.

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Reprogramming Human T Cell Function and Specificity With Non–Viral Genome Targeting

PURPOSE OF THE STUDY: To develop and optimize nonviral CRISPR-Cas9 genome editing for primary T cells and apply this technique in part to correct a pathogenic mutation in a monogenic autoimmune disease.

STUDY POPULATION: Using CRISPR-Cas9, primary human T cells from healthy donors and a family with monogenic autoimmune disease were engineered ex vivo along with other important proofs of concept.

METHODS: The CRISPR-Cas9 system was first described as a prokaryotic adaptive immune response, and it has since been widely used as a gene editing tool. CRISPR sequences identify homologous areas in the DNA, and Cas9 creates precise double-stranded breaks. Double-stranded breaks are repaired by either nonhomologous end joining or homology-directed repair (HDR). HDR is less error prone, and by using CRISPR-Cas9 with HDR templates, transgenes can be integrated into the targeted genome with precision. In this study, an electroporation method was optimized for ex vivo primary human T cells to allow for uptake of CRISPR-Cas9 ribonucleoprotein complexes and large (>1 kb) double-stranded DNA (dsDNA) templates for HDR. The technique allowed for optimized cell viability along with efficiency under the endogenous promoter. Using these approaches, T cells from a family with recessive loss of function mutations in the gene encoding the interleukin-2α receptor (IL2RA), which is needed for healthy T regulatory cell functioning, were edited to correct the faulty receptor genes. In a separate set of experiments, and as an additional proof of utility of the optimized methods, healthy donor T cells were edited to express a new T-cell receptor (TCR) targeting the NYESO-1 tumor antigen and then tested in an in vivo preclinical tumor model.

RESULTS: Optimized coelectroporation of T cells with CRISPR-Cas9 ribonucleoprotein complexes and long (>1 kb) dsDNA had reduced cell toxicity and improved viability (average: ~68% in bulk T cells) and efficiency (average: ~40%). Successful gene modification of unsorted T cells as well as different T-cell subsets (CD4, CD8, T regulatory cells) were demonstrated all under endogenous promoter control with minimal off-target effects. In the first proof of concept application of this technique, T cells in 2 out of 3 children with compound heterozygous mutations in the IL2RA gene were edited successfully, with up to 25% expressing IL2Rα after HDR. Edited T cells showed improvements in cell signaling, successfully activating STAT5 after interleukin-2 stimulation. Moreover, edited T regulatory cells expressing IL2RA and FOXP3 demonstrated suppressive ability that matched the activity of single heterozygotes. The technique was also applied to cancer immunotherapy, in which the T-cell receptor was edited to display specificity to a melanoma tumor antigen (NYESO-1) by insertion of a dsDNA cassette in line with the TCR constant region locus (α or β or both), with ~12% of cells having an engineered TCR. TCR-engineered T cells, specifically CD8 cells, recognized and elicited antigen-specific degranulation to kill the NYESO-1+ melanoma cells in vitro and eradicate tumor cells in a mouse model. The engineered T cells
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