Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score

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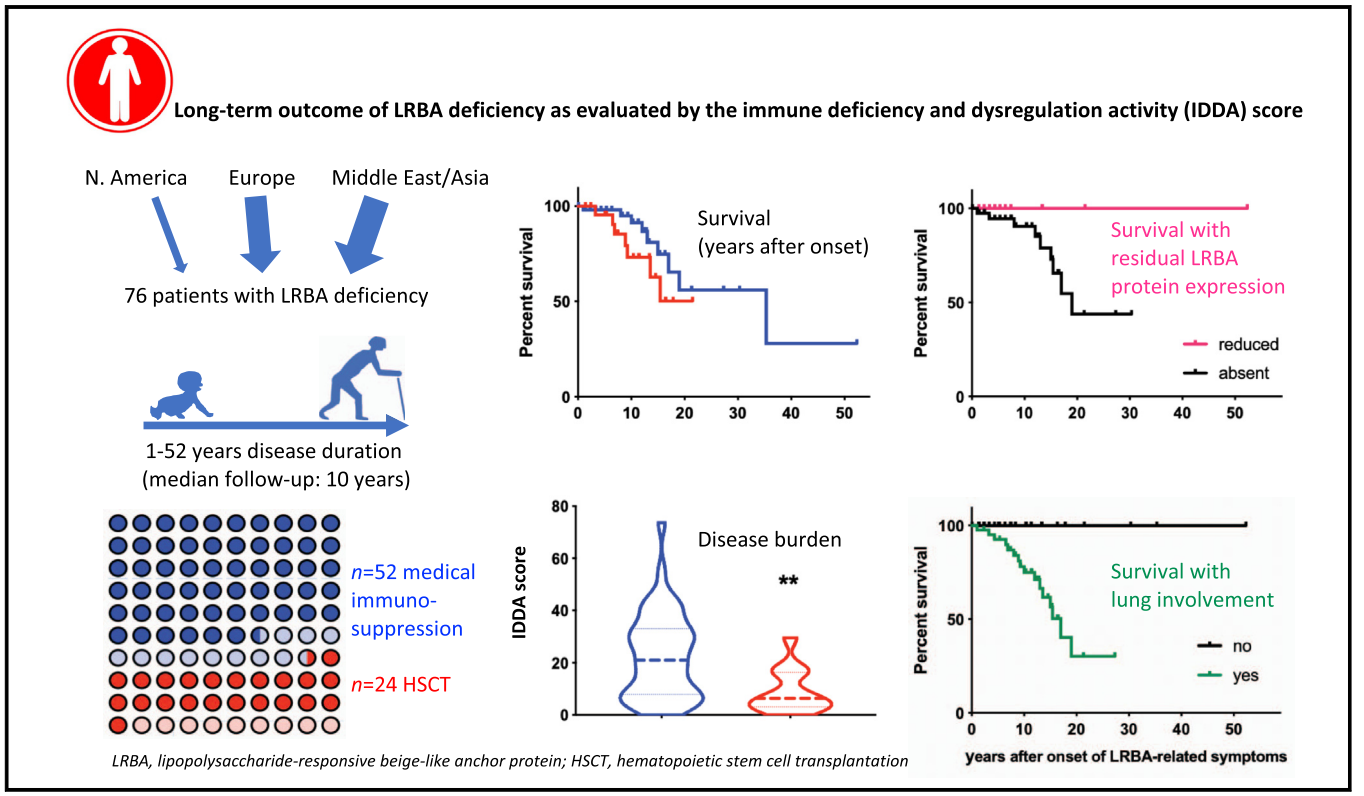
GRAPHICAL ABSTRACT



Background: Recent findings strongly support hematopoietic stem cell transplantation (HSCT) in patients with severe presentation of LPS-responsive beige-like anchor protein (LRBA) deficiency, but long-term follow-up and survival data beyond previous patient reports or meta-reviews are scarce for those patients who do not receive a transplant.

Objective: This international retrospective study was conducted to elucidate the longitudinal clinical course of patients with LRBA deficiency who do and do not receive a transplant.

Method: We assessed disease burden and treatment responses with a specially developed immune deficiency and dysregulation activity score, reflecting the sum and severity of organ involvement and infections, days of hospitalization, supportive care requirements, and performance indices.

Results: Of 76 patients with LRBA deficiency from 29 centers (median follow-up, 10 years; range, 1-52), 24 underwent HSCT from 2005 to 2019. The overall survival rate after HSCT (median follow-up, 20 months) was 70.8% (17 of 24 patients); all deaths were due to nonspecific, early, transplant-related mortality. Currently, 82.7% of patients who did not receive a transplant (43 of 52; age range, 3-69 years) are alive. Of 17 HSCT survivors, 7 are in complete remission and 5 are in good partial remission without treatment (together, 12 of 17 [70.6%]). In contrast, only 5 of 43 patients who did not receive a transplant (11.6%) are without immunosuppression. Immune deficiency and dysregulation activity scores were significantly lower in patients who survived HSCT than in those receiving conventional treatment ($P = .005$) or in patients who received abatacept or sirolimus as compared with other therapies, and in patients with residual LRBA expression. Higher disease burden, longer duration before HSCT, and lung involvement were associated with poor outcome.

Conclusion: The lifelong disease activity, implying a need for immunosuppression and risk of malignancy, must be weighed against the risks of HSCT. (J Allergy Clin Immunol 2020;145:1452-63.)

Key words: *Inborn error of immunity, primary immunodeficiency disorder, immune dysregulation, clinical score, performance scale, hematopoietic stem cell transplantation, CTLA4, abatacept, sirolimus, combined immunodeficiency*

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Abbreviations used
CNS: Central nervous system
CTLA4: Cytotoxic T-lymphocyte antigen 4
HSCT: Hematopoietic stem cell transplantation
IDDA: Immune deficiency and dysregulation activity score
IPEX: Immunodysregulation polyendocrinopathy enteropathy X-linked
LRBA: LPS-responsive beige-like anchor
PR: Partial remission
Treg: Regulatory T
TRM: Transplant-related mortality
WBC: White blood cell

LPS-responsive beige-like anchor protein (LRBA) deficiency, first described in 2012,[1] is a severe primary immunodeficiency with a broad spectrum of clinical and immunologic manifestations caused by biallelic mutations in the *LRBA* gene.[2-6] LRBA is ubiquitously expressed and involved in signal transduction, vesicular trafficking, autophagy, and apoptosis; abolished expression may impair key processes related to immunity.[1,7,8] LRBA normally prevents cytotoxic T-lymphocyte protein-4 (CTLA4) from lysosomal degradation by bringing it back to the cell surface; its absence leads to decreased CTLA4 expression.[9] The resulting regulatory T (Treg)-cell defect causes immune dysregulation and autoimmunity, the symptoms of which partially resemble those of CTLA4 insufficiency (see Fig E1 in this article's Online Repository at www.jacionline.org).[2,4-6,10-13]

Until recently, the conventional treatment options for LRBA deficiency have included various immunosuppressive agents, such as corticosteroids, sirolimus, and abatacept (a soluble CTLA4 immunoglobulin fusion protein that appears to partially restore Treg-cell function).[5,6,9] One prospective study[14] and others[9,15-19] reported on the effectiveness of the latter. However, soluble CTLA4 might not fully replace membrane-bound CTLA4 or other LRBA functions. Thus, the use of purely conventional treatment options might not prevent the long-term deterioration of patients with LRBA deficiency.[8] Furthermore, risks associated with the need for continuous immunosuppressive treatment (eg, immunosuppression-associated infection or malignancy) remain.[8] Earlier studies reported that most patients with LRBA deficiency who have undergone hematopoietic stem cell transplantation (HSCT) achieved complete remission; however, the studies also detected higher transplant-related mortality (TRM) rates than have been seen in patients with other inborn errors of immunity.[5,8,20] No genotype-phenotype correlation has been detected,[2,4,5] but milder phenotypes with residual protein expression have been observed. Thus, doctors treating patients with LRBA deficiency need more information regarding whether and when to proceed with HSCT.

This international, retrospective study was conducted to broaden our knowledge of the transplant experience and chart the clinical course of patients with LRBA deficiency undergoing various targeted treatment modalities who did and did not receive a transplant. In addition, we assessed the disease activity and treatment responses by using a specially developed immune deficiency and dysregulation activity (IDDA) scoring method, which might also be useful in the management of patients with other combined immunodeficiencies with immune dysregulation.

METHODS

We performed an international European Society for Blood and Marrow Transplantation Inborn Errors and Clinical Working Parties and European Society for Immunodeficiencies Registry Working Party–wide retrospective multicenter study. Pseudonymized data were obtained by retrospective chart review with the patient's informed consent according to Good Clinical Practice guidelines and institutional review board approvals (IRB00002556,

TABLE I. Patient cohort characteristics of 76 patients with LRBA deficiency under conventional treatment or after HSCT

Parameter	Conventional therapy	HSCT	Total
No. of patients	52	24	76
Male:female ratio	24:28	10:14	34:42
Survival status, alive/dead	43/9	17/7	60/16
Consanguinity, yes/no	Yes = 43/no = 9	Yes = 17/no = 7	Yes = 60/no = 16
Age at study inclusion	14 y (1.5-69 y)	13 y (3-25 y)	13 y (1.5-69 y)
Age at onset of symptoms	2 y (0-25 y) n = 49	2.5 y (0.1-10 y) n = 24	2 y (0-25 y) n = 73
Age at genetic diagnosis	12 y (0.3-66 y) n = 49	10 y (1.3-24 y) n = 21	11 y (0.3-66 y) n = 70
Diagnostic delay (time between onset of symptoms and genetic diagnosis)	8 y (0-49 y) n = 47	7 y (0-16.9 y) n = 21	7.6 y (0-49 y) n = 68
Age at HSCT	—	10 y (1.8-25.8 y)	—
Follow-up since onset of LRBA-related symptoms	10 y (1-52 y)	9.4 y (1-21 y)	10 y (1-52 y)
Follow-up since clinical diagnosis	5.3 y (1-35 y) n = 50	5.8 y (1.3-22.3 y) n = 24	5.5 y (1-35 y) n = 74
Follow-up since HSCT (mo)	—	20 mo (3-171 mo) n = 17	—
Median IDDA score before HSCT	—	32.9 (7.7-108.6) n = 13	—
Median IDDA score under medical treatment or after HSCT	20.8 (0-54.9) n = 44	6.3 (0-29.5) n = 13	—
Pulmonary involvement, yes/no	Yes = 29/no = 23	Yes = 12/no = 12	Yes = 41/no = 35

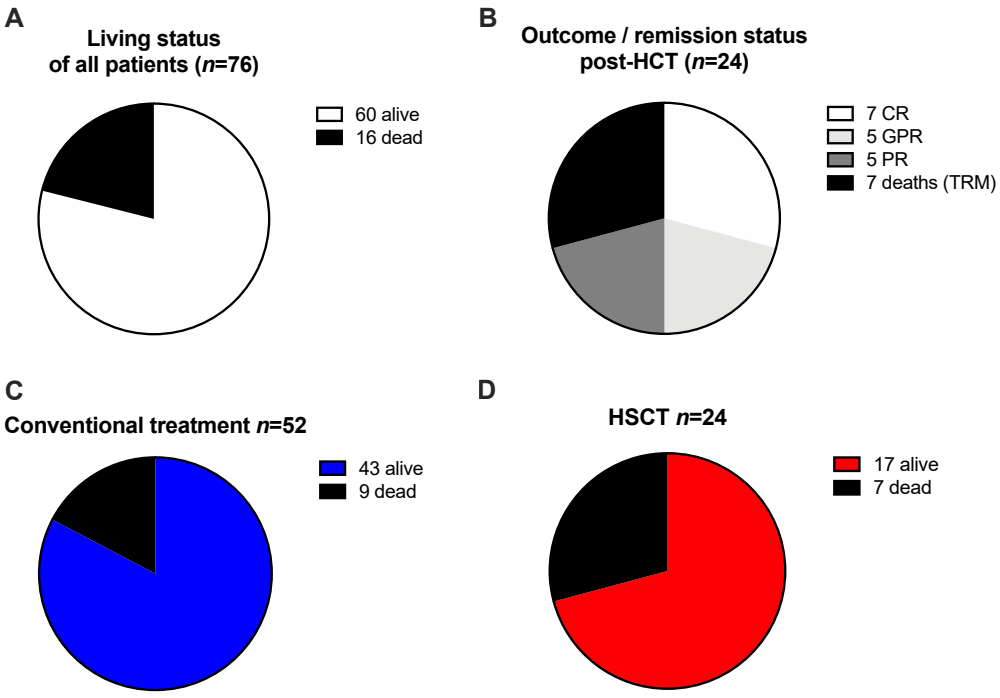

FIG 1. Survival status of a retrospective cohort of 76 patients with LRBA deficiency. **A,** At the time of analysis, 60 of 76 reported patients with LRBA deficiency, who had been followed for 1 to 52 years (median: 10 years), were alive. **B,** The outcome and remission status of patients with LRBA deficiency after HSCT is shown as complete remission (CR); good partial remission (GPR), indicating that some clinical symptoms potentially related to LRBA deficiency were still detectable but did not require immunosuppressive treatment; PR, indicating patients who had residual autoimmune symptoms that were treated; or death. All deaths were due to TRM. **C,** Of 52 patients receiving conventional, pharmacologic immunosuppression, 43 were alive. **D,** Of the 24 patients who received a transplant, 17 were alive at the time of analysis.

24-334 ex 11/12, and 29-142ex16/17) from May 2018 to May 2019 (see the Supplementary Material in this article's Online Repository at www.jacionline.org).

RESULTS

Baseline characteristics, clinical presentation, and overall survival

A total of 76 patients with a genetically confirmed diagnosis of LRBA deficiency (39 of whom were hitherto unreported) from 29 centers were included (42 females, 34 males; Table I and see Table E1 in this article's Online Repository at www.jacionline.org). Of the 76 patients, 24 (31.6%) had undergone HSCT and 47 (61.8%) had received only immunosuppressive therapy. Five patients (6.6%), aged 5, 8, 11, 21, and 37 years, did not require immunosuppressive treatment and presented with either mild symptoms (lymphopenia, thrombocytopenia, urinary tract infection) or were asymptomatic and identified through family screening. In all, 60 patients (78.9%) were still living at the time of the analysis (43 of 52 [82.7%] conventionally treated and 17 of 24 [70.8%] patients who had undergone HSCT; Table I and Fig 1, *A, C, D*). The median age at disease onset was 2 years (range, birth-25 years; Table I). HSCT survivors showed a favorable degree of remission, as 70.6% were currently without treatment (Fig 1, *B*), whereas 88.4% of the patients who did not undergo HSCT needed treatment at the time of analysis. The median follow-up after the onset of symptoms was 9.4 years in patients who had undergone HSCT (range, 1-21) versus 10 years (range, 1-52) in conventionally treated patients. The median current age of HSCT survivors and living patients under conventional treatment was 13 years (ranges, 3-23 and 3-69, respectively).

The probability of survival 15 to 20 years after disease onset was around 50% to 60% in both treatment cohorts (Fig 2, *A*), but this number might be misleading on account of the variable time points of initiation and modalities of treatment. Therefore, we compared the survival probability rates after HSCT with the rates after the introduction of pharmacologic immunosuppression (Fig 2, *B*). We observed that all post-HSCT deaths occurred within the first 3 months after HSCT. In contrast, the risk of mortality remained constant in patients who received conventional treatment (Fig 2, *B*), who also had an increased disease burden compared with that of HSCT survivors, as measured by organ involvement, performance in daily activities, and the intensity of the required care (see later; Fig 2, *C*). The causes of death are listed in Table II.

The frequency distribution of clinical findings was similar to that reported by previous studies (see the Supplementary Material). Of note, malignancies occurred in 3 patients (3.9%). One patient developed gastric cancer (at age 19 years) and malignant melanoma (at age 27 years); both cancers were surgically treated.[21] Malignancies of the central nervous system (CNS), an astrocytic tumor and a CNS lymphoma, were reported in 2 patients. Remarkably, all 16 deceased patients—7 who received a

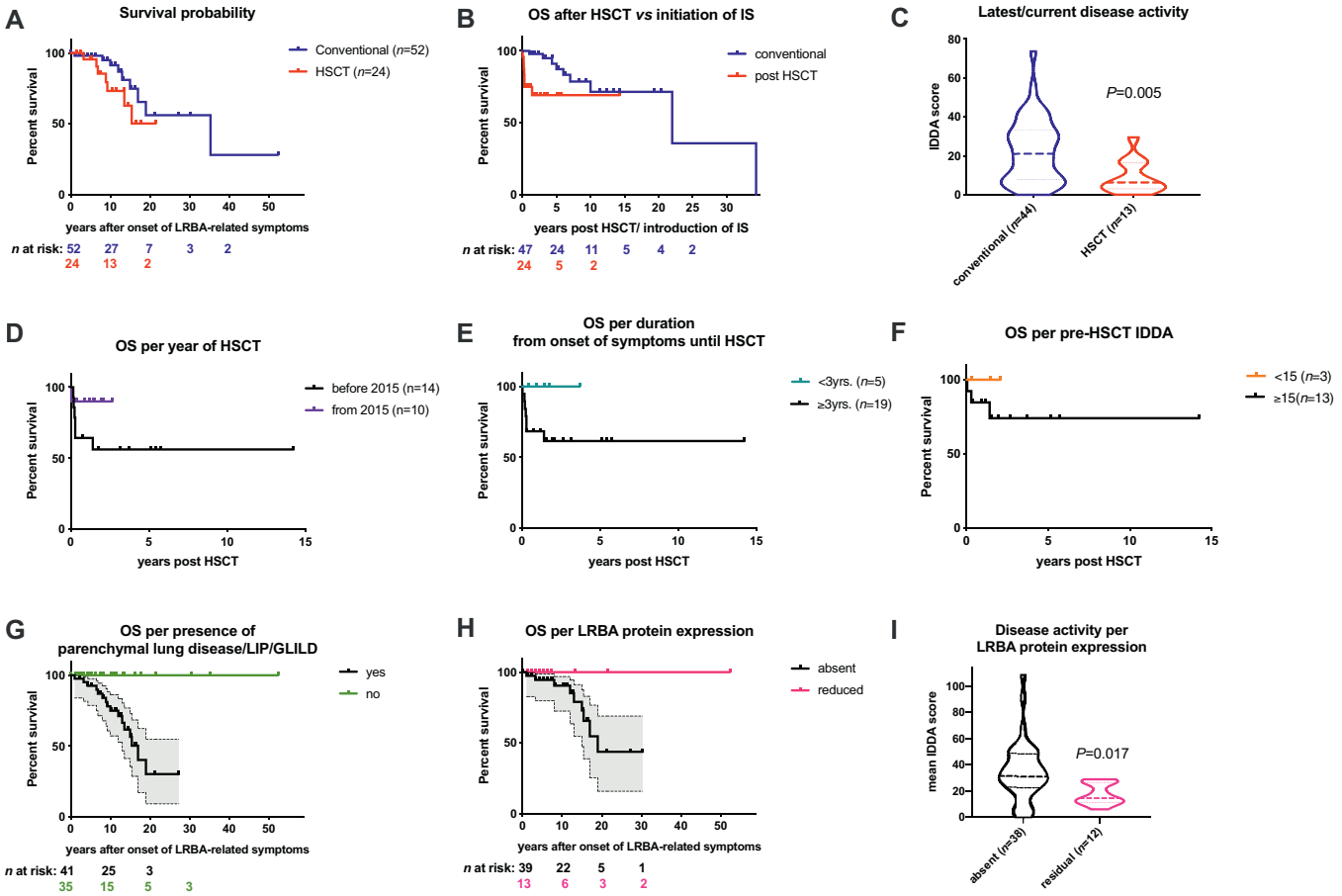

FIG 2. Survival probabilities of 76 patients with LRBA deficiency under various treatment modalities. The survival probability of patients receiving conventional treatment (*blue*) versus HSCT (*red*) is shown as a percentage in years from disease onset **(A)** or years from introduction of immunosuppression (IS) or after transplantation (post-HSCT) **(B)**. **C,** The latest reported disease activity, as evaluated by the IDDA scoring method, is shown with median error and SE ($P = 0.005$). **D,** For 24 patients who had undergone HSCT, the overall survival (OS) probability according to the year of transplantation is shown. **E,** The OS according to the time elapsed from onset of symptoms until performance of HSCT is shown. **F,** The OS of 16 patients after HSCT is shown according to their pre-HSCT IDDA score. **G,** The OS from disease onset is shown for all 76 patients with LRBA deficiency who did or did not have lung involvement (with 95% confidence intervals in **[G]** and **[H]**). **H,** The OS of 12 patients with reduced is shown along with the OS of 39 patients with absent (undetectable) protein expression. **I,** The average disease burden (IDDA score) of patients with residual or absent LRBA expression is shown with median error and SE ($P = .017$; IDDA scores of patients after HSCT were excluded).

transplant and 9 who did not—suffered from lung involvement (lymphocytic interstitial pneumonia, granulomatous-lymphocytic interstitial lung disease, or other parenchymal lung disease; Fig 2, *G*); the cause of death included respiratory failure or severe lung infections in 10 of these 16 patients (62.5%; Table II). The overall survival probability was significantly lower in patients with lung involvement than in patients without ($P = .002$); to date, all the patients with LRBA deficiency without lung involvement are alive, whereas 16 of the 41 patients with lung involvement (39%) have died (Fig 2, *G*). Furthermore, the multivariate analysis results showed that lung involvement ($P = .008$) and autoimmune cytopenia ($P = .017$) significantly correlated with a fatal disease outcome in LRBA deficiency (including all the organ systems involved in LRBA deficiency that are listed in Table III[22,23]). Other findings that were observed either before HSCT or before conventional treatment did not significantly correlate with the outcome. The residual expression of LRBA protein was intriguingly associated with a 100% survival rate, whereas 9 of 39 patients (23.1%) with absent protein expression died (n = 51, Fig 2, *H*; $P = .071$). Disease burden was significantly lower in patients with residual LRBA expression as compared with in those without it (Fig 2, *I*; $P = .017$).

Characteristics and courses of patients with LRBA deficiency undergoing HSCT

A total of 24 patients with LRBA deficiency, 8 of whom were previously unreported, underwent HSCT between 2005 and 2019 (see Table E2 in this article's Online Repository at www.jacionline.org). The median time that elapsed between the onset of symptoms and the transplantation procedure was 7.4 years (range, 0.4-15.8 years; Table I). Indications for HSCT included recurrent severe infections, refractory immune cytopenia (eg, Evans syndrome), chronic parenchymal lung disease, severe

TABLE II. Causes of 16 deaths among 76 patients with LRBA deficiency

Patient no.	Age at death	Time interval after onset of symptoms	Time interval after genetic diagnosis	Time interval after HSCT	Cause of death
6	25y	15.5 y	1.5 y	13 d	Sepsis, respiratory failure
10	9 y	8.5 y	After death	2 mo	MOF
13	10 y	5.5 y	After death	2 mo	Nonengraftment, MOF
16	14 y	13 y	After death	3.5 mo	Refractory GvHD, multiple infections
19	12 y	9 y	2.5 y	3 mo	Invasive pulmonary aspergillosis
20	6 y	3 y	n.a.	3 mo	Respiratory failure, lung fibrosis, adenovirus pneumonia, graft rejection
22	10 y	6 y	10 mo	2 mo	Adenoviremia, thrombotic microangiopathy, pneumonitis
25	17 y	15 y	1 y	—	Cardiac and renal failure
26	19 y	17 y	After death	—	Respiratory failure
27	11 y	8 y	After death	—	Respiratory failure
32	22 y	19 y	1 y	—	Respiratory failure
35	20 mo	14 mo	2 mo	—	CNS hemorrhage
39	15 y	13 y	2 y	—	Respiratory and renal failure
41	20 y	12 y	After death	—	Respiratory and renal failure
54	14 y	n.a.	n.a.	—	Severe lung infection
73	35 y	35 y	3 y	—	Respiratory failure

n.a., Not available; *MOF*, multiorgan failure; *GvHD*, graft versus host disease.

gastrointestinal problems, failure to thrive, severe autoimmunity, and severe neurologic complications (see Table E2).

The overall survival rate of patients undergoing HSCT was 70.8% (17 of 24 patients; Fig 1, *B* and *C*). All 7 deaths were due to early TRM (graft failure, multiorgan failure, preexisting severe infections, refractory acute graft-versus-host disease, or thrombotic microangiopathy; Table II). Of the 17 surviving patients, 7 were in complete remission, 5 were in good partial remission (PR) (with some mild or moderate, potentially LRBA-related symptoms not requiring immunosuppressive treatment), and 5 were in PR (with amelioration of the disease, but in need of immunosuppressive treatment for potentially LRBA-related symptoms; Fig 1, *B*). Thus, 70.6% of patients (12 of 17) who survived HSCT are currently without treatment. Furthermore, the performance scores increased, and the need for immunoglobulin replacement therapy decreased in all HSCT survivors (see Fig E2 in this article's Online Repository at www.jacionline.org). The mean follow-up time for the 17 surviving patients was 36.2 months (range, 3-171). Nine patients (37.5%) developed acute graft-versus-host disease (see Table E2; skin, grade I-II in 6 patients; gastrointestinal, grade II in 1; and gastrointestinal grade IV in 3). Ten of 11 patients (all in complete remission or with a good PR) for whom information was available had full donor chimerism (>95% donor white blood cells [WBCs]). We identified a positive association between full donor chimerism and the most favorable degrees of remission after HSCT. Graft failure was observed in 2 patients (8.3%). Patient 13 had 0% donor WBCs on day +30 and died 2 months after HSCT as a result of poor engraftment and sepsis. Patient 10 had 71% donor WBCs on day +30, followed by a total loss of graft on day +75, and died 2 months after the second transplantation as a result of multiorgan failure. The overall survival rates were significantly better in patients who underwent HSCT within the first 3 years after the onset of LRBA-related symptoms than in individuals with a longer disease duration ($P = .0001$; Fig 2, *E*). HSCT course and outcome were not dependent on the donors' LRBA carrier status, conditioning regimen, donor type, or age at HSCT (see Table E2), although a trend toward better survival rates in younger patients and those with lower disease activity scores (see later and Fig 2, *F*) was detected. In addition, survival of HSCT was associated with the transplantation year (Fig 2, *D*), although these data were not statistically significant ($P = .13$): Since 2015, only 1 of 10 patients (10%) who underwent HSCT has died, but up until 2015, the rate of TRM was 42.9% (6 of 14 patients who received a transplant).

IDDA score

We developed a special IDDA score that allowed us to conduct intraindividual, longitudinal monitoring and assess the interindividual disease burden carried by patients with LRBA deficiency. The score includes an assessment of organ involvement (graded 0-4, depending on the severity and need for treatment), which was weighted by performance indices. This weighted score was added to the score for days of hospitalization, the need for intensive or supportive care, and the number of infections (for details, see Table III). The IDDA score was assessed in 16 patients who had undergone HSCT (13 of whom are alive at the time of writing this publication) and in 51 patients who received conventional therapy. This assessment was conducted retrospectively at multiple time points (median 2, range, 1-10) to allow a longitudinal evaluation to be made (Fig 3).

The median IDDA score of the patients before HSCT was 32.9 (range, 7.7-108.6); this score was significantly higher than in patients receiving conventional treatment (median 20.8; $P = .006$). The IDDA score decreased significantly in all surviving patients after transplantation ($P = .005$, see Figs 3, *B* and 4, *C*). The latest median IDDA score obtained from HSCT survivors was 6.3 (range, 0-29.5, Table I and Fig 2, *C*). The pre-HSCT IDDA scores of the 3 patients who died and for whom data were available were 18.7, 28.8, and 102.5. A lower pre-HSCT IDDA score was associated with a better survival probability, as beginning HSCT with an IDDA score below 15 (n = 3) was correlated with an overall survival rate of 100%, whereas overall survival decreased in patients with higher pre-HSCT scores, although these data were not statistically significant on account of the small sample size (Fig 2, *F*). Furthermore, organ-specific, LRBA

TABLE III. IDDA score and data of the present cohort

	Parameter (use score 0-4)*	Grade†				
		0, n (%)	I, n (%)	II, n (%)	III, n (%)	IV, n (%)
A	Autoimmune cytopenia	24 (35.3%)	9 (13.2%)	10 (14.7%)	23 (33.8%)	2 2.9%9)
B	Enteropathy/inflammatory bowel disease	13 (19.1%)	5 (7.4%)	10 (14.7%)	31 (45.6%)	9 (13.2%)
C	Lymphoproliferation/splenomegaly/hepatomegaly	13 (19.1%)	14 (20.6%)	23 (33.8%)	17 (25.0%)	1 (1.5%)
D	Parenchymal lung disease/lymphocytic interstitial pneumonia/granulomatous lymphocytic Interstitial lung disease	28 (41.2%)	4 (5.9%)	7 (10.3%)	23 (33.8%)	6 (8.8%)
E	Skin or eye manifestations/eczema, uveitis, alopecia, vitiligo, other	43 (63.2%)	4 (5.9%)	11 (16.2%)	9 (13.2%)	1 (1.5%)
F	Endocrinopathy/insulin-dependent diabetes mellitus, thyroiditis, other	50 (73.5%)	5 (7.4%)	1 (1.5%)	10 (14.7%)	2 (2.9%)
G	Arthritis/other musculoskeletal	50 (73.5%)	4 (5.9%)	4 (5.9%)	9 (13.2%)	1 (1.5%)
H	Autoimmune hepatitis/cholangitis/pancreatitis	55 (80.9%)	8 (11.8%)	2 (2.9%)	3 (4.4%)	0 (0%)
I	Glomerulonephritis/nephropathy, tubulopathy	56 (82.4%)	2 (2.9%)	5 (7.4%)	2 (2.9%)	3 (4.4.%)
J	Neurologic manifestations	53 (77.9%)	1 (1.5%)	2 (2.9%)	6 (7.4%)	7 (10.3%)
K	Failure to thrive/malabsorption, wasting	19 (27.9%)	11 (16.2%)	13 (19.1%)	22 (32.4%)	3 (4.4%)
L	Severe infections/opportunistic (excluding chronic infestation)	18 (26.5%)	6 (8.8%)	22 (32.4%)	15 (22.1%)	7 (10.3%)
	Other factors and symptoms (will multiply or add to the score)‡,§,‖,#,¶					
M	Karnofsky/Lansky scale (%)‡	Median, 80%; range, 30%-100%				
N	Hospitalization (% = d/100 d; including day clinic stays, excluding intensive care unit)	Median, 5%; range, 0%-100%				
O	Mechanical ventilation or other ICU measures (% = d/100 d)	Median, 0%; range, 0%-10%				
P	Immunoglobulin substitution therapy (please read comment for scoring)§	10 (14.7%)		5 (7.4%)		53 (77.9%)
Q	Any relevant chronic or recurring infestation/infection (eg, Norovirus, Epstein-Barr virus)‖	29 (43.3%)	9 (13.4%)	18 (26.9%)	9 (13.4%)	2 (3.0%)
R	Any other organ dysfunction/malady (eg, cardiomyopathy, kidney failure)¶	39 (58.4%)	4 (6.0%)	11 (14.5%)	4 (6.0%)	9 (13.4%)
S	Nutrition/dietary status and habits (please read comment for scoring)#	27 (40.3%)	10 (14.9%)	12 (17.9%)	13 (19.4%)	5 (7.5%)
Z	Malignancy, lymphoma (separately noted, not added to score)	No, 73 (96.1%)		Yes, 3 (3.9%)		

IDDA score calculated as follows: IDDA = (A + B + C + D + E + F + G + H + I + J + K + L)/(M/150) + if (N < 40; N×0.1; 4) + if (O < 10; O×0,8; 8)+ P + Q + R + S

ICU, Intensive care unit.

*Grading: 0 = absent, inactive; 1 = mild, transient, not requiring treatment; 2 = moderate, intermittent therapy needed; 3 = severe, continuous therapy needed; 4 = life-threatening, refractory, irreversible.

†The number and percentage of the 68 patients with available complete IDDA scores at their worst clinical condition (episode, phase) are shown to depict the natural presentation of the disease, whereas qualitative organ involvement (yes/no) known from the other 8 patients is not included here.

‡Use age-specific Karnofsky or Lansky performance scales (0%-100%; see Karnofsky and Burchenal[22] and Lansky et al[23]).

§Values represent the following: 0 = no; 2 = sporadic; 3 (intravenous) = regularly intravenous immunoglobulin; 3 (subcutaneous) = regularly subcutaneous immunoglobulin.

‖Values represent the following: 0 = no; 1 = asymptomatic infestation; 2 = oligosymptomatic recurring infection; 3 = recurring symptomatic infection requiring on/off treatment; 4 = chronic infection requiring permanent treatment or refractory infection; only score one (worst) infection if more microbial agents are relevant.

#Values represent the following: 0 = no organopathy; 1 = mild transient dysfunction; 2 = chronic mild dysfunction; 3 = moderate-to-severe dysfunction; 4 = clinically compromising dysfunction requiring treatment or replacement therapy; only score 1 (worst) if more organs are involved.

¶Values represent the following: 0 = normal; 1 = modified, disease-adjusted; 2 = part-formula, medically advised; 3 = tube feeding, full-formula, partial parenteral nutrition (irregularly); 4 = total parenteral nutrition.

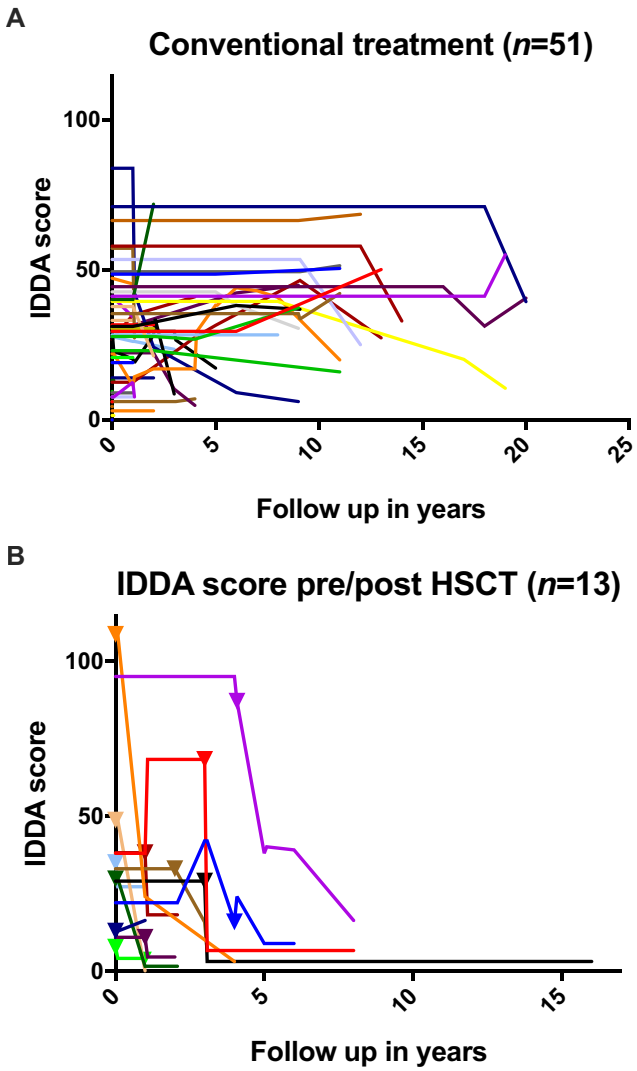

FIG 3. IDDA scores of patients with LRBA deficiency under conventional treatment or undergoing HSCT. The longitudinal changes of the disease activity, as measured by the IDDA scoring method at multiple time points per patient (1-10; median, 2), is shown for 51 conventionally treated patients (**A**) and 13 patients who received a transplant (**B**) over the time span of their follow-up during which IDDA scores could be obtained. IDDA scores before and after HSCT were available for only 13 of 24 patients who underwent HSCT. The triangle indicates the time point of HSCT; in 6 of 13 patients, the first IDDA scores were measured immediately before HSCT.

deficiency–related symptoms could all be resolved or ameliorated in 16 of 17 HSCT survivors (Fig 5, *A*). In a 7-year-old patient who received a transplant in 2019, new neurologic symptoms (absence seizures) and cytopenia were observed 4.5 months after HCST, although the patient's IDDA score also decreased after transplantation (patient 9 in Table E2).

Characteristics and disease courses of patients with LRBA deficiency under conventional immunosuppressive treatment

In all, 52 patients (68.4%) did not undergo transplantation. Of these 52 patients, 5 (aged 5, 8, 11, 21, and 37 years) were identified through family screening and presented with either very mild or mild symptoms (intermittent cough or mild lymphopenia, mild thrombocytopenia, urinary tract infection, or mild sinusitis) or were asymptomatic (n = 2) and did not require immunosuppressive treatment. The genotype did not predict the severity of the phenotype, as these patients' siblings or unrelated patients with the identical mutation showed highly variable disease activity. Of the 52 patients (90.1%) who did not undergo HSCT, 47 received immunosuppressive treatment.

A total of 43 patients (82.7%) were reported as still living at the time of the analysis. Nine patients (17.3%) died at a median age of 17 years (range, 1.5-35 years; Fig 2, *A* and *B*). The causes of death included multiorgan failure, respiratory failure, severe lung infection, and CNS hemorrhage (Table II). All deceased patients under conventional treatment suffered from lung involvement (parenchymal lung disease, lymphocytic interstitial pneumonia, or granulomatous-lymphocytic interstitial lung disease; $P = .0025$, Fig 2, *G*), as observed in our HSCT cohort, and 77.8% of these patients (7 of 9) died of respiratory failure or severe lung infections (Table II). The treatment of 47 patients who required immunosuppression started at a median age of 5 years (range, 0-60 years) with a median follow-up of 5.3 years (range, 1-35 years; Fig 2, *A* and *B*). Systemic steroids were administered in 39 of 47 patients (82.9%) who needed immunosuppression, 26 were treated with sirolimus (55.3%), and 23 received abatacept (48.9%; see Table E1). Nine patients received rituximab (19.1%), 9 (19.1%) were administered mycophenolate mofetil, 7 (14.9%) were treated with cyclosporine, and 3 (6.4%) received azathioprine (see Fig E3 in this article's Online Repository at www.jacionline.org). Other mAbs (adalimumab, tocilizumab, infliximab) were used in 2 patients (4.3%). Five patients did not receive treatment (9.6%).

One aim in conducting this study was to assess disease activity under different treatment modalities. The median current IDDA score of living patients who did not undergo HSCT was 20.8 (range, 0-54.9), which is significantly higher than that of HSCT survivors (median score of 6.3, range, 0-29.5; $P = .005$; Table I and Fig 2, *C*). The patients' IDDA scores varied over time (Fig 3, *A*), indicating that the overall disease progression could not be prevented by immunosuppression alone. As more than 1 immunosuppressive agent was administered simultaneously in many patients, the direct effects of single drugs could not always be determined in this retrospective study. Patients (n = 47) who received only conventional treatment underwent 112 scored treatment phases, with a median of 2 per patient (range, 1-10; Fig 4, *A* and see Fig E3). Treatment with abatacept or sirolimus was associated with significantly lower IDDA scores than was treatment with glucocorticosteroids; the latter was associated with the highest disease activity in this cohort. Even when these scores were compared with those of symptomatic patients who did not have therapy-requiring autoimmunity (IgG replacement only), the patients who received abatacept had significantly lower IDDA scores ($P = .0375$; Fig 4, *A*). Patients who received no treatment and were identified as LRBA-deficient in the family screening, showed the lowest disease activity, as they were either asymptomatic or displayed very mild symptoms.

Abatacept was administered to 23 patients of our cohort, with a follow-up of 400 patient-months (range, 0.1-5 years). No immunosuppression-associated malignancy occurred in our cohort, and no side effects were reported apart from newly developed eczema in 2 patients after the initiation of abatacept. IDDA scores decreased significantly in 14 patients who were

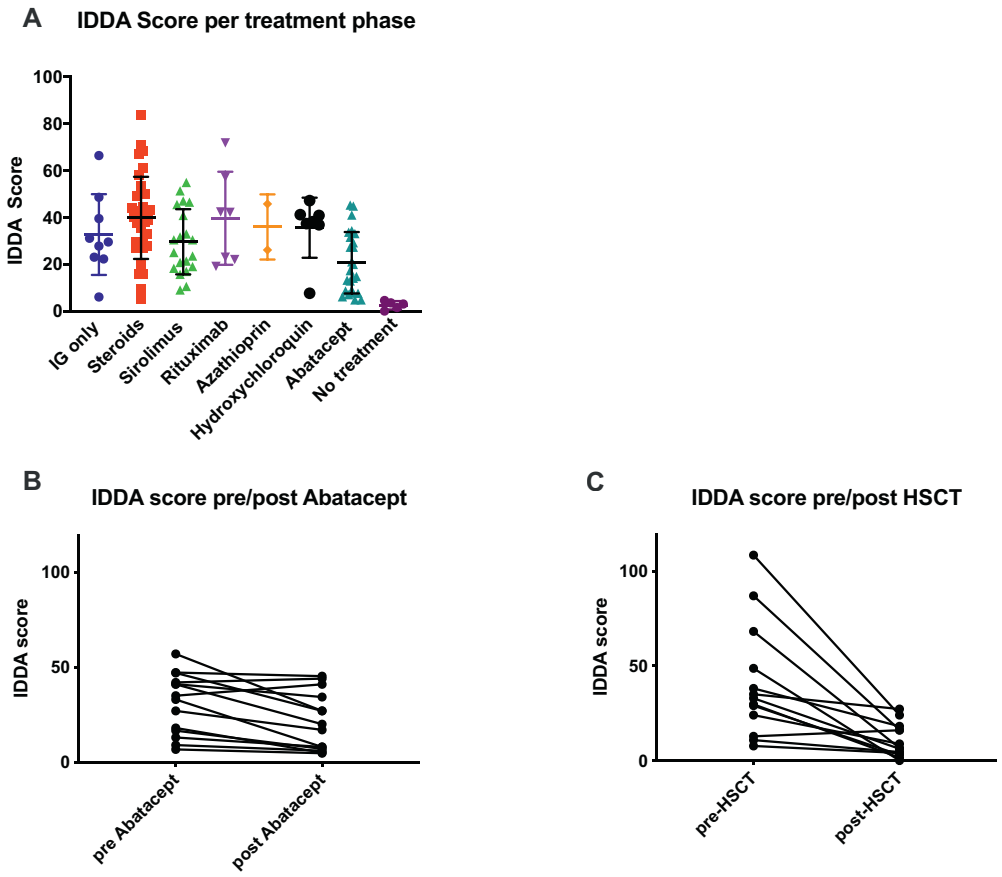

FIG 4. IDDA scores of patients with LRBA deficiency under various single immunosuppressive drug regimens or before and after targeted treatment or HSCT. **A,** IDDA scores were measured (as described in the Results section and in Table III) for 9 patients under immunoglobulin treatment only (IG, n = 9; *first column from left to right*); treatment with glucocorticosteroids (steroids, n = 35), sirolimus (n = 20), rituximab (n = 7), azathioprine (n = 2), hydroxychloroquine (n = 7), or abatacept (n = 25); or no treatment (n =7; with very mild or no symptoms in patients identified mostly through family screening). Treatment with abatacept was associated with significantly lower IDDA scores than was treatment with steroids or even with immunoglobulin therapy only ($P = .0001$ and $P = .0375$, respectively*)*. Similarly, treatment courses with sirolimus were associated with lower IDDA scores than was treatment with steroids ($P = .0296$*)*. Error bars indicate mean and SE. **B,** IDDA scores in patients before and after abatacept monotherapy (n = 14; $P = .0039$). **C,** IDDA scores of surviving patients before and after HSCT (n = 13; $P = .0002$).

under no or different immunosuppressive treatment after the initiation of abatacept only: the median IDDA score before the initiation of abatacept was 34 (range, 9-57), and it decreased to 18.5 under abatacept (range, 4.8-45.2; $P = .0039$; Fig 4, *B*). Abatacept had effects on different, organ-specific, LRBA deficiency–related symptoms (scored as 0-4, depicted in Fig 5, *B*). The response to this treatment was not universal, as 3 patients (9, 10, and 13) showed neither a decrease in disease activity in different organ systems nor an amelioration of signs of autoimmunity and immune dysregulation. In 1 patient (12,) only autoimmune cytopenia could be resolved, but lymphoproliferation, parenchymal lung disease, endocrinopathy, failure to thrive, and severe infections were refractory to abatacept. All of the other 10 patients (71.4%), however, showed a good general response to abatacept, with an amelioration of almost all symptoms (Fig 5, *B*). A combined treatment with sirolimus and abatacept was reported in 1 patient only (follow-up for 1 year); this combined treatment showed good effects, especially on parenchymal lung disease. In our cohort, abatacept was, furthermore, combined with several other drugs, such as nivaquine, mycophenolate mofetil, and adalimumab, all of which ameliorated LRBA-related symptoms. No increase in the susceptibility to infections or malignancy was observed.

The effects of sirolimus on different organ-specific, LRBA deficiency–related symptoms (scored as 0-4) in 16 patients are depicted in Fig 5, *C*. Initiation of sirolimus ameliorated enteropathy in 57.0% of patients, whereas parenchymal lung disease improved in 38.5%. A more noticeable effect was seen on autoimmune cytopenia; this symptom completely resolved in 37.5% of patients and improved in an additional 25%. The symptoms of 4 of 5 patients (80%) with neurologic manifestations could be ameliorated by sirolimus. The failure to thrive and malabsorption improved in 29.4%, and fewer or less severe infections were noted in 35.3% of the patients.

DISCUSSION

This international, multicenter study provides a comprehensive, retrospective analysis of the long-term clinical courses of patients with LRBA deficiency treated with various conventional

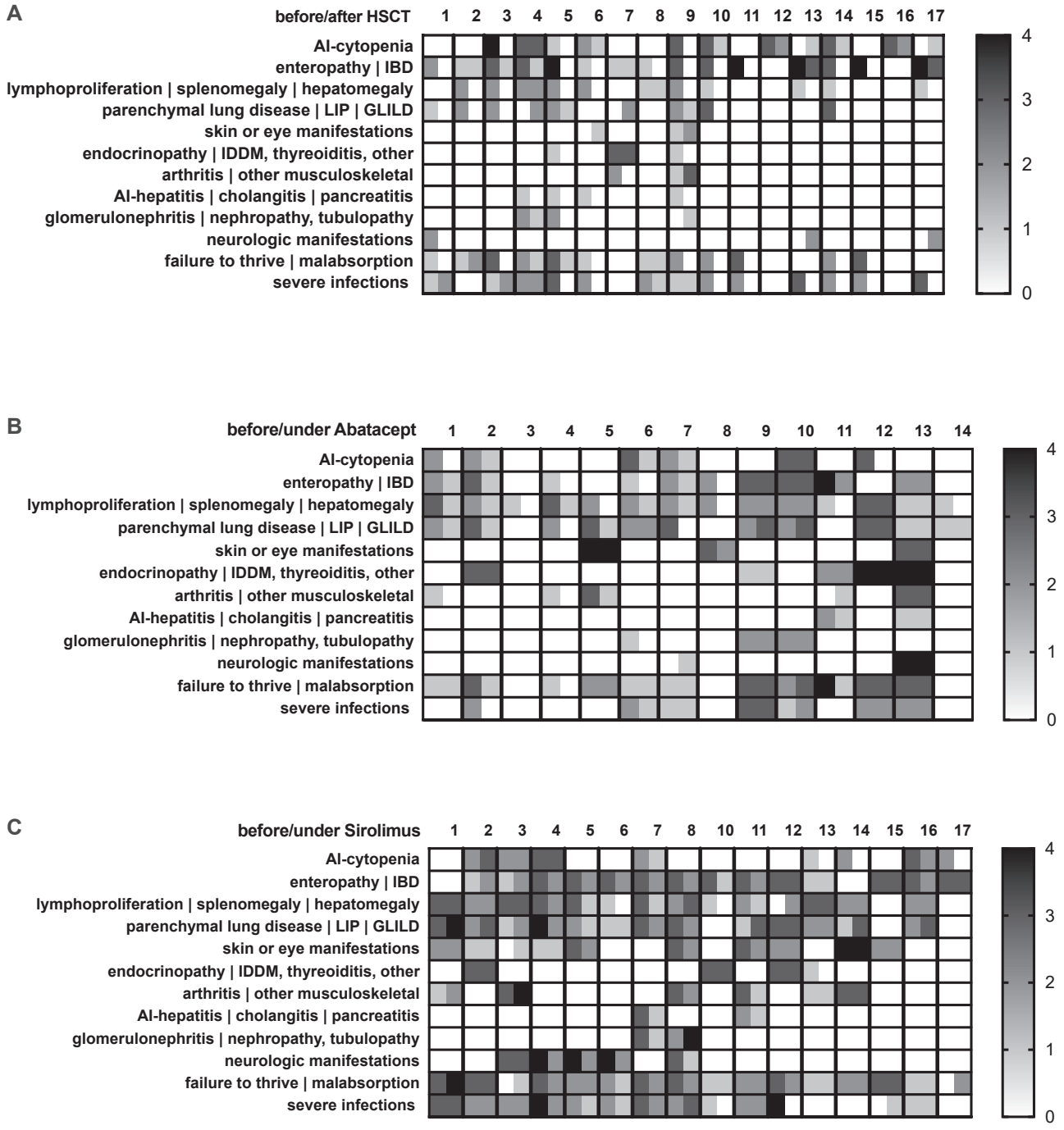

FIG 5. Graded organ involvement in patients with LRBA deficiency before and after HSCT, abatacept, or sirolimus therapy. The organ involvement was graded by the caring physicians from 0 (not affected), 1 (mild, transient, not requiring treatment), 2 (moderate, intermittent immunosuppressive therapy needed), or 3 (severe, continuous immunosuppression required), to 4 (refractory, life-threatening) before and after 3 different treatment interventions and is shown as a heatmap in column pairs per patient for HSCT (**A**), monotherapy with abatacept (**B**), and monotherapy with sirolimus (**C**). The patient numbers above the column pairs do not correspond to the patient identification number in the cohort as listed in Table E1. *AI*, Autoimmune; *GLILD*, granulomatous lymphocytic interstitial lung disease; *IBD*, inflammatory bowel disease; *IDDM*, insulin-dependent diabetes mellitus; *LIP*, lymphocytic interstitial pneumonia.

modalities of immunosuppression or stem cell transplantation, as evaluated by the newly introduced IDDA scoring method.

Doctors treating patients with LRBA deficiency are often uncertain whether and when to proceed with HSCT on account of the clinical variability of the disease. The lack of genotype-phenotype correlations[2,4,5] and a reportedly rather high TRM observed in these patients as compared with that in patients with other inborn errors, despite the potential for good outcomes

in surviving patients,[8] have increased this uncertainty. Although the number of patients with a follow-up exceeding 15 years after the onset of symptoms is small, our results indicate that the long-term survival probability in patients who did not receive a transplant is comparable to that of patients who have undergone HSCT so far. However, HSCT survivors showed a stable remission of LRBA deficiency–related symptoms and usually did not require further immunosuppression. Like patients with the immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome due to FOXP3 deficiency and defective Treg function,[24] patients with LRBA deficiency receiving conventional treatment had a higher disease burden throughout their lives and needed more drugs.

The therapeutic dilemma of proceeding to HSCT in *less profound than severe* combined immunodeficiencies[25] (P-CIDs) before clinical deterioration has been addressed in various studies and disease entities, and different clinical scoring scales have been proposed. In contrast to the *morbidity measure* of the ongoing P-CID study or the *organ impairment* score of a recent IPEX study[24,26] (see the Supplementary Material), the IDDA score adds the graded involvement scores of 10 organ systems known to be affected in LRBA deficiency at a certain time point or interval and does not include a correction for the patient age. Furthermore, extending the P-CID or the IPEX score, physician-reported Karnofsky or Lansky performance indices[22,23] are used to multiply the IDDA score, and the number of days of hospitalization, the need for intensive or supportive care, the requirement of immunoglobulin replacement therapy, nutritional support status, organ insufficiency, and chronic infections also increase the score. Together, consideration of all of these factors allows physicians to depict the actual disease burden (eg, derived at 1 time point for a defined time frame). IDDA scoring can be used for intraindividual longitudinal monitoring to facilitate objective assessment and enable interindividual comparisons (eg, in drug studies or multicenter trials) or during the regular clinical assessment of a patient's status as entered in a patient registry. This study was not designed to correlate other immunologic parameters (eg, immunoglobulin concentrations, lymphocyte subsets, soluble IL-2 receptor level) with the disease activity or IDDA score.

All patients with residual LRBA protein expression were still alive at the time of writing this publication and had a lower median disease burden (IDDA score), whereas absent protein expression was associated with a worse disease outcome. Although many variants reported to yield residual protein are compound heterozygous and located at the C-terminus of the protein (including the DUF1088, BEACH, and WD40 domains), other mutations with the same characteristics lead to a complete absence of LRBA, again precluding a genotype-phenotype correlation. Thus, quantification of protein expression should be used as an additional and relatively simple tool to guide treatment decisions, and residual expression should be monitored over time.[27] Patients with residual LRBA expression appeared to be at lower risk with less requirement for intensive therapy, but the relatively small number of such patients precludes general treatment recommendations for this subcohort with regard to immunosuppression or HSCT.

Among all immunosuppressive drugs reportedly used, abatacept and sirolimus were clearly favored over other conventional treatment modalities in our cohort with regard to the amelioration of symptoms and the IDDA score. The response to targeted treatment with abatacept was organ unspecific but not universal, although a significant decrease in disease activity as measured by the IDDA score could be achieved in the majority of patients. Combinations of abatacept with sirolimus and other immunosuppressive drugs and mAbs might act synergistically in refractory courses, and they were successfully used in selected patients in the present study without increasing the patients' susceptibility to infections or malignancy. However, the data on these combinations are still too preliminary to draw conclusions.

The rate of HSCT-related mortality in our cohort of 24 patients, who underwent transplantation between 2005 and 2019 and were in part (n = 12) included in our previous study,[8] was relatively high (29.2%). Relapse due to rejection was observed in 1 patient. The fact that many patients received a transplant before their diagnosis of LRBA deficiency had been made, and the fact that the disease of 3 of 7 deceased patients was not diagnosed until after death, could partially explain the similarly high TRM observed in our current study. In these patients HSCT might have been conducted as a last resort after the development of many organ complications, which reduced the chances of successful HSCT. The HSCT outcome in cases of LRBA deficiency apparently improved over the years, most probably owing to the concurrent increase in knowledge about the disease. We observed that only 1 of 10 patients who received a transplant had died after the transplantation procedures that were performed after 2015; in addition, 7 patients with LRBA deficiency of a Turkish cohort who received a transplant were recently reported (but not included in the present study) to be well and still living, with a median follow-up of 2 years after their transplantation procedure.[3] These findings suggest that the conclusions from early reports suggesting that LRBA deficiency *per se* was associated with a high TRM should be revised. In the current study, the transplantation outcome was clearly better in patients with lower IDDA scores (100% survival in patients with an IDDA score of <15) and thus better pre-HSCT clinical conditions. Lung involvement could be ameliorated in a percentage of patients under abatacept or sirolimus treatment and resolved in many patients after HSCT (Fig 5), but patients with uncontrolled pulmonary disease should be considered at highest risk. Our findings indicate that doctors should strive to ameliorate the clinical condition before transplantation in patients with higher disease activity, especially in cases of lung involvement. This goal might be achieved by using a "bridging" therapy with, for example, abatacept, as was administered to 6 patients of our cohort. The longitudinal monitoring results show that severe phenotypes have no tendency to resolve entirely; instead, they persist and, as in cases of CTLA4 insufficiency, even progress or predispose the patient to malignancy.[2-4,6,28] Taken together, these findings call into question the prior recommendations to consider HSCT only in cases of severe phenotypes of LRBA deficiency[8] and instead indicate that transplantation should be considered before the disease progresses.

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Clinical implications: This international, retrospective study on 76 patients with LRBA deficiency with long-term follow-up detected the best outcomes in patients with residual protein expression, low pre-HSCT disease burden, absent lung involvement, or targeted therapy.

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