Therapeutic modalities and clinical outcomes in a large cohort with LRBA deficiency and CTLA4 insufficiency

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Background: LPS-responsive beige-like anchor (LRBA) deficiency (*LRBA*$^{-/-}$) and cytotoxic T-lymphocyte–associated antigen-4 (CTLA4) insufficiency (*CTLA4*$^{+/-}$) are mechanistically overlapped diseases presenting with recurrent infections and autoimmunity. The effectiveness of different treatment regimens remains unknown.

Objective: Our aim was to determine the comparative efficacy and long-term outcome of therapy with immunosuppressants, CTLA4-immunoglobulin (abatacept), and hematopoietic stem cell transplantation (HSCT) in a single-country multicenter cohort of 98 patients with a 5-year median follow-up.

Methods: The 98 patients (63 *LRBA*$^{-/-}$ and 35 *CTLA4*$^{+/-}$) were followed and evaluated at baseline and every 6 months for clinical manifestations and response to the respective therapies.

Results: The *LRBA*$^{-/-}$ patients exhibited a more severe disease course than did the *CTLA4*$^{+/-}$ patients, requiring more immunosuppressants, abatacept, and HSCT to control their symptoms. Among the 58 patients who received abatacept as either a primary or rescue therapy, sustained complete control was achieved in 46 (79.3%) without severe side effects. In contrast, most patients who received immunosuppressants as primary therapy (n = 61) showed either partial or no disease control (72.1%), necessitating additional immunosuppressants, abatacept, or transplantation. Patients with partial or no response to abatacept (n = 12) had longer disease activity before abatacept therapy, with higher organ involvement and poorer disease outcomes than those with a complete response. HSCT was performed in 14 *LRBA*$^{-/-}$ patients; 9 patients (64.2%)

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showed complete remission, and 3 (21.3%) continued to receive immunosuppressants after transplantation. HSCT and abatacept therapy gave rise to similar probabilities of survival. Conclusions: Abatacept is superior to immunosuppressants in controlling disease manifestations over the long term, especially when started early, and it may provide a safe and effective therapeutic alternative to transplantation. (J Allergy Clin Immunol 2023;■■■:■■■-■■■.)

Key words: *Inborn errors of immunity, LPS-responsive beige-like anchor, cytotoxic T-lymphocyte-associated antigen-4, immune dysregulation, natural history, abatacept, hematopoietic stem cell transplantation*

Abbreviations used

AIHA:	Autoimmune hemolytic anemia
ALPS:	Autoimmune lymphoproliferative syndrome
CM:	Cytotoxic T-lymphocyte–associated antigen-4 mutation
CMV:	Cytomegalovirus
COVID-19:	Coronavirus disease 2019
CR:	Complete response
CTLA4:	Cytotoxic T-lymphocyte–associated antigen-4
CVID:	Common variable immunodeficiency
GI:	Gastrointestinal
GLILD:	Granulomatous–lymphocytic interstitial lung disease
GvHD:	Graft-versus-host disease
HSCT:	Hematopoietic stem cell transplantation
ID:	Immune dysregulation
IEI:	Inborn error of immunity
IgRT:	Immunoglobulin replacement therapy
IPEX:	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked
ITP:	Immune thrombocytopenia
LM:	LPS-responsive beige-like anchor mutation
LRBA:	LPS-responsive beige-like anchor
min-max:	Minimum-maximum
MMF:	Mycophenolate mofetil
NR:	Nonresponsive
OR:	Odds ratio
OS:	Overall survival
PIRD:	Primary immune regulatory disorder
PR:	Partial response
PSM:	Propensity score matching
RTI:	Respiratory tract infection
Treg:	Regulatory T

Inborn errors of immunity (IEIs) are a group of inherited immune diseases presenting with recurrent infections, autoimmunity, autoinflammation, and malignancies.[1,2] A subgroup of IEIs that affect the development and/or function of regulatory T (Treg) cells present predominantly with immune dysregulation (ID), giving rise to primary immune regulatory disorders (PIRDs).[3-5] The first described PIRD is immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), which is caused by mutations in the *FOXP3* gene.[6-8] Subsequent studies identified additional PIRDs, notably including autosomal recessive LPS-responsive beige-like anchor (LRBA) deficiency ($LRBA^{-/-}$) and autosomal dominant cytotoxic T-lymphocyte–associated antigen-4 (CTLA4) insufficiency ($CTLA4^{+/-}$).[9-12] CTLA4 is a potent checkpoint inhibitor that is critical in maintaining peripheral immune tolerance.[13,14] CTLA4 is constitutively expressed on $FOXP3^+$ Treg cells and transiently expressed after activation in $CD4^+$ and $CD8^+$ T cells.[13] After recycling to the plasma membrane, CTLA4 enters into a rivalry with CD28 to bind CD80 (B7-1) and CD86 (B7-2) ligands expressed on antigen-presenting cells and removes the CD80/CD86 by transendocytosis ending with T-cell inhibition.[14-16] On the other hand, LRBA protein, via its concanavalin A and beige and Chediak-Higashi domains, binds to the YVKM motif of the cytosolic tail of CTLA4, controlling vesicular trafficking of CTLA4 by preventing its lysosomal degradation and allowing recycling to the cell surface.[17-19] Recently, an investigational study revealed that CD80 and CD86 initiate divergent CTLA-4 fates after internalization, explaining that the role of LRBA in CTLA4 metabolism is specifically related to the binding of CD86 protein, which provides normal Treg functioning. In contrast, CD80 binding causes CTLA4 degradation via ubiquitination.[20]

Human biallelic LRBA deficiency and monoallelic CTLA4 insufficiency are characterized by recurrent respiratory tract infections, lymphoproliferation, and immunodysregulation, manifesting as enteropathy, cytopenias, autoimmune disorders, and malignancies.[9-11,18,21-24] In addition, immunologic analyses revealed that the patients had reduced Treg cell numbers with low CTLA4 expression and suppressive capacity, corroborating the phenotypic intertwined between both diseases.[11,12]

Studies examining clinical manifestations and treatment modalities were reported for both disorders by defining the efficacy of the conventional (immunoglobulin replacement therapy [IgRT], antimicrobial prophylaxis, and classical immunosuppressants), targeted therapies (abatacept–CTLA4-immunoglobulin fusion protein and sirolimus–mechanistic target of rapamycin inhibitor), and hematopoietic stem cell transplantation (HSCT).[25-30] In most patients, abatacept effectively controlled disease activity, especially lymphoproliferation, immune cytopenia, and chronic diarrhea in LRBA deficiency.[25,27,29,31] Furthermore, in CTLA4 insufficiency, abatacept also proved effective in controlling symptoms of enteropathy, granulomatous–lymphocytic interstitial lung disease (GLILD), autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), and lymphoproliferation.[27,32] Combining abatacept with sirolimus also synergistically mitigated severe symptoms in patients.[26,27] On the other hand, HSCT has been reported in small patient cohorts with end-organ damage, and the rates of success of symptom control were 17 of 24 (70.8%) for LRBA and 13 of 18 (72%) for CTLA4.[26,27] Post-HSCT complications have included graft-versus-host disease (GvHD), graft rejection, multiorgan failure, autoimmunity, and cytomegalovirus (CMV) reactivation. Notwithstanding the aforementioned studies of the various treatment options, their comparative efficacy in disease control needs further evaluation. For example, the benefits and risks of targeted therapy with CTLA4-immunoglobulin versus transplantation remain unclear. The debate regarding long-term use of immunosupperssants or early HSCT is ongoing. By the same token, which disease features can be controlled with abatacept is not fully established. Finally, factors determining the rates of response to treatments are also obscure. Therefore, detailed studies combining $LRBA^{-/-}$ and $CTLA4^{+/-}$ cohorts are warranted to address the aforementioned questions that have been raised.

In this single-country, multicenter cohort, we evaluate 98 $LRBA^{-/-}$ and $CTLA4^{+/-}$ patients with the overarching aim of

revealing the efficacy of different treatment modalities in controlling disease manifestations. In addition, our study showcases where and when abatacept can be more effective. Finally, we also present comparative results regarding outcomes between immunosupperssants and transplantation, bestowing better prediction for prognosis.

METHODS

Patients and inclusion criteria

The study population comprised 98 patients with confirmed *LRBA* and *CTLA4* mutations. The patients were recruited from 24 different immunology centers in Turkey. Patients were enrolled in the study at different time points starting in November 2016 and followed up prospectively until February 2023. Patients with *LRBA* mutations (LMs) (ie, patients LM1-LM29, LM35, and LM45-LM50) and patients with *CTLA4* mutations (CMs) (ie, patients CM1-CM12) were reported previously.[29,33,34] The study protocol was approved by the local ethics committee of Marmara University (institutional review board approval no. IRB00009067), and written informed consent according to Good Clinical Practice guidelines was obtained from all parents of pediatric patients and adult patients.

Study design

The patients were enrolled in the study prospectively from related centers. A questionnaire including demographic and clinical data (age at onset of symptoms, age at diagnosis, family history, past infections, autoimmunity, systems involved, and treatments with side effects) was filled out for every patient at baseline and updated every 6 months. We focused on the detailed responses regarding immunosupperssants, abatacept, and HSCT treatments. In addition, we categorized the response rate in terms of the administered drugs as complete response (CR), partial response (PR), or nonresponsive (NR). Blood samples from all of the participating patients were sent to the Marmara University Pediatric Allergy and Immunology laboratory for immunologic assessments, including measurement of serum immunoglobulin levels and extensive lymphocyte subset analysis, as described previously.[25,29]

Statistical analysis

The data were presented as means plus or minus SDs or medians with minimum-maximum (min-max) ranges. The Kolmogorov-Smirnov distribution test was conducted to determine normal distribution. The chi-square test was used for comparison of categoric values. Comparisons between patients and control groups for continuous values were made by using a Student unpaired *t* test. We performed propensity score matching (PSM) analysis to reveal the efficacy of abatacept to other immunosuppressants.[35] The analysis was performed in R programming language using the MatchIt package.[36] The method of 1:1 nearest neighbor matching was used for the delay in diagnosis, respiratory tract infection, autoimmunity, immune cytopenia, and parenchymal lung disease covariates. Covariate balance using standardized mean differences less than 0.2 after matching was accepted as indicating successful balance.[37] Following successful PSM, chi-square analysis was conducted on the matched data to establish the efficacy of different treatments with regard to CR rate using the odds ratio (OR) and corresponding 95% CI. We also performed a logistic regression analysis examining age as a risk factor for clinical outcomes. Analysis of overall survival (OS) was done using the Kaplan-Meier method (log-rank test). Differences were considered significant at P values less than .05. Statistical analysis was done using IBM SPSS Statistics, version 23.0 (IBM, Armonk, Ill), and GraphPad Prism 9 (GraphPad Software Inc, San Diego, Calif).

RESULTS

Demographic characteristics, clinical presentations, and immunologic features of *LRBA*$^{-/-}$ and *CTLA4*$^{+/-}$ patients

We enrolled 63 *LRBA*$^{-/-}$ patients (64.3%) and 35 *CTLA4*$^{+/-}$ patients (35.7%) from 48 and 21 families, respectively (Fig 1, *A*). The cohort comprised 52 males (53.1%) and 46 females (46.9%). The patients' demographic characteristics are presented in Table I. Mean current age, age at diagnosis, and age at symptom onset were all lower in patients with LRBA deficiency (Fig 1, *B*). The median follow-up period for the 98 patients was 5 years (min-max = 0.08-25.5 years). The OS rate was 89.7% (88 of 98 patients), with higher mortality in those with LRBA deficiency (Fig 1, *C* and *D*).

When the patients were evaluated according to their first clinical presentation (Fig 1, *E*), respiratory tract infections (RTIs) were the most common presenting symptom in both diseases (n = 38 [38.8%]), followed by chronic diarrhea (n = 17 [17.3%]), thrombocytopenia (n = 10 [10.2%]), anemia (n = 9 [9.2%]), type 1 diabetes (n = 7 [7.1%]), lymphoproliferation (n = 7 [7.1%]), arthritis (n = 5 [5.1%]), and alopecia (n = 1 [1.0%]). Chronic diarrhea was detected at a higher rate in *LRBA*$^{-/-}$ patients (n = 15 [23.8%]) than in *CTLA4*$^{+/-}$patients (n = 2 [5.7%]) (P = .03). The clinical phenotype of patients was predominantly characterized by common variable immunodeficiency (CVID) (n = 57 [58.1%]); the other phenotypes were autoimmune lymphoproliferative syndrome (ALPS) and IPEX (Fig 1, *F*). In total, there were 5 asymptomatic *CTLA4*$^{+/-}$ carriers, whereas full penetrance was observed in all of the *LRBA*$^{-/-}$ patients (P = .007).

As we showed previously,[29] *LRBA*$^{-/-}$ patients showed a more severe disease course than did *CTLA4*$^{+/-}$ patients (Fig 2, *A*). After controlling for the age factor, the *LRBA*$^{-/-}$ patients exhibited a higher risk of lower RTI (P = .01; OR = 3.63; 95% CI = 1.35-9.73), chronic diarrhea (P = .005; OR = 4.34; 95% CI = 1.54-12.25), and failure to thrive (P = .002, OR = 6.14; 95% CI = 1.97-11.12) than did the *CTLA4*$^{+/-}$ patients. The date showed that gastrointestinal (GI) tract pathologies (in 40 *LRBA*$^{-/-}$ patients and 15 *CTLA4*$^{+/-}$ patients) were similar between the respective diseases and revealed diverse upper and lower GI findings; the majority were not associated with a specific diagnosis and termed *unclassified diarrhea* (see Fig E1, *A* in the Online Repository at www.jacionline.org). In contrast, the radiologic evaluations showed a higher (P = .04) rate of parenchymal lung diseases in *LRBA*$^{-/-}$ patients (n = 40 [63.5%] vs n = 15 [42.9%] in *CTLA4*$^{+/-}$ patients), especially for parenchymal consolidation (P = .007 [see Fig E1, *B*]). The ID was mirrored by increased lymphocytic infiltration of different target organs (see Fig E1, *C*).

Viral infections, including cytomegalovirus (27% vs 25.7%), EBV (12.7% vs 8.6%), coronavirus disease 2019 (COVID-19) (22.2% vs 37.1%), and varicella virus (11.1% vs 5.7%) were observed equally in both diseases. All of the patients infected with

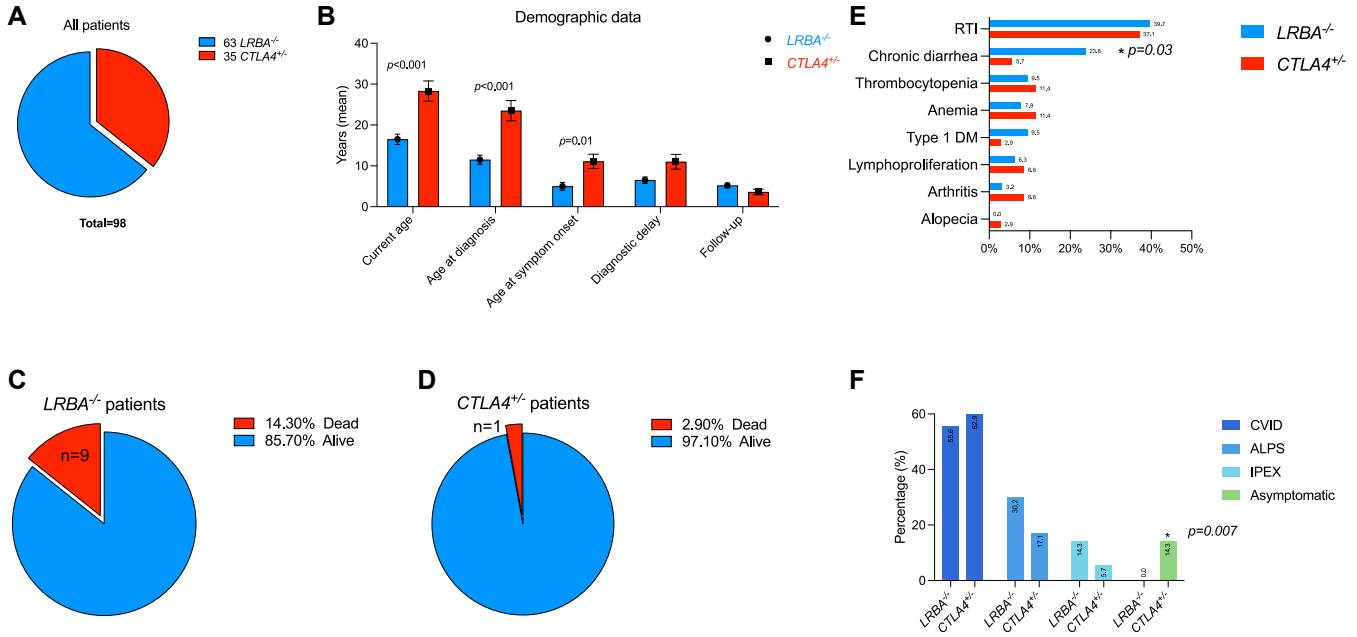


FIG 1. Demographic and clinical features of *LRBA*$^{-/-}$ and *CTLA4*$^{+/-}$ patients. **A**, Distribution of the patients. **B**, Comparisons of demographic characteristics between *LRBA*$^{-/-}$ and *CTLA4*$^{+/-}$ patients. **C** and **D**, Percentages of dead and live patients. **E**, Main presenting features of *LRBA*$^{-/-}$ and *CTLA4*$^{+/-}$ patients. **F**, Patients' clinical phenotypes. Error bars indicate SEM. **B**, Data obtained using the Student unpaired *t* test. **E** and **F**, Chi-square test used to compare categoric variables. Asterisks indicate differences. *DM*, Diabetes mellitus.

TABLE I. The demographic features of the study cohort

Feature	Value
Patients, no. (%)	
LRBA$^{-/-}$	63 (64.3)
CTLA4$^{+/-}$	35 (35.7)
Males/females, no. (%)	52/46 (53.1/46.9)
Current age (y), median (min-max)	17 (2-67)
Age at symptom onset (y), median (min-max)	4 (0.08-45)
Diagnostic age (y), median (min-max)	12 (0.4-60)
Diagnostic delay (y), median (min-max)	5.6 (0.08-40)
Family history, no. (%)	
Consanguinity rate	65 (66.3)
Affected relatives	29 (42.0)
HSCT, no. (%)	14 (14.3)
Outcome: alive, no. (%)	
LRBA$^{-/-}$	54 (85.7)
CTLA4$^{+/-}$	34 (97.1)

max, Maximum; *min*, minimum.

COVID-19 showed only upper respiratory tract symptoms not requiring hospitalization, the only exception being patient LM10, who experienced a severe COVID-19 infection that led to her death. *Haemophilus influenzae* was the most commonly isolated bacterial pathogen. Documented bacterial and viral microorganisms are presented in Tables E1 and E2 (in the Online Repository at www.jacionline.org). Furthermore, malignancies (ie, gastric adenocarcinoma [patient LM5], Hodgkin lymphoma [patient LM15], non-Hodgkin lymphoma [patient LM47], gastric adenocarcinoma together with non-Hodgkin lymphoma [patient LM60], acute lymphocytic leukemia [patient CM14], Burkitt lymphoma [patient CM27], and intracranial myofibroblastic tumor [patient CM26]) were observed equally in both study populations (ie, *LRBA*$^{-/-}$ patients and *CTLA4*$^{+/-}$ patients). The detailed clinical symptoms and treatment modalities, including targeted therapies administered to patients, are presented in Tables E3 and E4 (in the Online Repository at www.jacionline.org).

In *LRBA*$^{-/-}$ patients, there were 27 frameshift, 27 nonsense, 8 missense, and 2 splice site mutations as well as 6 deletions, whereas in *CTLA4*$^{+/-}$ patients, we observed 15 missense, 14 nonsense, and 5 frameshift mutations and 1 deletion (Fig 2, *B* and *C* and see Tables E5 and E6 in the Online Repository at www.jacionline.org). Consanguinity was prominent in our cohort (65.3%), leading to multiple affected subjects in the same families (n = 29). Interestingly, this rate was also high in patients with CTLA4 insufficiency (n = 14 [40%]). As shown previously,[32] among *CTLA4*$^{+/-}$ patients, we did not detect mutation in *CTLA4* exon 4 (cytoplasmic tail). There was no strong genotype-phenotype relationship that governed the manifestations in both diseases. However, in *LRBA*$^{-/-}$ patients, when we compared nonsense mutations with missense mutations, the rates of lymphoproliferation (n = 20 [83%] vs n = 2 [33%]; $P = .029$) and autoimmunity (n = 24 [100%] vs n = 4 [67%]; $P = .034$) were statistically higher in the group with nonsense mutations. Furthermore, we noticed that identical *LRBA* mutation gave rise to divergent clinical outcomes even among siblings but otherwise showed complete penetrance; among *CTLA4*$^{+/-}$ subjects, there were 4 unaffected mutation carriers displaying incomplete penetrance, as observed in previous studies.[24]

Data indicating serum immunoglobulin levels before intravenous immunoglobulin therapy were available for all *LRBA*$^{-/-}$ and *CTLA4*$^{+/-}$ patients; the data demonstrated proportionally similar distribution in both disorders (see Fig E2, *A* in the Online Repository at www.jacionline.org). In the whole cohort, there were low

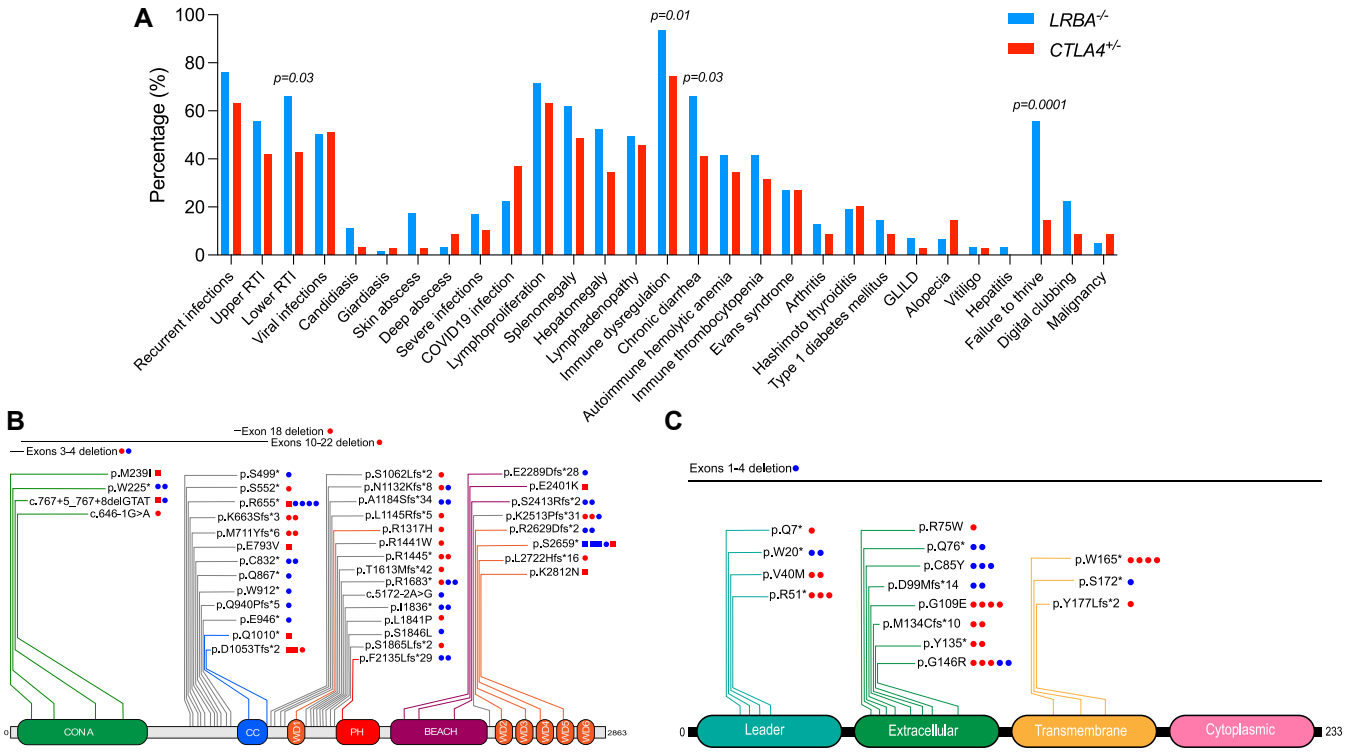


FIG 2. *LRBA*$^{-/-}$ patients display a more severe phenotype than *CTLA4*$^{+/-}$ patients do. **A**, Main clinical manifestations in *LRBA*$^{-/-}$ and *CTLA4*$^{+/-}$ patients. The mutations affect different domains of the LRBA (**B**) and CTLA4 (**C**) proteins. Most biallelic variants are nonsense and frameshift mutations in *LRBA*$^{-/-}$ patients, whereas heterozygous missense and nonsense mutations are common in *CTLA4*$^{+/-}$ patients. Red depicts new patients, blue shows old patients, and square indicates patients with the compound heterozygous mutation. The chi-square test was performed to compare categoric variables. *BEACH*, Beige and Chediak-Higashi domain; *CC*, coiled-coil; *CONA*, concanavalin A–like lectin domain; *PH*, PH domain associated with beige/BEACH; *WD*, WD-40 repeat.

IgG levels in 54 patients (55.1%), low IgM levels in 57 patients (58.1%), and low IgA levels in 71 patients (72.4%). Flow cytometric analysis at diagnosis, including analysis of T, B, and natural killer cells and T-cell, and B-cell subtypes, was performed in all patients (see Fig E2, *B* and Tables E7 and E8 in the Online Repository at www.jacionline.org). According to the age-matched healthy control reference values,[38] decreased CD3$^+$ T-cell counts were observed in 25 *LRBA*$^{-/-}$ patients (39.7%) and 19 *CTLA4*$^{+/-}$ patients (54.3%). At the same time, the levels of recent thymic emigrants were low in 52.3% of *LRBA*$^{-/-}$ patients and 62.5% of *CTLA4*$^{+/-}$ patients. There were no differences in B-cell and natural killer cell subtypes between the 2 diseases, and both showed low percentages of memory B cells versus in the age-matched healthy controls.

Therapeutic options and response rates in *LRBA*$^{-/-}$ patients and *CTLA4*$^{+/-}$ patients

In our cohort, because of recurrent infections and hypogammaglobulinemia, patients were usually followed up with antimicrobial prophylaxis and IgRT (with intravenous preparations used in 73 patients and subcutaneous preparations used in 9 patients) (Fig 3, *A* and see Tables E3 and E4). The most commonly used prophylactic agents were trimethoprim-sulfamethoxazole (85%) for antibacterial prophylaxis, fluconazole (81.8%) for antifungal prophylaxis, and aciclovir (68.8%) for antiviral prophylaxis. The indication of antifungal and antiviral prophylaxis was not primary and preferred after *Candida* and herpes infections. *LRBA*$^{-/-}$ patients received the aforementioned therapies more often than *CTLA4*$^{+/-}$ patients did (Fig 3, *A*). Splenectomy was performed in 13 patients (61.5% in *LRBA*$^{-/-}$ patients) because of intractable chronic cytopenia with splenomegaly. HSCT was performed only in *LRBA*$^{-/-}$ patients (n = 14 [22.2%]).

To control the immune dysregulatory features observed in the patients, numerous monotherapies or combination therapies with immunosuppressive agents were used (Fig 3, *A-C*). These agents were as follows: abatacept (n = 58 [59.1%]), prednisolone (n = 54 [55.1%]), mycophenolate mofetil (MMF) (n = 14 [14.2%]), sirolimus (n = 9 [9.1%]), cyclosporine A (n = 9 [9.1%]), azathioprine (n = 7 [7.1%]), rituximab (n = 7 [7.1%]), hydroxychloroquine (n = 3 [3.0%]), methotrexate (n = 4 [4.0%]), budesonide (n = 2 [2.0%]), adalimumab (n = 2 [2.0%]), and sulfasalazine (n = 1 [1.0%]). Chemotherapy regimens for malignancies were used in 6 patients (6.1%). The management chart of immunosuppressants used is presented in Fig E3 (in the Online Repository at www.jacionline.org). Abatacept use was greater in *LRBA*$^{-/-}$ patients (n = 42 [66.7%]) than in *CTLA4*$^{+/-}$ patients (n = 16 [42.9%]) (P = .02). In contrast, there was no difference in rate of use for the other immunosuppressants (65.1% vs 57.1%) (Fig 3, *B*). Corticosteroids and MMF were the most-administered immunosuppressants, followed by sirolimus and cyclosporine A (Fig 3, *C*). The indications for starting

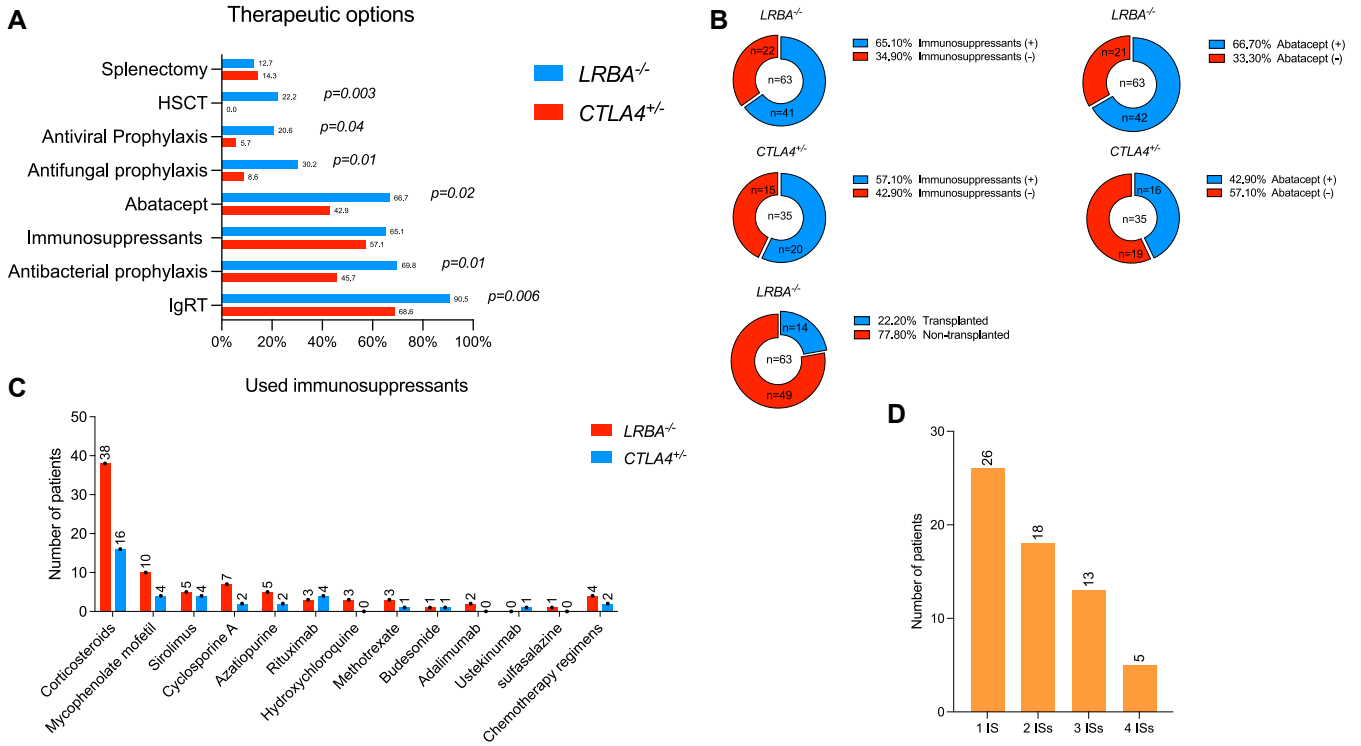


FIG 3. *LRBA*$^{-/-}$ patients require more therapies than do *CTLA4*$^{+/-}$ to control symptoms. **A**, Therapeutic options in *LRBA*$^{-/-}$ patients and *CTLA4*$^{+/-}$ patients. **B,** Proportions of the immunosuppressants used, abatacept, and transplantation in *LRBA*$^{-/-}$ patients and *CTLA4*$^{+/-}$ patients. **C,** Number of various immunosuppressants used to control patients' symptoms. **D,** Number of patients who receive 1, 2, 3, or 4 immunosuppressants (ISs). **A,** Chi-square test performed to compare categoric variables.

immunosuppressants in 61 patients were AIHA (n = 31 [50.8%]), ITP (n = 29 [47.5%]), chronic diarrhea (n = 14 [22.9%]), lymphoproliferation (n = 10 [16.3%]), arthritis (n = 9 [14.7%]), ILD (n = 5 [8.1%]), demyelinating disease (n = 4 [6.5%]), malignancies (n = 4 [6.5%]), hereditary lymphohistiocytosis (n = 2 [3.2%]), SLE (n = 1 [1.6%]), uveitis (n = 1 [1.6%]), and alopecia (n = 1 [1.6%]). The detailed indications for immunosuppressants in every patient are presented in Table E9 (in the Online Repository at www.jacionline.org). Of note, in patients with autoimmunity, lymphoproliferation, or parenchymal lung disease, the need for immunosuppressants was more common than in patients without symptoms ($P < .0001$) (see Fig E4 in the Online Repository at www.jacionline.org). Control of the ID manifestations usually required repeated courses of immunosuppressant regimens; 36 patients received 2 or more immunosuppressants before genetic diagnosis or administration of abatacept (Fig 3, *D*). Furthermore, in general, patients who received immunosuppressants showed a PR or were NR, indicating that applicable immunosuppressants are not an appropriate way to achieve sustained disease control (Fig 4, *A*). Sirolimus was used for enteropathy (in patients LM1 and LM17), lymphoproliferation (in patient LM5), AIHA (in patients CM9 and CM21), ITP (in patients LM5, CM3, CM9, and CM21), and parenchymal lung disease (in patients LM10, LM16, and LM17). Two patients (CM3 and CM9) showed a CR to sirolimus in terms of control of cytopenia; in the rest of the patients who received it, sirolimus alleviated their symptoms without a CR.

In total, 58 patients (59.1%) received abatacept as primary or rescue therapy (see Fig E3). The rate of abatacept use was higher in *LRBA*$^{-/-}$ patients than in *CTLA4*$^{+/-}$ patients (n = 42 [66.7%] vs n = 16 [42.6%]; $P = .02$). The detailed indications for abatacept are presented in Table E10 (in the Online Repository at www.jacionline.org). The median duration of abatacept therapy was 2.3 years (min-max = 0.8-6.7 years), with a maintenance intravenous dose of 10 to 20 mg/kg per 3 to 4 weeks in 53 patients (91.3%) and a subcutaneous dose of 125 mg/per week in 5 patients (8.7%). In contrast to other immunosuppressants, abatacept displayed striking control of disease manifestations, demonstrating a CR in 74% of *LRBA*$^{-/-}$ patients and 93% of *CTLA4*$^{+/-}$ patients. The remaining patients had a PR or were NR (Fig 4, *B* and see Table E10). These responses were stable during the follow-up. In addition, when the main clinical phenotypes of the patients who received abatacept were categorized as ID, chronic diarrhea, or lymphoproliferation, the responses by each phenotype after abatacept therapy were calculated; all of the patients responded to abatacept therapy but to various degrees (Fig 4, *C* and *D*). As we reported previously,[25] abatacept therapy revealed better a CR rate in terms of lymphoproliferation (88%), followed by chronic diarrhea (84.4%), and these rates were equal in the groups with both disorders. On the other hand, the ID symptoms showed more heterogenous response rates (CR, 62.8%; PR, 32.6%; and NR, 4.6%) because in nature, ID presents with many diseases and is expected to be associated with different pathophysiologic mechanisms.[5,39] More specifically, CR was observed in the majority of those with AIHA (100%), those with ITP (94.1%), and those with autoimmune hepatitis (100%). Lesser CR rates were detected in other IDs, namely, arthritis (83.3%), ILD (70.0%), and demyelinating disease (33.3%). All patients

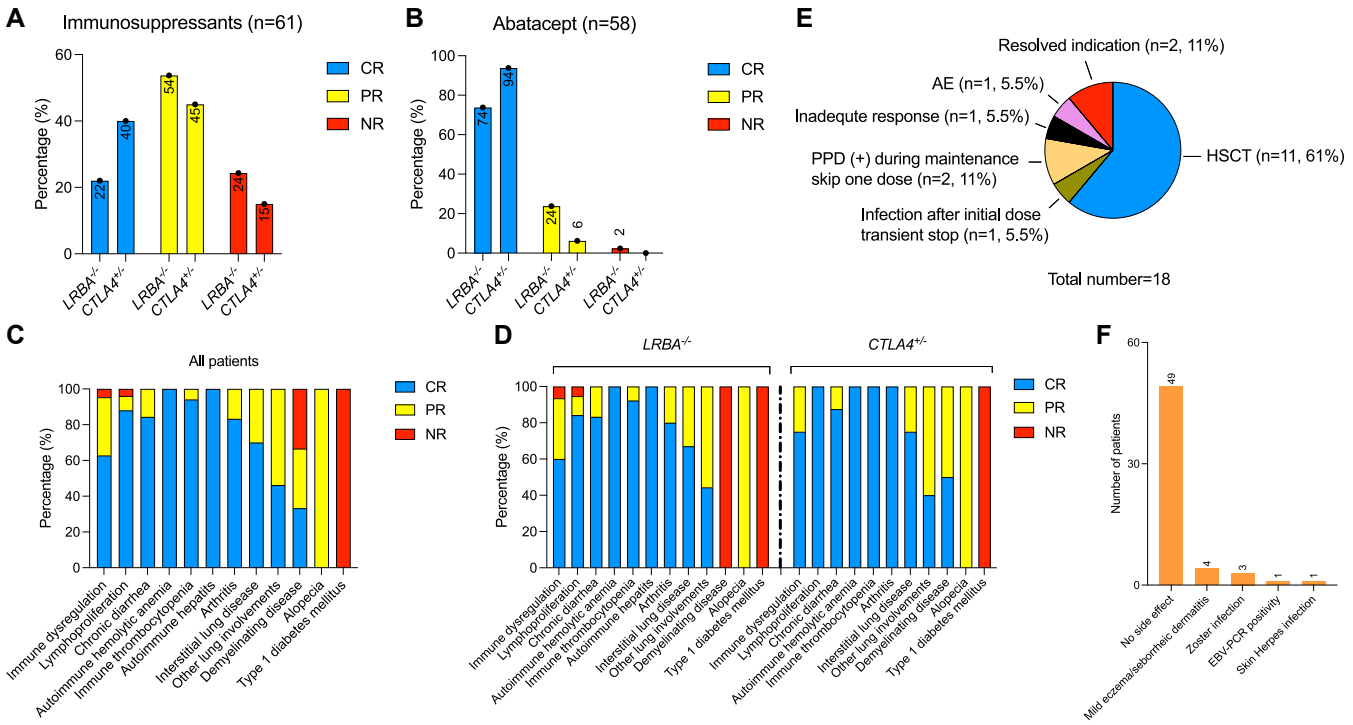


FIG 4. Abatacept demonstrates better disease control with fewer side effects than with other immunosuppressants. Levels of symptom control after immunosuppressants (**A**) or abatacept (**B**). Impact of abatacept on various disease symptoms in all patients (**C**) and in *LRBA*$^{-/-}$ patients and *CTLA4*$^{+/-}$ patients (**D**). **E,** Reasons for abatacept discontinuation during the study. **F,** Number of patients experiencing side effects during abatacept use. *AE,* Adverse effect; *PPD,* Purified Protein Derivative.

with alopecia showed a PR to abatacept, whereas those with type 1 diabetes mellitus were NR. We also analyzed the response rates separately in *LRBA*$^{-/-}$ patients and *CTLA4*$^{+/-}$ patients; the results showed a similar control pattern, mirroring the shared ID in both disorders (Fig 4, *D*).

The difference in efficacy of therapeutic approaches between abatacept and other immunosuppressants was evaluated by using PSM.[35,40] For this analysis, we accepted patients who received only abatacept (n = 25) as the treatment group and patients who used only immunosuppressants (n = 20) as the control group. The outcome was the difference in CR rate between the groups. After performing a successful PSM matching analysis, we found that 18 patients in the treatment group matched with 18 members of the control group with standardized mean differences less than 0.2 for the analyzed covariates (see Fig E5, *A* and *B* in the Online Repository at www.jacionline.org). Receiving only abatacept versus the other immunosuppressants showed a statistically better CR rate (72.2% vs 33.3% [P = .04; OR = 5.2; 95% CI = 1.25-12.57]).

During the follow-up period, we stopped abatacept administration in 18 patients for the following reasons: HSCT in 11 patients (61%); resolved indications in 2 patients (patient CM5 showed complete control for AIHA, chronic diarrhea, and lymphoproliferation and patient CM22 demonstrated complete control for ITP and arthritis); inadequate response of parenchymal lung disease in patient LM10; adverse effect with EBV reactivation in patient CM24; and purified protein derivative positivity with a negative *Mycobacterium tuberculosis* culture result in patients LM37 and LM38 at their ninth abatacept maintenance doses, in whom abatacept was started again after 1 month of skipping. Patient LM16 had *Aspergillus fumigatus* pneumonia after the first dose of abatacept, leading to treatment discontinuation. However, administration of abatacept was reinitiated after 9 months without side effects (Fig 4, *E*). Of 14 patients who received transplants, 11 received abatacept as a bridge treatment, resulting in good disease control; 9 of them showed a CR (patients LM2, LM4, LM5, LM9, LM13, LM18, LM29, LM49, and LM57), whereas 2 demonstrated a PR (patients LM12 and LM21). Generally, the adverse effects of abatacept were uncommon and usually mild and transient. These adverse effects were characterized by mild eczema in patients LM2, LM3, CM5, and CM8; skin zoster infection in patients LM29 and CM7, and herpes virus in patient CM25 (Fig 4, *F*). At the end of the study, there was no change in rate of IgRT or other prophylaxis rates after abatacept. Notably, with the use of abatacept, all patients except for 4 (patients LM10, LM16, LM17, and CM26) were weaned off their other immunosuppressants, (see Table E11 in the Online Repository at www.jacionline.org).

There were 10 patients (17.2%) with a PR and 2 NR patients (3.4%) during abatacept therapy. To determine the factors pertaining to responses, we investigated the distinguishing clinical and immunologic features of those patients by comparing them with those patients who experienced a CR (n = 46) (Fig 5, *A*). Patients who had a PR or were NR statistically showed a longer disease course (8.3 ± 4.7 years) than did those patients with a CR (4.5 ± 3.1 years) (P = .002). Those patients who had a PR or were NR also had more organ involvement characterized by colitis (17% vs none [P = .013]) and GLILD (25% vs

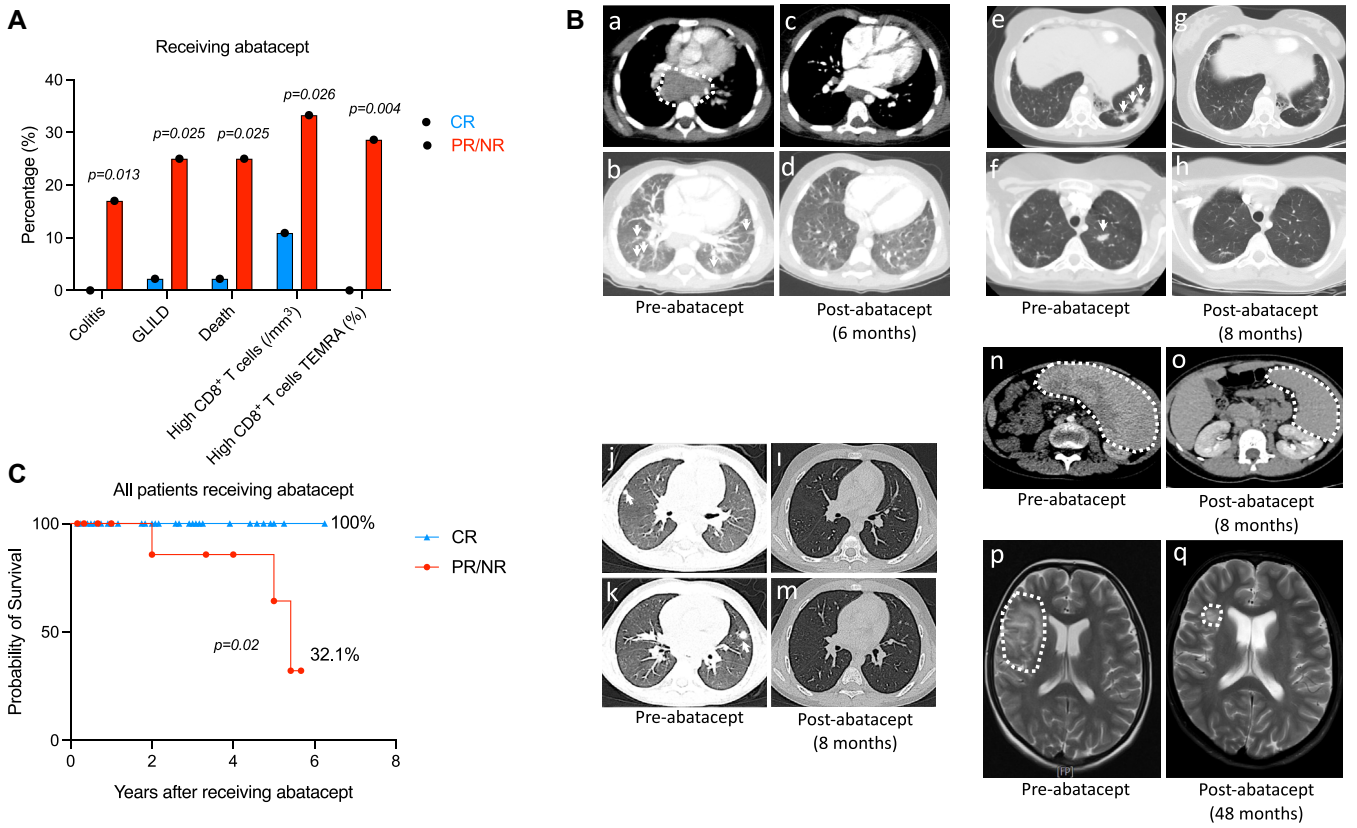


FIG 5. Patients with end-organ involvement show a PR to abatacept. **A,** Comparisons between patients who exhibit a CR versus a PR or are NR to abatacept. **B,** Radiologic improvements after abatacept. Computed tomography (CT) scan showing that the bulk mediastinal lymphadenopathies (circle drawn with a dashed line circle [*a*]), patchy consolidation, and inflammatory nodules (*arrows* [*b*]) in patient LM61 regressed after abatacept (*c* and *d*). CT scan of patient CM16 demonstrating that the inflammatory nodules with parenchymal tractions (*arrows* [*e* and *f*]) disappeared after abatacept (*g* and *h*). CT image revealing inflammatory nodules in patient LM30 before abatacept (arrows, [*j* and *k*]) and regression after treatment (*l* and *m*). Enlarged splenomegaly (circle drawn with a dashed line [*n*]) in patient LM30 before abatacept and decreased in size after treatment (*o*). Magnetic resonance imaging image of patient CM3 showing inflammatory lesions with edema in the right parietal and temporal lobes (circle drawn with a dashed line [*p*]) that healed with minimal gliosis after treatment (circle drawn with a dashed line circle [*q*]). **C,** Kaplan-Meier curve showing the probability of survival between a patients with CR versus who had a PR or were NR. **A,** Chi-square test performed to compare categoric variables.

2.2% [$P = .025$]). Further, 2 of the patients in the PR/NR group developed cirrhosis during the follow-up (patients LM19 and LM44). The mortality rate in the PR/NR group was significantly higher than in patients with a CR (n = 3 [25%] vs n = 1 [2.2%]; $P = .025$), and they also demonstrated a more dysregulated phenotype characterized by elevated $CD8^+$ T-cell counts and exhausted $CD8^+$ T-cell percentages. Abatacept therapy achieved good disease control for various types of organ involvement in patients within the CR group (Fig 5, *B*). Finally, the probability of survival after receiving abatacept revealed better outcomes in the patients with a CR than in those patients in the PR/NR group (Fig 5, *C*). The details of the patients who had a PR or were NR to abatacept are presented in Table E11.

In all, 14 patients (patients LM2, LM4, LM5, LM6, LM8, LM9, LM12, LM13, LM18, LM21, LM29, LM45, LM49, and LM57) received transplants because of the advanced disease and poor response to treatment (see Table E12 in the Online Repository at www.jacionline.org). Their median age at time of HSCT was 12.1 years (min-max = 7.6-27.3 years), with a median post-HSCT follow-up period of 2.8 years (min-max = 0-8.6). In particular, the indications for transplantation were persistent hematologic findings (patients LM2, LM5, LM6, LM8, LM9, LM12, LM29, LM49, and LM57), severe RTI (patient LM18), uncontrolled lymphoproliferation and bronchiolitis obliterans (patient LM6), and uncontrolled chronic diarrhea and RTI (patients LM4, LM6, LM13, LM21, LM45, and LM49). Diverse donors were used, including matched-HLA donors (n = 13 [92.3%]) and a haploidentical donor (n = 1 [7.7%]). Conditioning regimens were applied in 12 patients (85.7%), including 3 myeloablative, 2 reduced toxicity, 7 reduced intensity, and 2 nonconditioning regimens. GvHD was observed in 4 patients (28.5%). CMV reactivation was detected in 7 patients (50%). One patient (LM12) developed ITP after HSCT, requiring immunosuppressants (a corticosteroid) for 6 months; another patient (LM49) required abatacept because of chronic diarrhea and persistent ITP, and he was continuing to use it at the end of the study. Patient LM57 experienced ITP, and he is taking corticosteroids and MMF at 7 months after HSCT. Patient LM13 is still receiving corticosteroids for chronic diarrhea at 3 years after HSCT. Patient LM21 developed bronchiolitis obliterans after HSCT. In total, 10

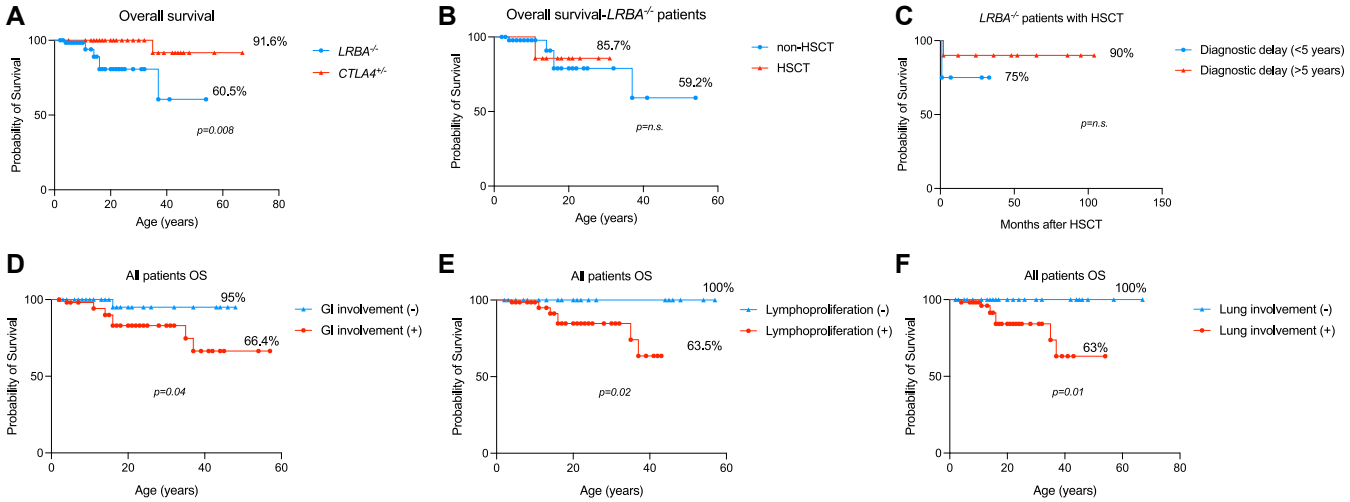


FIG 6. *LRBA*$^{-/-}$ patients demonstrate poorer outcomes than *CTLA4*$^{+/-}$ patients do. **A,** Kaplan-Meier curve indicating the probability of survival between *LRBA*$^{-/-}$ patients and *CTLA4*$^{+/-}$ patients. **B,** Overall survival in *LRBA*$^{-/-}$ patients in terms of HSCT. **C,** Impact of diagnostic delay on survival after HSCT in *LRBA*$^{-/-}$ patients. End-organ involvement, including GI symptoms (**D**), lymphoproliferation (**E**), and lung involvement (**F**), and their effect on survival.

patients (71.4%) were able to discontinue their previous use of IgRT after HSCT—7 of them (50%) within 6 months, whereas the other 3 (21.4%) were able to do so 6 months after transplantation. Two patients had no donor chimerism (patients LM2 and LM6). Both died within 1 month of transplantation (patient LM2 died of GvHD, thrombotic microangiopathy, and multiorgan failure, and patient LM6 died of sinusoidal obstruction syndrome and sepsis). LM13 also had no donor chimerism and survived with chronic diarrhea. Patient LM29 showed 29% donor lymphocyte chimerism with complete remission. The rest of the patients demonstrated chimerism levels ranging between 92% and 100%. Transplantation from matched sibling donors showed a 100% rate of survival. Overall, the outcome was complete remission in 9 patients (64.2%), partial remission in 2 (14.2%), no remission in 1 (7.1%), and death in 2 (14.2%).

Survival rates and factors affecting the outcomes

At the end of the study, there were 10 deaths (for a rate of 10.2%); they occurred in patients LM2, LM6, LM10, LM11, LM17, LM35, LM46, LM47, LM56, and CM26. These deaths were due to severe parenchymal lung disease and COVID-19 (patient LM10), pneumonia, lymphoproliferation and sepsis (patient LM11), ILD and sepsis (patient LM35), intracranial hemorrhage (patient LM47), and sepsis (patients LM17, LM46, LM56, and CM26). Patients LM2 and LM6 died after HSCT.

The probability of OS was better in *CTLA4*$^{+/-}$ patients than in *LRBA*$^{-/-}$ patients (91.6% vs 60.5%, respectively [$P = .008$]) (Fig 6, *A*). The OS rate did not differ between disease phenotypes classified as CVID, IPEX, ALPS, and unaffected mutation carrier (data not shown). Although frameshift mutations showed less favorable survival in *LRBA*$^{-/-}$ patients, no statistical differences existed between groups (see Fig E6, *A* and *B* in the Online Repository at www.jacionline.org). HSCT was performed only in *LRBA*$^{-/-}$ patients; therefore, we compared the OS rate between *LRBA*$^{-/-}$ patients who did and did not receive a transplant. As shown in Fig 6, *B*, there was no difference between the 2 groups, although the probability of OS was better in the patients who underwent transplantation. In addition, to understand whether the outcome of HSCT was associated with diagnostic delay, we compared patients in terms of diagnostic delay (<5 years vs >5 years). The comparison revealed similar outcomes between the 2 groups (Fig 6, *C*). Additionally, in both disease groups, those patients with organ involvement characterized by GI manifestations, lymphoproliferation, and parenchymal lung disease demonstrated significantly less favorable OS rates than in patients without organ involvement (Fig 6, *D-F*).

We evaluated the impact of receiving immunosuppressants or abatacept on OS. Patients who received immunosuppressants showed inferior OS (Fig 7, *A*). This did not change between the CR and PR groups (Fig 7, *B*), indirectly mirroring the burden of the disease requiring more medications to control its symptoms. Furthermore, the LRBA-deficient patients with transplantation demonstrated significantly better outcomes when compared with those who received immunosuppressants other than abatacept (Fig 7, *C* [$P = .020$]). Notably, the time elapsed after use of abatacept showed a probability of patient survival similar to that during the post-HSCT period, indicating that abatacept treatment effectively controls disease activity and can change the global course of LRBA deficiency (Fig 7, *D*). Finally, because the patients' ages range from 2 to 67 years, we stratified patients according to age. We observed lower survival for the whole cohort (n = 98) in the age range from 11 to 20 years ($P = .002$) (see Fig E7, *A* in the Online Repository at www.jacionline.org). The *LRBA*$^{-/-}$ patients also exhibited lower survival for the group of those aged 11 to 20 years ($P = .01$) (see Fig E7, *B*). The age factor did not show an impact on GI involvement or lymphoproliferation (see Fig E8, *A-F* in the Online Repository at www.jacionline.org). However, for the 11- to 20-years age group, HSCT was associated with better survival than that among patients receiving immunosuppressants other than abatacept (see Fig E9, *A* in the Online Repository at www.jacionline.org). A comparison of HSCT and abatacept revealed similar outcomes for those aged 11 to 20 years and those aged 21 years or older (see Fig E9, *B* and *C*).

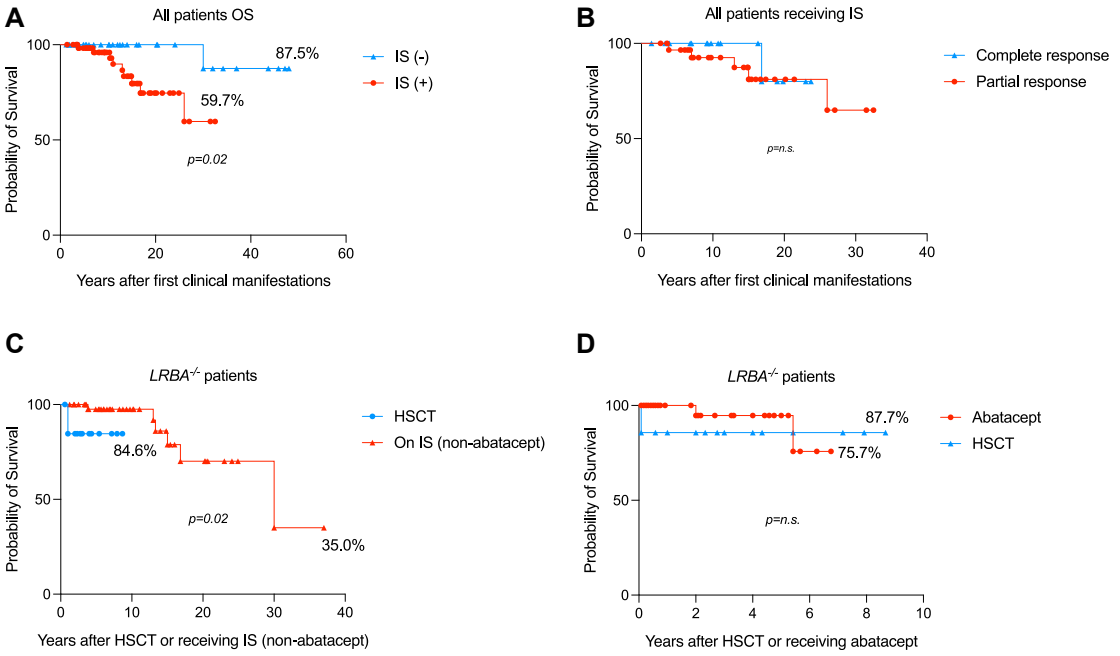


FIG 7. Receiving abatacept provides survival similar to that with achieved by undergoing transplantation. **A,** Impact of receiving immunosuppressants (ISs) on survival. **B,** Comparison of survival between patients who show CRs and PRs to ISs. Probability of survival with HSCT versus with ISs (**C**) or abatacept (**D**).

DISCUSSION

Here, we have presented detailed clinical outcomes of different treatment modalities for LRBA deficiency and CTLA4 insufficiency in a large multicenter prospectively evaluated cohort. To our knowledge, our study is the first to provide a long-term comparative evaluation of the different types of treatments, including targeted CTLA4-immunoglobulin therapy, immunosuppressants other than abatacept, and HSCT. We found that *LRBA*$^{-/-}$ patients showed early onset of disease with a more severe phenotype than *CTLA4*$^{+/-}$ patients did. Therefore, *LRBA*$^{-/-}$ patients required more immunosuppressants, abatacept, and HSCT to control their disease activity. Abatacept was able to achieve sustained CR in the majority of patients who used it. At the same time, patients on other immunosuppressants showed transient control that usually provided a PR or no response, requiring more therapies such as abatacept or transplantation. Our results also addressed the clinical and immunologic features that can predict the response to abatacept. Patients with colitis or GLILD showed a higher rate of PR to targeted therapy, with a poorer outcome than in patients with a CR. Importantly, in our study, we observed that conducting HSCT or receiving abatacept showed a similar probability of survival, demonstrating that abatacept therapy can result in sustainable disease control.

Diseases in *LRBA*$^{-/-}$ and *CTLA4*$^{+/-}$ patients are characterized by CVID and ALPS-like phenotypes, which affect many organs and are usually present with several autoimmune phenomena, lymphoproliferation, and parenchymal lung disorders, leading to the death of the patients.[24,26,32,33,41] In presenting patients, early onset of chronic diarrhea, lymphoproliferation, and lung disease should prompt consideration of both diseases.[14,25] We observed that patients with early diagnosis without end-organ involvement demonstrated better outcomes than seen in patients with lymphoproliferation and GI and lung involvement. We also showed that disease burden requiring use of multiple drugs inversely affects the outcomes over time. Further, nonsense mutations in *LRBA*$^{-/-}$ patients were linked to higher rates of lymphoproliferation and autoimmunity, demonstrating another factor influencing the clinical course. Therefore, the prognosis of the respective diseases depends on early diagnosis and prevention of end-organ damage and, to some extent, the patient's mutation type.

Previous studies showed that abatacept, sirolimus, and HSCT could provide global disease control in *LRBA*$^{-/-}$ patients and *CTLA4*$^{+/-}$ patients.[26,27] There is currently no unanimous consensus regarding the precise treatment of these disorders. However, according to our current findings, which constitute the largest set of results of abatacept treatment in the literature, initiating abatacept late in the disease course with involvement of multiple organs may not be sufficient to induce disease remission or prevent life-threatening ID. Therefore, once autoimmune, lymphoproliferative, or GI manifestations occur (after exclusion of other possible etiologic factors such as infections and malignancies), abatacept can be considered a first-line targeted drug to achieve better disease control. On the other hand, in our study, the abatacept dose varied between centers, with a maintenance dose of 10 to 20 mg/kg per month being the more frequently used dose. In addition, the efficacy of abatacept in controlling symptoms was variable and depended on the type of manifestation (lymphoproliferation > chronic diarrhea > ID); therefore, every case should be evaluated separately in terms of response to treatment. Our results also provided long-term good disease control (for ≤7 years) without severe side effects, showing that abatacept is providing an immune-regulatory effect for these disorders rather than immunosuppression. Data regarding the efficacy of sirolimus in controlling various disease symptoms were available in both disorders.[24] In particular, sirolimus completely

controlled cytopenia in 37.5% of patients, while ameliorating enteropathy in 57% of *LRBA*$^{-/-}$ patients.[26] Similarly, 78% of GI manifestations and 62% of GLILD lesions were resolved with sirolimus in *CTLA4*$^{+/-}$ patients.[27] Our results also demonstrated similar results with regard to CR in patients with cytopenia.

Our cohort shares similarities with the patients reported in retrospective review by Jamee et al,[24] especially regarding sex ratio, current median age, age of symptom onset, and age at first presentation with autoimmunity and infections. Notably, consanguinity rates were higher in our cohort, particularly among *CTLA4*$^{+/-}$ patients. The lower mortality in our patients than in others reported (10.2% vs 17.3%) could be attributed to several factors; 1 of the main reasons is the increased knowledge about the diseases, making early diagnosis possible before chronic and severe organ involvement.[24] In this respect, our study showed a shorter median time of diagnosis and reduced diagnostic delay than did other published studies.[24] The other reason could be associated with a higher rate of abatacept use (ie, 59.1% in our cohort vs 23.8% in previously reported patients).[24] The rates of use of other immunosuppressants, including rituximab, sirolimus, MMF, and cyclosporine A, were lower in our cohort than those in previously reported patients.[24] Overall, our findings indicate a shift in treatment decisions toward increased utilization of abatacept as a primary therapeutic option for controlling disease manifestations.

On the basis of our results, the following management approaches can be construed. First, we suggest starting IgRT and antimicrobial prophylaxis in both diseases, especially in patients with the CVID phenotype. Second, regular screening for viral pathogens should be performed, particularly in patients receiving abatacept on account of the relatively high number of CMV and EBV infections. Third, once autoimmune manifestations have been controlled, in some cases with good disease control, abatacept can be stopped while continuing to closely monitor these patients and provide IgRT and antimicrobial prophylaxis. Along these lines, 2 patients in our cohort (patients CM5 and CM22) were able to discontinue treatment after demonstrating control of their manifestations.

With regard to transplantation, because of the variable clinical course of diseases, even with the same mutation among family members, the indication for and time of transplantation are still obscure.[24,26-28,32] Our results and previous reports show similar successful transplantation results, which were inferior to those with other IEIs, and in our study, 21.3% of patients continued to receive immunosuppressants after HSCT. The majority of *LRBA*$^{-/-}$ and *CTLA4*$^{+/-}$ patients in the literature who received a transplant were in the late disease stage, with multiple chronic problems; in particular, lung involvement was found to be associated with poor outcomes.[24,33] Likewise, our patients who received transplants had multiorgan symptomatology, contributing to high posttransplant complications and less sustained disease control. Therefore, as stated previously, performing HSCT at an early stage can show a better outcome,[26,42] yet further evidence regarding conducting transplantation at an early stage is needed. Although the OS rate did not differ between *LRBA*$^{-/-}$ patients who did and did not receive a transplant, the post-HSCT time elapsed compared with IS treatment showed a better probability of survival, which may favor transplantation. Nevertheless, no comparative study has evaluated the post-HSCT period versus abatacept treatment. In our study, we provided comprehensive data comparing the outcomes of HSCT and abatacept. This study is, to our knowledge, the first to demonstrate similar outcomes between the 2 treatment options when evaluated in terms of the time elapsed after each therapy. Our findings highlight the efficacy of abatacept in altering the disease course and suggest its potential as a bridging therapy for patients who may require transplantation. Hence, our results support early consideration of HSCT in patients with no access to abatacept, those with resistance to conventional immunosuppressants and abatacept, and those who experience significant drug-related adverse effects.

The other ongoing debate concerns development of malignancies in in *LRBA*$^{-/-}$ and *CTLA4*$^{+/-}$ patients with prolonged disease courses. None of our patients showed malignant transformation while taking abatacept, suggesting that this therapy may reestablish functional immune surveillance to prevent malignant transformation. However, longer-term studies are necessary to investigate this potential benefit.[42-44]

Finally, we wanted to mention some limitations of our study. The relatively short follow-up period restricts the ability to ascertain the ultimate clinical course and/or effects of treatment approaches in some patients. Studies with longer follow-up periods are warranted to answer these questions. The other limitation is related to the various management attempts between centers, impeding establishing a decision for standardized management protocols for both diseases. Also, the results may not be fully generalizable to other countries. Lastly, the fact that there were fewer patients with certain disease manifestations hinders conclusions as to the best therapeutic options.

In conclusion, we showed that abatacept therapy could be successfully used to control and stabilize the diseases on a long-term basis without serious side effects. From a therapeutic perspective, an individualized evaluation should be performed for each patient. However, initially considering early administration of abatacept to patients with ID symptoms and close monitoring of its effectiveness may be a preferred approach to achieve better disease control. Furthermore, suitable donors should be investigated promptly for possible transplantation during the follow-up.

DISCLOSURE STATEMENT

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Clinical implications: This multicenter, observational study of 63 patients with LRBA deficiency and 35 patients with CTLA4 insufficiency provided comprehensive clinical evaluation and long-term outcomes for different therapeutic options. Early use of abatacept achieves better disease control and can replace transplantation without severe side effects. In cases of resistance to targeted therapy transplantation should be prioritized.

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