

IDDA-Scored Abatacept-to-HSCT Course in Pediatric LRBA Deficiency

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Research Article

Keywords:

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10708695/v1>

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Additional Declarations: No competing interests reported.

Abstract

LRBA deficiency is a rare inborn error of immunity in which impaired CTLA-4 recycling causes immune dysregulation; haematopoietic stem cell transplantation (HSCT) is curative, but no standardised measure of pre-transplant disease activity exists and the role of abatacept as a bridge to HSCT remains ill-defined. We report a 4-year-old girl with compound heterozygous LRBA variants in whom abatacept, given as a planned bridge to transplantation, reduced disease activity within four months (Immune Deficiency and Dysregulation Activity [IDDA] score 54.5 to 22.6), maintained control until transplant, and was followed by an IDDA of 1.0 at 22 months after fully matched unrelated-donor HSCT. Retrospective IDDA scoring was feasible in 32 of 46 published LRBA HSCT patients (22 with and 10 without pre-HSCT abatacept; baseline scores 11.1 vs 11.5), with descriptively higher survival in abatacept-bridged patients (95.8% vs 86.4%; $P = 0.34$). The IDDA provides a practical metric to quantify disease activity and to evaluate the contribution of pre-HSCT abatacept in LRBA deficiency.

FullText

To the Editor, LRBA deficiency is a rare inborn error of immunity in which biallelic loss-of-function variants impair CTLA-4 recycling, causing immune dysregulation with recurrent infections, cytopenias, organomegaly, lymphoproliferation, and autoimmune manifestations [1–3]. Intravenous immunoglobulin (IVIG) and immunosuppressants provide only incomplete control in severe disease; hematopoietic stem cell transplantation (HSCT) is the only curative option, and abatacept, a CTLA4-Ig fusion protein that directly counteracts the shared CTLA-4 insufficiency, can serve as a bridge to transplantation [4, 5]. Although abatacept is increasingly used before HSCT, its impact on subsequent transplant outcomes remains unclear, and comparisons across reports currently rely on heterogeneous, investigator-defined categories of disease severity rather than on a standardized measure. The Immune Deficiency and Dysregulation Activity (IDDA) score addresses this gap: it grades 13 clinical domains (cytopenia, enteropathy, lymphoproliferation, pulmonary, cutaneous/ocular, granulomatous, endocrine, articular, hepatic, renal, neurologic, nutritional, and infectious), each from 0 to 4, and combines them with supportive-care adjustments and a performance-status coefficient [5]. The IDDA score was developed in a 76-patient cohort of LRBA deficiency [5] and, to our knowledge, has not previously been applied as a comparative instrument across transplant reports. We applied the IDDA score to a child treated sequentially with abatacept and HSCT and, for the first time to our knowledge, used uniform IDDA scoring to compare published LRBA HSCT cohorts according to pre-HSCT abatacept exposure.

A 4-year-old girl presented with a 1.5-year history of hepatosplenomegaly, lymphadenopathy, and polyarthritis involving the ankles, knees, wrists, and small joints of the hands and feet, together with recurrent respiratory infections. Examination showed the liver 3.4 cm and the spleen 3.5 cm below the costal margins; laboratory tests revealed anemia (hemoglobin 88 g/L), thrombocytopenia (platelets 90×10^9 /L), hypogammaglobulinemia (IgG 0.54 g/L), and an inverted CD4/CD8 ratio, and chest CT showed interstitial pneumonia. Whole-exome sequencing identified compound heterozygous LRBA variants—c.5580 + 1G > A (pathogenic splice-site) and c.4321C > T (p.Arg1441Trp; variant of uncertain significance

in the conserved BEACH domain)—confirmed by Sanger sequencing; the father and one brother carried the splice-site variant, the mother the missense variant, and one younger brother carried both variants without clinical disease, consistent with autosomal recessive inheritance with incomplete penetrance (Fig. 1a).

Treatment with monthly IVIG and sirolimus achieved only partial control: arthritis, hepatosplenomegaly, and recurrent pulmonary infections persisted. Abatacept (10 mg/kg subcutaneously weekly) was therefore started on November 28, 2022. Within weeks the arthritis improved markedly (JADAS-71 fell from 28 to 6), splenomegaly regressed substantially, and infections diminished; laboratory parameters improved, and the IDDA score—assessed independently by two clinicians—fell from 54.5 at presentation to 22.6 after four months of abatacept, with disease control maintained until transplantation (Supplementary Table S1). On April 3, 2023, the patient underwent allogeneic HSCT from a fully matched unrelated donor (10/10 HLA; donor A+, recipient B+) after conditioning with fludarabine, targeted busulfan, thiotepea, cyclophosphamide, and antithymocyte globulin, with *Pneumocystis jirovecii* pneumonia prophylaxis. Neutrophil and platelet engraftment occurred on days + 17 and + 20, with full donor chimerism in T, B, and NK cells; no severe acute or chronic graft-versus-host disease (GVHD) developed, and apart from transient CMV reactivation that resolved with antiviral therapy, the peri-transplant course was uncomplicated. At 22 months after HSCT the patient remained infection-free with stable joint function, normalized liver and spleen size, and resolution of the interstitial pneumonia on follow-up imaging, and the IDDA score had fallen to 1.0 (Fig. 1b–c; Supplementary Tables S1 and S2).

To place this trajectory in context, we performed a structured review of LRBA-deficient patients reported to have undergone allogeneic HSCT. PubMed and Embase were searched from inception to August 2026 (Supplementary Methods): 199 records were identified (73 PubMed, 126 Embase), 51 duplicates were removed, and 148 records were screened; 131 were excluded (reviews, conference abstracts or preprints, preclinical studies, or reports without HSCT outcome data), leaving 16 studies reporting 46 patients for final analysis (estimated 40–43 unique patients after conservative deduplication; Supplementary Figure S1). All 16 studies were case series or single-case reports, and none had prospectively quantified disease activity before HSCT; study quality, rated with the NIH Quality Assessment Tool, was good in six studies and fair in ten. Overall survival was 91% (42/46). Uniform 13-domain IDDA scoring proved feasible for 32 patients from seven studies—22 who had received pre-HSCT abatacept and 10 who had not; the remainder could not be scored because individual supportive-care parameters (e.g., nutritional support, immunoglobulin replacement, antimicrobial prophylaxis) were not reported, itself an argument for standardized reporting. Mean pre-HSCT IDDA scores were closely similar between the groups (11.1 vs 11.5), indicating comparable baseline disease activity; abatacept-exposed patients had descriptively higher overall survival (95.8%, 23/24, vs 86.4%, 19/22; Fisher exact test $P = 0.34$), with overlapping rates of grade $\geq$ II acute GVHD ($\sim 22\%$ vs $\sim 26\%$), chronic GVHD ($\sim 11\%$ vs $\sim 11\%$), severe infections ($\sim 36\%$ vs $\sim 45\%$), and full donor chimerism ($\sim 70\%$ vs $\sim 65\%$) (Supplementary Tables S3–S5; quality assessment in Supplementary Table S6). Cytopenia, enteropathy, and lymphoproliferation were the most frequently represented IDDA domains among scored patients.

These observations carry two practical messages. First, in the individual patient, the IDDA score provided a quantifiable, multidomain, and treatment-responsive measure of disease control: it decreased by 59% after four months of abatacept and to near-zero after HSCT, closely paralleling the clinical course and the independent JADAS-71 trajectory. Second, across cohorts, the score can serve as a common yardstick: reports of LRBA transplantation have relied largely on binary outcomes such as survival, engraftment, and GVHD, whereas pre-HSCT disease activity—the factor that determines transplant urgency and peritransplant risk—has rarely been quantified. The score is practical: it can be reconstructed retrospectively when supportive-care parameters are reported and applied prospectively with minimal training. In practice, serial IDDA assessment could inform decisions on abatacept dosing and duration, the timing of transplantation, and post-transplant surveillance. Our finding of similar pre-HSCT scores in abatacept-treated and untreated patients argues that the better survival in the abatacept group reflects the intervention rather than milder baseline disease, although the comparison remains descriptive, underpowered, and potentially confounded by cohort overlap, heterogeneous conditioning, and variable outcome reporting [3]; no causal inference was attempted. The predominance of cytopenia, enteropathy, and lymphoproliferation among scored patients also illustrates which domains carry the pre-HSCT burden in LRBA deficiency. Limitations include the retrospective design, incomplete reporting of supportive-care parameters in published cases, and the small sample size; the missense variant c.4321C > T (p.Arg1441Trp) remains a variant of uncertain significance by ACMG/AMP criteria (Supplementary Table S7).

We believe that standardized IDDA-based assessment will be essential to define the optimal role and timing of abatacept before HSCT in LRBA deficiency and related CTLA-4 insufficiency disorders. Embedding the score—together with a minimum set of supportive-care parameters—in prospective multicenter registries would allow future cohorts to be compared on common ground, and we encourage its routine use in clinical practice and in future reports. Pending prospective validation, we suggest that reports of HSCT in LRBA deficiency include the IDDA score at diagnosis and immediately before transplantation.

Declarations

Funding: This study received no external funding.

Author Contribution

BH and ML designed the study. BH collected the clinical data. YZ and LT performed the literature review and data analysis. ZW was responsible for the ethics application and coordination of research data. BH wrote the manuscript. All authors read and approved the final manuscript. The authors report there are no competing interests to declare.

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Figures

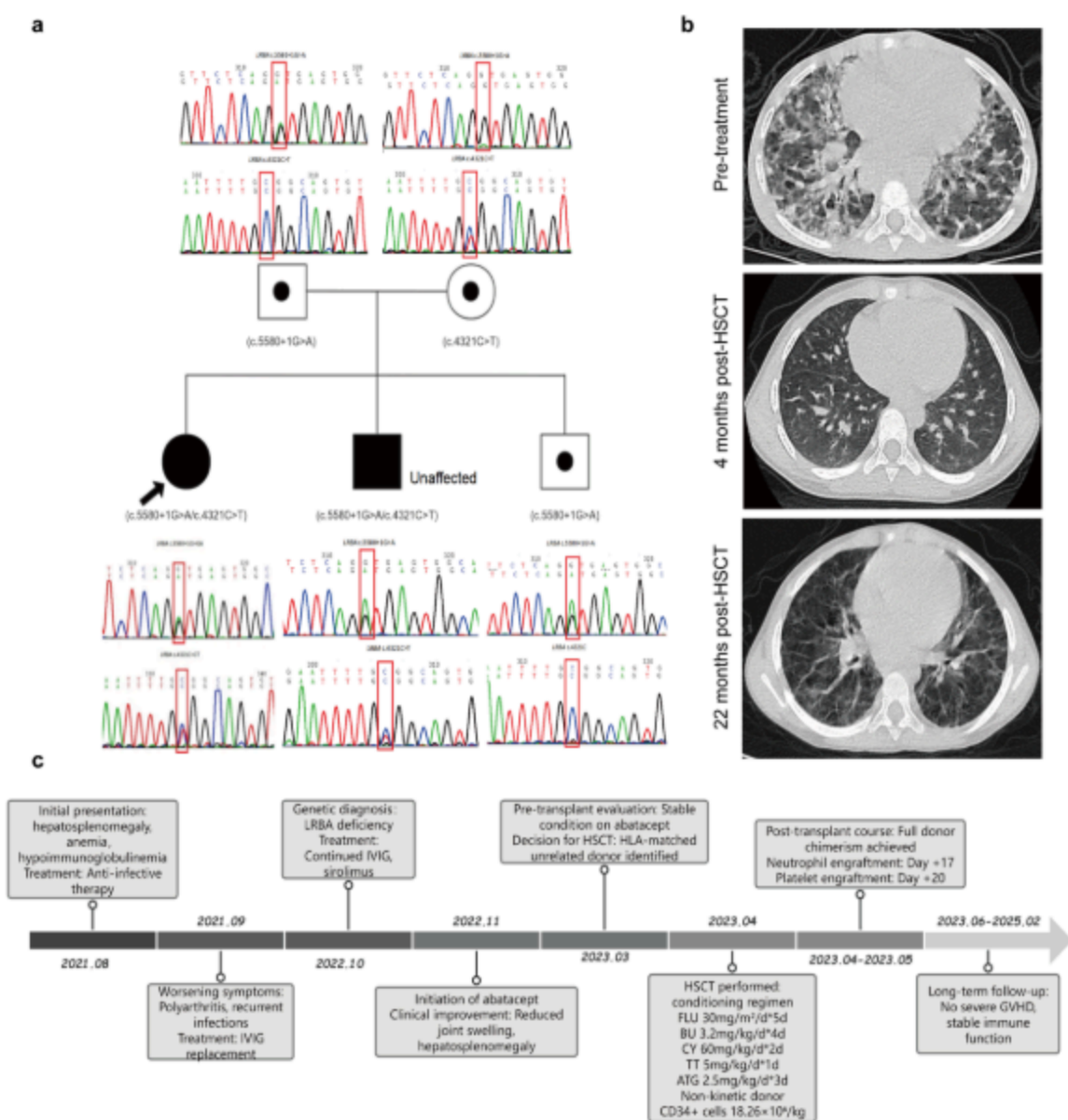


Figure 1

IDDA-scored disease course in a pediatric patient with LRBA deficiency. (a) Family pedigree and Sanger sequencing confirmation of the compound heterozygous LRBA variants (c.5580+1G>A; c.4321C>T). (b) Serial chest computed tomography showing interstitial pneumonia before treatment and radiological resolution after HSCT. (c) Clinical timeline with the IDDA score decreasing from 54.5 at presentation to 22.6 after four months of abatacept and to 1.0 at 22 months after HSCT; treatments, engraftment, and key clinical events are indicated.

Supplementary Files

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- [Supplementary20260906.docx](#)