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Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Allogeneic stem cell transplantation compared to conservative management in adults with inborn errors of immunity

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KEY POINTS

- **Nontransplanted adults with severe IEI have an ongoing risk of severe events compared to transplanted patients.**
- **AlloSCT prevents progressive morbidity associated with IEI, which may outweigh the negative impact of transplant-related mortality.**

Allogeneic hematopoietic stem cell transplantation (alloSCT) is curative for severe inborn errors of immunity (IEIs), with recent data suggesting alloSCT in adulthood is safe and effective in selected patients. However, questions remain regarding the indications for and optimal timing of transplant. We retrospectively compared outcomes of transplanted vs matched nontransplanted adults with severe IEIs. Seventy-nine patients (aged ≥ 15 years) underwent alloSCT between 2008 and 2018 for IEIs such as chronic granulomatous disease (n = 20) and various combined immune deficiencies (n = 59). A cohort of nontransplanted patients from the French Centre de Référence Déficits Immunitaires Héréditaires registry was identified blindly for case-control analysis, with ≤3 matched controls per index patient, without replacement. The nontransplanted patients were matched for birth decade, age at last review greater than index patient age at alloSCT, chronic granulomatous disease or combined immune deficiencies, and autoimmune/lymphoproliferative complications. A total of 281 patients were included (79 transplanted, 202 nontransplanted). Median age at transplant was 21 years. Transplant indications were mainly lymphoproliferative disease (n = 23) or colitis (n = 15). Median follow-up was 4.8 years (interquartile range, 2.5-7.2). One-year transplant-related mortality rate was 13%. Estimated disease-free survival at 5 years was higher in transplanted patients (58% vs 33%; *P* = .007). Nontransplanted patients had an ongoing risk of severe events, with an increased mean cumulative number of recurrent events compared with transplanted patients. Sensitivity analyses removing patients with common variable immune deficiency and their matched transplanted patients confirm these results. AlloSCT prevents progressive morbidity associated with IEIs in adults, which may outweigh the negative impact of transplant-related mortality.

Introduction

Inborn errors of immunity (IEIs) are a heterogeneous group of diseases leading to a predisposition to infections, autoimmune or autoinflammatory manifestations, lymphoproliferation, and malignancies. In cases of less severe IEIs, near-normal life expectancy can be achieved with supportive care. However, in many IEIs, life-threatening complications severely compromise quality of life and result in premature mortality. Allogeneic stem cell transplantation (alloSCT) is the standard of care for patients with severe combined immune deficiency (CID) and is commonly performed for children with various life-threatening IEIs.[1-6] In older patients, transplant outcomes were historically poor, and, despite improved results with reduced-intensity conditioning (RIC), indications for and timing of transplant remain controversial in older patients.[7] The role of non-alloSCT therapies such as targeted agents and the so far exceptional gene therapy techniques in treatment algorithms for older patients are still mostly undefined.[8-11]

Risks of alloSCT in older patients are outweighed by the potential benefits in IEIs with predictably severe clinical phenotype, such as primary hemophagocytic lymphohistiocytosis or inherited bone marrow failure. However, decisions around transplantation in IEIs with a variable clinical phenotype or sparse long-term outcome data are more challenging.[11-19] This includes patients with immunodeficiency affecting cellular and humoral immunity termed combined immunodeficiencies (CIDs), including immune dysregulation syndrome (IDS), late-onset CID (LoCID), and common variable immune deficiency (CVID) with serious noninfectious complications ("complex CVID"), as well as patients with chronic granulomatous disease (CGD) remaining reasonably well until adulthood without prior alloSCT.

In adults with severe IEI, comorbidities and organ dysfunction are frequent, leading to higher transplant-related mortality (TRM) rates.[20-22] RIC regimens have been used to reduce TRM. A large prospective study demonstrated that RIC with alloSCT was safe and effective in patients with CGD, including 25 (45%) adolescents and young adults (14-39 years).[23] In addition, more recent data have demonstrated that RIC approaches in carefully selected patients result in excellent overall survival in young adult patients.[11,24] We have recently reported similarly excellent outcomes after reduced-intensity conditioned alloSCT in adults with IEIs (85.2% 3-year OS).[25] Very recently, a large retrospective study of alloSCT in CGD reported excellent outcomes, with a 76% 3-year OS for patients aged ≥18 years, independent of conditioning regimen used,[22] in line with a recent European Society for Blood and Marrow Transplantation retrospective study demonstrating no impact of conditioning intensity on OS in a wider group of patients with IEIs who had received a transplant at ≥15 years.[26]

Prospective randomized clinical trials are not possible in rare diseases with heterogeneous clinical presentations. To determine the risks and benefits of alloSCT in older patients with IEIs, we performed a matched-pair analysis of transplanted adult patients vs nontransplanted control patients and compared their outcomes.

Patients and methods

Patients

The study population included all patients with IEIs recorded in the French National Reference Center for IEI (Centre de Référence Déficits Immunitaires Héréditaires [CEREDIH]) or the Royal Free London Hospitals registries. All living patients gave their written informed consent (supplemental Data, available on the *Blood* website). Patients who had received transplants were included if they (1) were ≥15 years of age at first alloSCT, (2) received a transplant between January 2008 and December 2018, and (3) had an IEI diagnosis of CGD or CID. The CID group included patients diagnosed with an IDS, LoCID, or CVID according to the diagnostic framework of the referring physician (supplemental Table 1). Twenty-two patients have been previously reported.[25] Data were collected retrospectively from the medical notes and registries. The dataset was censored in November 2019.

AlloSCT procedure

Conditioning regimens were classified as full-intensity conditioning or RIC regimens (including intravenous busulfan ≤9.6 mg/kg total dose) as previously described.[27] For patients with CGD, the recommended conditioning regimen is based on a large study showing the safety of a RIC regimen consisting of high-dose fludarabine, serotherapy, and low-dose or targeted busulfan administration.[23] For patients with CID, the clinical practice is more heterogenous and depends on the patient's comorbidities, the characteristics of the underlined IEI, and the usual practice in the center. The recently published updated European Society for Blood and Marrow Transplantation/European Society for Immunodeficiencies Inborn Errors Working Party guidelines for alloSCT for IEIs include a chapter on recommendations for the management of adolescent and adult patients together with guidance on disease-specific conditioning regimens.[28] Patients and donors were matched for HLA-A, -B, -C, -DRB1, and -DQB1 by intermediate or high-resolution DNA typing as appropriate. Peripheral blood chimerism was defined as "mixed" if donor DNA was ≤95%. The pretransplant hematopoietic cell transplantation–specific comorbidity index (HCT-CI) scores before transplant were calculated for all patients.[29,30]

Matching procedure

To accurately match alloSCT patients with nontransplanted control patients, we defined matching criteria based on patient and IEI (underlying disease and comorbidities) characteristics. Matched nontransplanted patients were collected from the French CEREDIH registry database. Matching criteria were (1) decade of birth, (2) age at last review greater than index patient age at alloSCT, (3) one of 2 IEI categories (CGD vs CID, where CID included profound T-cell deficiency, CVID, and IDS), and (4) severity of CID (including autoimmune/inflammatory manifestation and/or malignant lymphoproliferative disease; supplemental Data and supplemental Table 2). A random draw without replacement was then performed to select ≤3 controls per index case. Sensitivity analyses were performed to validate the matching and to identify the impact of the different numbers of CVID patients and/or lung involvement within the CID transplant and nontransplant groups on outcomes. To do that, we repeated the comparisons of both cohorts by removing patients identified as having CVID and/or with lung involvement and their matched transplanted patients, without breaking the matching.

Statistics

Categorical and continuous variables were compared by χ^2 or Fisher exact tests where relevant and by Mann-Whitney test, respectively. The baseline of all survival analyses was the age at alloSCT (randomization age for the controls). OS was defined as the time between baseline until death from any cause, and disease-free survival (DFS) as time between baseline and IEI-related events (defined by infection requiring hospitalization, severe autoimmune or inflammatory manifestation requiring systemic immunosuppression, malignancy) or death, whichever occurred first. Patients with no event were censored at the time of their last follow-up. The probability of dying from transplant-related complications (ie, TRM) was estimated. To further analyze outcomes for patients who survived the first year following transplant, conditional OS was defined as the probability of surviving an additional number of years given that the patient has already survived 1 year. OS, conditional OS, and DFS curves were estimated using the Kaplan-Meier estimator, and comparisons between alloSCT and nontransplanted patients were performed using the log-rank test. We then estimated the mean cumulative number of recurrent events (REs) using Ghosh's estimator,[31] which accommodates the competing risk of death. REs were categorized as IEIs and/or alloSCT-related events (defined as infection requiring hospitalization, severe autoimmune or inflammatory manifestations, malignancy, grade 3/4 acute and extensive chronic graft-versus-host disease [GVHD], graft failure, $CD34^+$ cell top-up, donor lymphocyte infusion, posttransplant lymphoproliferative disease, viral reactivation requiring systemic antiviral or cellular therapies). We emphasize that accounting for competing risks is critically important for this study because deceased patients can no longer be considered at risk for experiencing REs. Without incorporating competing risks into the analysis, an overestimation of the mean cumulative number of REs would occur. Cox regression models were implemented for death (from all causes) and for REs. The Cox model for death was clustered on match criteria and included the identified risk factors (sex, birth decade, IEI category [CGD or CID], genetic diagnosis, lymphoproliferative disease, autoimmunity, aspergillosis, solid cancer, age >25 or <25 years at alloSCT) as well as treatment group (alloSCT vs non-alloSCT) with backward selection (selection criteria was $\alpha = 0.2$; lymphoproliferative disease, autoimmunity, aspergillosis, alloSCT vs non-alloSCT). Moreover, considering that complications have a limited impact on survival after 5 years, complications were coded in the Cox model as binary time-dependent covariates that indicate at any time point if patients had the complication in the past 5 years. The Cox model for REs was implemented with the same set of covariates, and robust sandwich standard error estimates were used to adjust for multiple events for the same patient.[32] In both Cox models, time-dependent covariates were taken into account using the counting process approach[33] (https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf; supplemental Figure 1). All analyses were performed using R software version 3.6.1 (R Core Team, Vienna, Austria).

Results

Patients' characteristics at baseline

In total, 281 patients were included, comprising 79 transplanted and 202 nontransplanted patients. Twenty patients with CGD and 59 with CID received a first alloSCT between 2008 and 2018 in London or in France (Figure 1). According to matching criteria, patients were equally distributed with respect to age at last review (median age, 25 years; interquartile range [IQR], 20-30; vs 26 years; IQR, 21-33 in nontransplanted patients; $P = .152$), IEI category (CGD or CID), and lymphoproliferative disease (28% vs 24% in nontransplanted patients; $P = .533$). The distribution of IEI diagnoses was different in patients with CID ($P < .001$), with fewer CVID diagnoses (1% vs 31% in nontransplanted patients) and more profound T-cell deficiencies (73% vs 45% in nontransplanted patients; supplemental Table 3). However, nontransplanted patients identified as having CVID by their referring physician were similar to those identified as having LoCID/IDS in terms of IEI-related complications (supplemental Table 4). Moreover, a profound T-cell deficiency (identified by CD4 <200/mm^3 or naive T-cell deficiency) was identified in 19% of patients with CVID. In contrast, 30% of patients with CID/IDS did not have a quantitative T-cell deficiency (supplemental Table 5). Transplanted CID patients had higher comorbidity scores, with an increased incidence of prior or active infections compared with the nontransplanted CID control group ($P < .001$). Nontransplanted CID patients had more frequent interstitial pulmonary involvement (3% in transplanted vs 15% in nontransplanted patients; $P = .017$). Of the 23 nontransplanted patients with lung involvement, 9 had CTLA-4/LRBA deficiency (Table 1). Patients with CGD had similar comorbidities between the 2 groups (Table 2).

Indications for alloSCT in the transplanted group and reasons for nonreferral to alloSCT in the control nontransplanted group

Common reasons for transplant referral were lymphoproliferative disease (n = 22 of 79) or gastrointestinal complications of IEI (n = 15 of 79; Table 3). Patients with CGD received

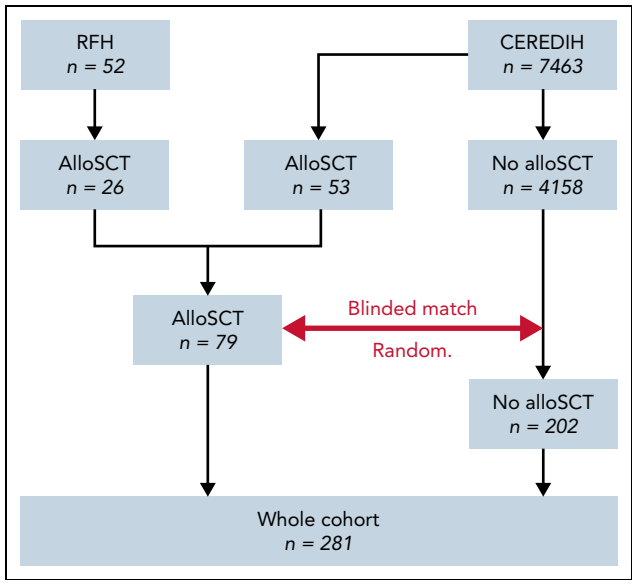

Figure 1. Flowchart. Transplanted patients were included in the study if they fulfilled the following criteria: (1) age at first alloSCT ≥15 years, (2) transplant performed between January 2008 and December 2018, and (3) underlying IEI diagnosis of CGD or CID. Matching criteria were (1) decade of birth, (2) age at last review greater than index patient age at alloSCT, and (3) one of 2 IEI categories (CGD vs CID, including profound T-cell deficiency, CVID, and IDS). Patients in the CID category were further matched by disease severity (including autoimmune/inflammatory manifestation and/or malignant lymphoproliferative disease) regardless of the date of this complication. A random draw without replacement was then performed to select ≤3 controls per index case.

Table 1. Comparisons of IEI-related complications in transplanted and matched non-transplanted patients with CID

Complications at baseline	All patients (n = 212)	No alloSCT (n = 153)	alloSCT (n = 59)	*P* value
Infections				
Bacterial infection	101 (48%)	60 (39%)	41 (69%)	<.001*
Viral infection†	32 (15%)	7 (5%)	25 (42%)	<.001*
Parasitic infection	8 (4%)	2 (1%)	6 (10%)	.007*
Invasive aspergillosis	11 (5%)	5 (3%)	6 (10%)	.042*
Autoimmune cytopenia				
Autoimmune neutropenia	27 (14%)	19 (12%)	8 (18%)	.327
Autoimmune hemolytic anemia	47 (23%)	42 (27%)	5 (10%)	.011*
Autoimmune thrombocytopenia	35 (17%)	28 (18%)	7 (12%)	.258
Colitis	43 (20%)	29 (19%)	14 (24%)	.438
Granuloma	28 (13%)	21 (14%)	7 (12%)	.72
Liver involvement‡	27 (13%)	19 (12%)	8 (14%)	.823
Interstitial pulmonary involvement§	25 (12%)	23 (15%)	2 (3%)	.017*
Hemophagocytic syndrome	14 (7%)	8 (5%)	6 (10%)	.194
Vasculitis	6 (3%)	3 (2%)	3 (5%)	.351
Malignancy				
Lymphoid proliferation	70 (33%)	48 (31%)	22 (37%)	.412
Myeloid malignancy	2 (1%)	1 (1%)	1 (2%)	.48
Solid cancer	11 (5%)	8 (5%)	3 (5%)	1

EBV, Epstein-Barr virus.

*Significant at $P < .05$.

†Viral infections included extensive warts, EBV-associated ulcers, complicated VZV infection, HPV-CIN, EBV viremia, and varicella without complication, herpesvirus, and HPV-CIN in nontransplanted patients.

‡Liver involvement included nodular regenerative hyperplasia, sclerosing cholangitis, and 1 patient with hepatitis T cell infiltration and another with EBV hepatitis.

§Lung involvement included 9 of 23 nontransplanted patients with CTLA-4/LRBA deficiency.

transplants for colitis (n = 8 of 20; 40%) or infection (n = 12 of 20; 60%), mainly invasive aspergillosis (n = 9 of 20; 45%). Patients with CID mostly received transplants for malignant lymphoproliferative disease (n = 22 of 59; 37%), including 3 patients with Wiskott-Aldrich syndrome, 3 with XLP1 (*SH2D1A*), 2 with activated phosphoinositide 3-kinase δ syndrome (*PIK3R1* and *PIK3CD* mutations), and 8 with genetically undefined CID. In addition, seven patients with CID received transplants for colitis (including 3 with XLP2, *XIAP*), 7 for infection, 8 for autoimmune neutropenia (including 3 with hypomorphic RAG deficiency), 7 for liver involvement (including 3 with CD40-ligand deficiency), 2 for hemophagocytic syndrome, and 2 with Wiskott-Aldrich syndrome for renal and cutaneous vasculitis. Only 1 patient was asymptomatic and preemptively given a transplant following a diagnosis of XLP1 in the context of family screening (supplemental Table 6).

Overall, only 12 of the nontransplanted control IEI patients (6%) received alloSCT after the end of the study. One-hundred thirty-six of the nontransplanted control IEI patients (67%) did not receive alloSCT because of nonreferral to a specialized center to discuss the indication of alloSCT (n = 81), an initial milder clinical phenotype or late presentation (n = 39), the absence of an appropriately antigen-matched donor (n = 5), and patient choice (n = 11). Moreover, targeted therapies are now available for some monogenic IEIs, such as CTLA-4/LRBA deficiency or activated phosphoinositide 3-kinase δ syndrome, and alloSCT may be delayed in these patients. The role of alloSCT remains uncertain for a few IEIs such as CVID. These patients all received anti-infective treatments for curative or prophylactic purposes (mainly antibiotic and antifungal agents). Ongoing immunoglobulin replacement therapy was given to 106 of 186 patients with available data. Autoimmune and inflammatory diseases were treated with corticosteroids (n = 141), other immunosuppressive agents (n = 55), and/or abatacept (n = 7). Fifty-two patients received rituximab (alone or in combination) for autoimmune or lymphoproliferative complications. The 48 patients with lymphoproliferation were treated with chemotherapy (n = 35) including autologous stem cell transplantation (n = 4), rituximab alone (n = 2), or splenectomy (n = 7; information unavailable for 5 patients). In total, 17 patients had splenectomy. Two patients received liver transplants, and one had a lung transplant.

AlloSCT procedures

Fourteen female (18%) and 65 male (82%) patients received an alloSCT at a median age of 21 years (IQR, 17–28; supplemental

Table 2. Comparisons of IEI-related complications in transplanted and matched nontransplanted patients with CGD

Complications at baseline	All patients (n = 69)	No alloSCT (n = 49)	alloSCT (n = 20)	*P* value
Infections				
Bacterial infection	56 (81%)	37 (76%)	19 (95%)	.09
Viral infection	1 (1%)	1 (2%)	0 (0%)	1
Fungal infection	33 (48%)	22 (45%)	11 (55%)	.446
Invasive aspergillosis	28 (41%)	19 (39%)	9 (45%)	.633
Autoimmune cytopenia	1 (1%)	1 (2%)	0	1
Colitis	29 (42%)	19 (39%)	10 (50%)	.391
Granuloma	20 (29%)	14 (29%)	6 (30%)	.906
Liver involvement*	4 (6%)	4 (8%)	0 (0%)	.315
Interstitial pulmonary involvement	8 (12%)	7 (14%)	1 (5%)	.422
Hemophagocytic syndrome	1 (1%)	1 (2%)	0	1
Lymphoid proliferation	1 (1%)	1 (2%)	0	1

*Liver involvement included hepatic fibrosis in 2 patients and granulomatous hepatitis in 2 patients.

Figure 2A). The median time from age at clinical diagnosis of IEI to alloSCT was 13.3 years (IQR, 5.0-19.2). Most of the patients received transplants after 2015 (n = 47 of 79; supplemental Figure 2B). Forty-six patients received RIC (58%), and 33 received myeloablative conditioning regimens (42%).[27] Conditioning for patients with CGD consisted of fludarabine, busulfan with alemtuzumab for 9 patients, or rabbit anti-thymocyte globulin for 11 patients. Patients with CID mainly received fludarabine combined with melphalan 140 mg/m^2, busulfan, or treosulfan. Patients who received a transplant with a haploidentical donor received a Baltimore regimen using high-dose posttransplant cyclophosphamide.[34] Details are shown in Table 4. Thirty patients had matched related donors (siblings), 33 had matched unrelated donors (10 of 10 antigen-matched unrelated donors), 12 had mismatched unrelated donors (1 antigen-mismatched unrelated donor), and 4 had haploidentical donors. Sixty-five patients received transplants using serotherapy-containing regimens (alemtuzumab or anti-thymocyte globulin) for in vivo T-cell depletion. GVHD prophylaxis included cyclosporine combined with mycophenolate mofetil in 73% of patients transplanted with matched related or unrelated donors and 67% of patients transplanted with

Table 3. Indications for alloSCT

Indication	All transplanted patients (n = 79)	CGD (n = 20)	CID (n = 59)
Preemptive	1 (1%)	0	1 (2%)
Infection	10 (13%)	3 (15%)	7 (12%)
Invasive aspergillosis	9 (12%)	9 (45%)	0
Malignancy*	23 (29%)	0	23 (40%)
Autoimmune neutropenia	8 (10%)	0	8 (14%)
Autoimmune hemolytic anemia	1 (1%)	0	1 (2%)
Colitis†	15 (19%)	8 (40%)	7 (12%)
Liver involvement‡	7 (9%)	0	7 (12%)
Hemophagocytic syndrome	2 (3%)	0	2 (3%)
Vasculitis	2 (3%)	0	2 (3%)
Not available	1	0	1

*Malignant lymphoproliferative disease (except one patient with Bowen disease).

†Crohn-like colitis (except one patient with *Cryptosporidium* associated-enteropathy).

‡Nodular regenerative hyperplasia, sclerosing cholangitis, hepatitis T-cell infiltration in 1 patient, and EBV-associated hepatitis in 1 patient.

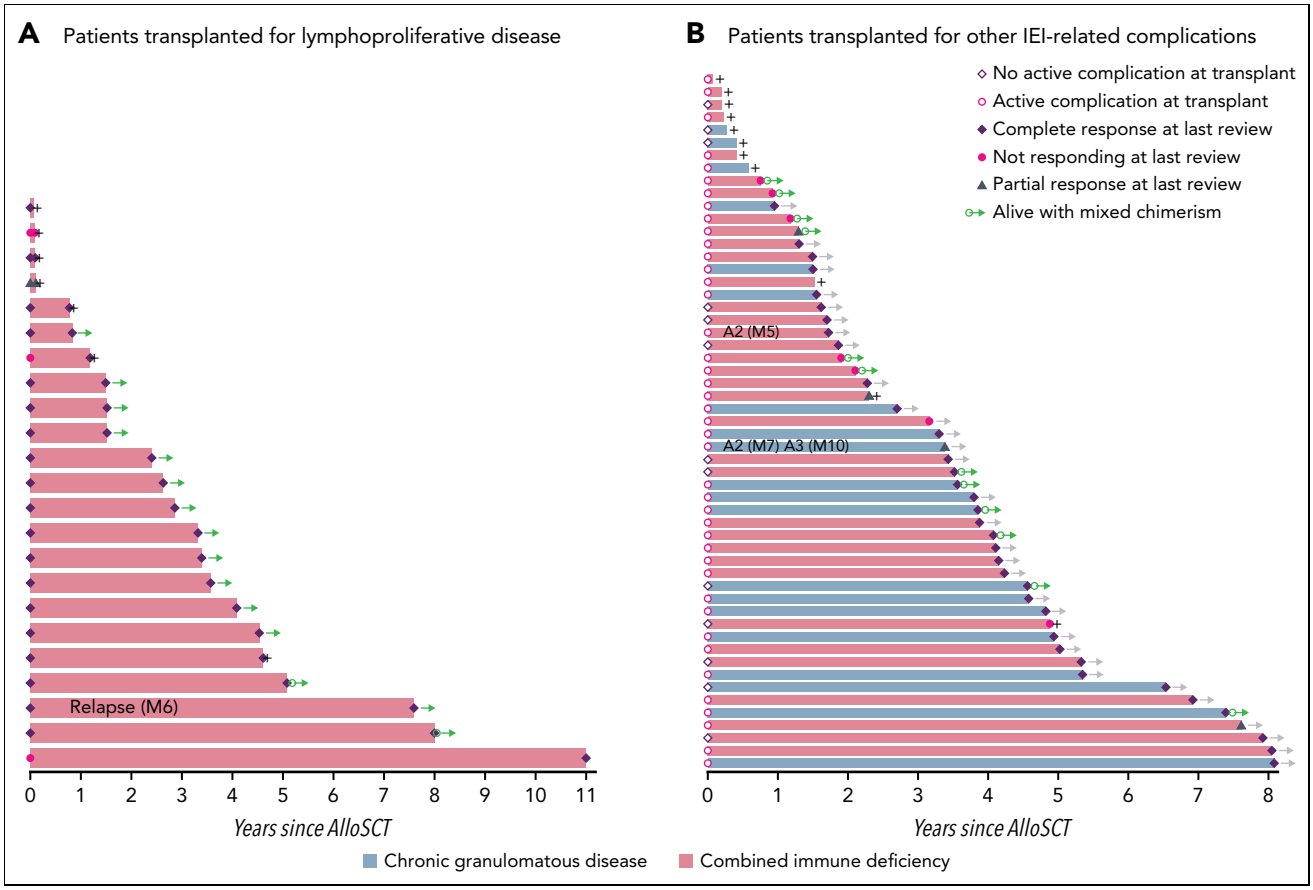

Figure 2. Evolution of disease following alloSCT. (A) Evolution of patients who received a transplant with previous lymphoproliferative disease by status of malignancy at alloSCT. All patients had CID (n = 22). Two patients were alive in complete remission with mixed chimerism at last review. (B) Evolution of patients who received a transplant with no prior lymphoproliferative disease by status of IEI-related complication at alloSCT. Patients had CID (n = 36, light gray) or CGD (n = 20 patients, dark gray). Twelve patients were alive with mixed chimerism at last review, of whom 6 were in complete remission. Arrows and circles indicate living patients and mixed chimerism, respectively, at last review. The letter A indicates subsequent alloSCT performed 5, 7, and 10 months after the first alloSCT, respectively.

mismatched unrelated donors (further details provided in supplemental Tables 6 and 7). Ten patients (13%) had a morbidity HCT-CI of 0, whereas 24 (31%) had scores ≥3 (Table 4).

With a median follow-up of 4.8 years (IQR, 2.5-7.2), 61 patients (77%) were alive following alloSCT. Of the surviving patients, 90% (55 of 61) were in remission with respect to the underlying IEI; notably, 80% (49 of 61) were in complete remission without transplant-related complications, including 8 patients with mixed chimerism at last review (Figure 2; supplemental Table 10). AlloSCT survivors experienced a continuous improvement in outcome over time, including those with mixed chimerism. Eighteen patients died after alloSCT, including 14 of TRM and 3 of IEI-related complications (all in the CID group). Mortality rate was higher in patients aged >25 years at alloSCT (P = .029). There was a trend for a higher mortality rate in the 24 patients with HCT-CI ≥3 (1-year OS, 71% vs 89% in the 54 patients with HCT-CI <3; P = .082). Outcome was similar regardless of the donor and in vivo T-cell depletion. Insufficient numbers of haploidentical transplants were performed to specifically comment on their use in this patient cohort.

Figure 2 shows the clinical course after transplant. Among the 23 patients with CID who received a transplant following the development of IEI-related malignancy (Figure 2A), 19 were in complete remission, 1 was in partial remission, and 3 had refractory disease at the time of transplant. Three patients with XLP1 (*SH2D1A* deficiency) died >1 year after transplant from TRM (2 from GVHD and 1 from sepsis). Among patients who received a transplant for other indications (Figure 2B), 42 of 55 (76%) had an active disease requiring treatment at the time of transplant (supplemental Table 9). Complete or partial remission of these complications was achieved after alloSCT in all surviving patients with CGD and the majority of surviving patients with CID (n = 21 of 27; 78%). Three patients died >1 year after transplant from chronic GVHD (n = 2) or IEI-related complications (n = 1; supplemental Table 10).

Causes of death in the transplanted patient group are detailed in supplemental Table 11, and transplant-related morbidity is included in supplemental Table 12. Three patients with CGD and eight with CID experienced graft failure, including partial engraftment at 6 months, requiring a second alloSCT in 2 patients, $CD34^+$ cell top-up in 3, and donor lymphocyte infusion in 1. Among these 11 patients, 5 were alive and well at last follow-up. Grade III/IV acute GVHD occurred in 10 patients (2 with CGD and 8 with CID), of whom 8 died. Three patients developed extensive chronic GVHD that led to death in 2 of them. Two patients with CID developed an Epstein-Barr virus–associated

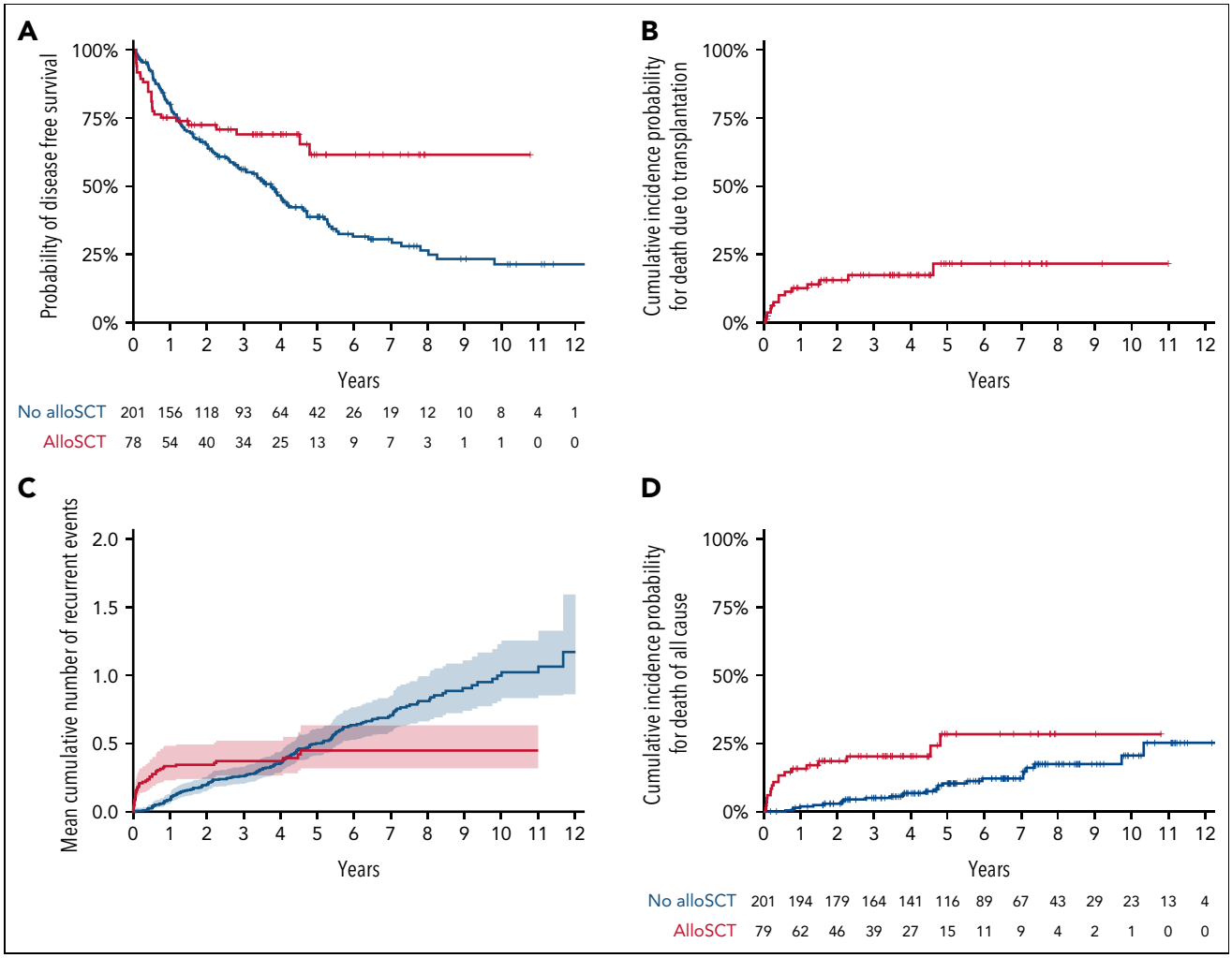

Figure 3. Outcome of transplanted vs matched nontransplanted patients. (A) Kaplan-Meier estimated DFS for transplanted (red) and nontransplanted (blue) patients. (B) Cumulative incidence of TRM for transplanted patients. (C) Mean cumulative number of REs and (D) cumulative incidence probability for death from all causes in transplanted (red) vs matched nontransplanted control (blue) patients. DFS was defined as time between baseline and IEI-related events (events defined as infection requiring hospitalization, severe autoimmune or inflammatory manifestation, or malignancy) or death, whichever occurred first. For analysis of REs, an event was defined as an IEI-related severe complication (including infection requiring hospitalization, severe autoimmune or inflammatory manifestation, or malignancy) or a transplant-related severe event (including grade 3/4 acute GVHD and extensive chronic GVHD, graft failure, $CD34^+$ top-up, donor lymphocyte infusion, secondary malignancy, posttransplant lymphoproliferative disease, and viral reactivations requiring systemic antiviral or cellular therapy).

posttransplant lymphoproliferative disease, which was successfully treated by rituximab. Two patients with CID developed a solid secondary malignancy, a neuroendocrine tumor 4.5 years posttransplant and a renal cancer 1.2 years posttransplant. Both patients were in complete remission at last review.

Outcome of transplanted vs matched nontransplanted patients

With a median follow-up of 4.8 years (IQR, 2.5-7.2), the projected 5-year DFS was 58% (95% CI, 46%-75%) in the alloSCT group vs 33% (95% CI, 27%-42%) in nontransplanted patients ($P = .007$; Figure 3A). The estimated 1-year TRM was 13% (95% CI, 5%-20%; Figure 3B). The projected 5-year cumulative incidence of mortality was higher in the alloSCT group (30%; 95% CI, 14%-42%; vs 11%; 95% CI, 6%-15% in nontransplanted patients; $P < .001$; Figure 3D). Because the effect of alloSCT on survival is time-dependent, we considered 2 periods for the multivariate analysis: the first period covering the first year after the procedure and the late period after the first year. The 5-year conditional OS was similar for 1-year survivors between cohorts (84%; 95% CI, 71%-100%; vs 90%; 95% CI, 86%-95% in nontransplanted patients; supplemental Figure 3). Multivariable analysis revealed that alloSCT during the first period, invasive aspergillosis, autoimmunity, and lymphoid malignancy were significantly associated with death (hazard ratio for alloSCT, first year, 5.43; 95% CI, 1.84-16.02; $P < .01$). Conversely, after the first year following the procedure, alloSCT was no longer associated with death (hazard ratio for alloSCT, late period, 1.49; 95% CI, 0.51-4.31; $P = .46$; Figure 4). Therefore, the excess risk of alloSCT on OS was significant only during the first year posttransplant.

To estimate the quality of life of nontransplanted vs transplanted patients with IEIs, we assessed the mean cumulative number of REs, examining first and subsequent events simultaneously, including both IEI-related and transplant-related morbidities. At 1 year, the mean cumulative number of REs was 0.42 in the alloSCT group vs 0.12 in nontransplanted

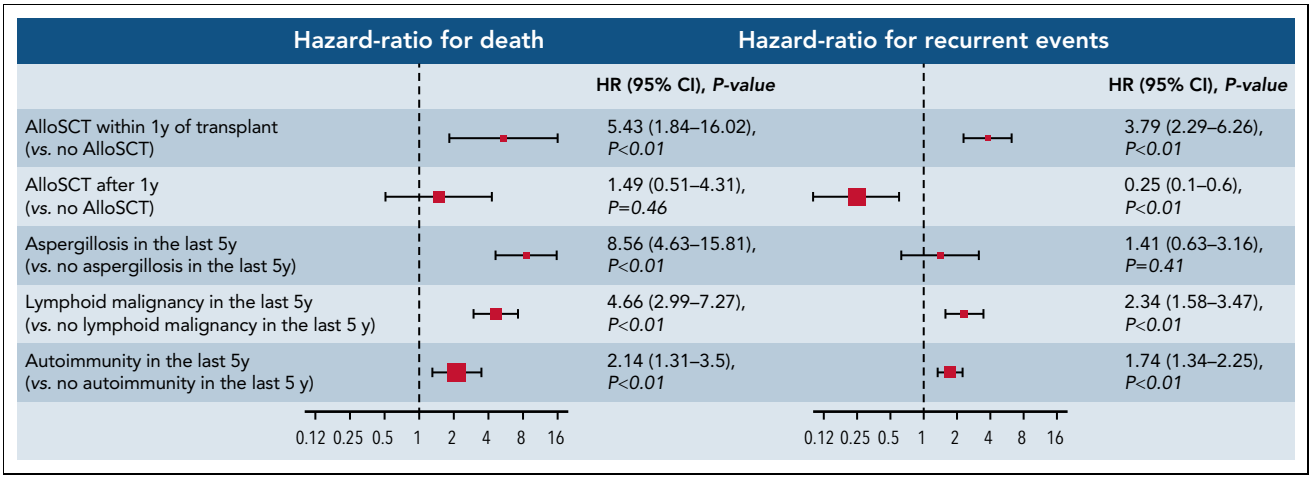

Figure 4. Cox multivariate analysis. Forest plots of the effects of alloSCT vs conservative treatment and identified risk factors. The effects are shown by proportional hazard risks for death and by Cox proportional hazards regression for REs.

patients. After 4 years, the number of REs was reversed between the 2 groups (for example, at 8 years, the mean numbers of REs were 0.59 in transplanted patients and 1.08 in nontransplanted patients). Overall, beyond 1 year after alloSCT, transplanted patients developed very few complications, resulting in a plateau, whereas nontransplanted patients had a continuously increased and progressive risk for severe IEI-related complications (Figure 3C). Multivariate analysis revealed that alloSCT during the first period, autoimmunity, and lymphoid malignancy were significantly associated with REs (hazard ratio for alloSCT, first year, 3.79; 95% CI, 2.29-6.26; $P < .01$). However, transplanted patients had significantly fewer REs after the first year following the alloSCT procedure (hazard ratio for alloSCT after the first year, 0.25; 95% CI, 0.1-0.6; $P < .01$; Figure 4). Separate analyses for the CGD and CID groups are shown in supplemental Figures 4 and 5. Because the number of patients labeled with a diagnosis of CVID, a complex, heterogeneous, and incompletely understood disease entity, is much higher in the nontransplanted group, which may indicate that intrinsic disease characteristics and disease manifestations were not properly matched between the alloSCT and non-alloSCT group, we performed sensitivity analysis by removing patients identified as having CVID without breaking the matching. After their removal, 139 nontransplanted patients were compared with 72 transplanted patients, with similar results in terms of OS, DFS, and mean cumulative number of REs (supplemental Figure 6), suggesting that patients with severe CVID had a similar prognosis to patients with severe CID/IDS. These results were also similar in the subgroup of patients with CID (without those with CGD) and in sensitivity analysis with patients with CVID and/or lung involvement removed (data not shown).

Discussion

We report the results of a large multicenter Franco-British study in which adults and adolescents aged >15 years undergoing alloSCT for IEIs were paired and compared with matched nontransplanted controls collected from the French CEREDIH registry database. We show that alloSCT prevents the progressive morbidity associated with IEI in adults and is predicted to outweigh the negative impact of TRM.

There is ongoing debate about the role of alloSCT in older adolescents and adults with IEIs, including specific indications for transplant and optimal timing. Because prospective studies in such rare, heterogeneous diseases are difficult, we conducted a retrospective case-control study to explore the role of alloSCT. As expected, transplanted patients had severe IEI phenotypes; most had active complications at the time of alloSCT and high HCT-CI scores; 86% of patients had an HCT-CI of ≥1. As previously published, the most common indications for alloSCT were severe active colitis or invasive aspergillosis in patients with CGD[22,23] and malignant lymphoproliferative disease,[35] infection, or complex immune dysregulation in patients with CID.[20,25] The TRM rate was 15% in patients with CGD (3 of 20), which is consistent with previous reports[23] and a recently reported 2-year OS of 78% in a large retrospective European Society for Blood and Marrow Transplantation study including 77 adults with CGD.[22] In the CID patient group, the TRM was 19% (11 of 59). A retrospective study of patients with complex CVID who underwent alloSCT reported higher mortality rates in 14 patients aged 18 to 50 years, who had an OS of 57%, 21% graft failure rate, and 21% severe GVHD.[20] On the contrary, an excellent outcome was recently reported in 6 patients with CGD and 12 with other IEIs aged 15 to 22 years, with an OS of 94%,[11] in line with our previous study of RIC alloSCT in adults with IEIs, which reported a 3-year OS of 85%.[25] A prospective clinical trial of a novel radiation-free and serotherapy-free RIC, the T-replete transplant platform, in patients with IEIs (including CID with various genetic diagnoses) showed encouraging preliminary results for the first 20 patients (including 10 aged >18 years), with a 1-year OS of 90% and low incidence of GVHD (ClinicalTrials.gov ID code NCT02579967).[24] The majority of recent data in adults with IEIs has shown RIC alloSCT to be safe and effective, even in patients with high-risk pretransplant morbidity scores.[11,20,22,24,25] In contrast, a recent European Society for Blood and Marrow Transplantation retrospective study analyzing outcomes after alloSCT for adults with IEIs demonstrated no impact of conditioning intensity on OS or event-free survival.[26] In our study and other published studies, mortality rates were higher in patients aged >25 years at the time of alloSCT and in those with higher comorbidity scores, suggesting that alloSCT should be undertaken earlier in the medical history of a patient with a severe IEI.

Table 4. Characteristics of alloSCT procedure

Characteristic	All patients (n = 79)	CGD (n = 20)	CID (n = 59)
Donor			
Matched related	30 (38%)	7 (35%)	23 (39%)
Mismatched related	4 (5%)	0	4 (7%)
Mismatched unrelated	12 (15%)	3 (15%)	9 (15%)
Matched unrelated	33 (42%)	10 (50%)	23 (39%)
Stem cell source			
Bone marrow	35 (44%)	13 (65%)	22 (37%)
PBSCs	44 (56%)	7 (35%)	37 (63%)
Conditioning intensity			
Full	33 (42%)	5 (25%)	28 (47%)
Reduced	46 (58%)	15 (75%)	31 (53%)
HCT-CI score			
0	10 (13%)	1 (5%)	9 (16%)
1-2	44 (56%)	13 (65%)	31 (53%)
≥3	24 (31%)	6 (30%)	18 (31%)
Not available	1	0	1
Regimen			
Flu/Mel	19 (24%)	0	19 (32%)
Flu/Bu (≤9.6 mg/kg)	21 (27%)	15 (75%)	6 (10%)
Flu/Bu (>9.6 mg/kg)	26 (33%)	5 (15%)	21 (36%)
Baltimore regimen	4 (5%)	0	4 (8%)
Flu/treosulfan	2 (3%)	0	2 (3%)
Flu/Bu/Thiotepa	2 (3%)	0	2 (3%)
CCP/Bu	1 (1%)	0	1 (2%)
CCP/TBI (12 Gy)	2 (3%)	0	2 (3%)
CCP/Flu	1 (1%)	0	1 (2%)
Flu/TBI (2 Gy)	1 (1%)	0	1 (2%)
In vivo T-cell depletion			
Alemtuzumab	36 (46%)	9 (45%)	27 (46%)
Anti-thymocyte globulin	29 (37%)	11 (55%)	18 (31%)
GVHD prophylaxis			
Cyclosporine	75 (95%)	19 (95%)	56 (95%)
MMF	56 (71%)	16 (80%)	40 (68%)
Methotrexate	15 (19%)	2 (10%)	13 (22%)
Posttransplant cyclophosphamide	4 (5%)	0	4 (7%)

Bu, busulfan; CCP, cyclophosphamide; Flu, fludarabine; Mel, melphalan; MMF, mycophenolate mofetil; PBSC, peripheral blood stem cell; TBI, total body irradiation.

Finally, alloSCT survivors experienced a continuous improvement with evidence of phenotype reversal over time, including those with mixed chimerism at last review.

To better define the role of alloSCT, we compared outcomes of transplanted vs nontransplanted matched patients. In our transplant group, serious events were limited to the first year after transplant, whereas nontransplanted patients continued to accrue serious complications over time. This is highlighted by the DFS and RE curves that demonstrate a linear increase in the number of serious events in nontransplanted patients. AlloSCT has the potential to cure the underlying IEIs but carries an immediate risk of TRM, which translated into lower short-term survival. However, short-term OS could not be compared without bias because some nontransplanted patients may have developed significant complications a long time before reaching the age of the matched patients at alloSCT, and the transplant group has an additional risk of transplant-related death within the months after alloSCT. Our study has demonstrated a clear benefit for transplanted

patients compared with nontransplanted controls, with improved DFS and reduced cumulative incidence of REs. Longer follow-up in future studies is required to determine the impact of alloSCT on survival.

Our study has several limitations, including those intrinsic to its retrospective design. In our matching strategy, we aimed to limit bias linked to treatment decades or heterogeneity of IEI subtypes while not excluding large numbers of patients and depleting the pool of matched controls for these rare conditions. For the same reason, patients were matched to controls who had reached the same age as the transplanted index patient, and the time of analysis was calculated from the transplant age (randomization age for the controls; supplemental Figure 1). The degree of severity in the CID group was considered to avoid matching a patient with mild CVID to a patient with complex CVID or CID. The large group of patients with CID was thus defined as having a similar phenotype based on the occurrence of autoimmune complications, lymphoproliferative disease, or both. Selection of controls was blinded and performed by random sampling from the CEREDIH register. Despite these precautions, the alloSCT cohort showed an increased incidence of infections. By contrast, nontransplanted patients had more pulmonary involvement. This may reflect selection bias before referral for alloSCT, which is impossible in this study to completely eradicate. Further, there may be a tendency to reclassify patients with severe CVID referred for alloSCT as having CID, leading to a seemingly CID-dominated transplant cohort and a CVID-rich control group. Nevertheless, there was no difference in IEI-related complications in nontransplanted patients classified as having CVID compared with patients with other CIDs (IDS and LoCID), in keeping with the clinical overlap between complex CVID, IDS, and LoCID (supplemental Table 4). Moreover, sensitivity analyses performed by removing patients with CVID and/or with lung involvement showed similar survival outcomes. Taking into account these limitations, our data show that transplanted patients had significantly better DFS than controls. We believe this is an important message. As in other studies, our findings highlight the need for improved immunological and genetic assessment of patients with severe or complex CVID.

The results of our study highlight the need for consensus recommendations on the timing of and indication for alloSCT in adult patients with severe IEIs,[7] and, indeed, the most recent international published guidelines on alloSCT include a section on adults with IEIs.[28] In patients with CGD, complications increase as patients age, justifying the discussion of alloSCT whenever a patient has a suitable donor. In patients with severe CID, the decision is more complex and is influenced by the type of CID, disease severity, comorbidities, and donor availability. Typically, there are 2 main categories of patients: (1) those for whom the indication for alloSCT is clear (eg, well-characterized gene defect with predictable poor prognosis and severe previous IEI-related complications), HCT-CI score is between 0 and 2, and there is an appropriately matched donor; and (2) those in whom alloSCT is predicted to result in excessively high TRM (patients with an HCT-CI score ≥3 and multiple IEI-associated complications at transplant) or is impossible because of the absence of a suitable donor.[26] In these patients, the individual benefit-risk balance should be carefully discussed with the patient and at a specialist multidisciplinary team meeting. Proceeding to alloSCT may be indicated depending on the severity of the underlying IEIs. In all cases, recommendations need to be balanced by the availability of and response to potentially effective targeted therapies (such as abatacept in LRBA/CTLA-4 deficiency). Patients should be discussed at a specialist multidisciplinary team meeting with clinicians experienced in alloSCT for adults with IEIs. Work is in progress to validate the immune deficiency and immune dysregulation activity score[36] in predicting outcomes following alloSCT in adults with IEIs.

In summary, the findings from this study demonstrate that alloSCT in adolescents >15 years of age and adults for CGD and CID can halt the otherwise progressive increase in IEI-related events and associated morbidity, which contribute to a worsening quality of life and increased hospital admissions. Continued advances in transplant-specific supportive care in specialist adult IEI transplant centers may further reduce the TRM and improve the applicability of alloSCT as a treatment strategy for adults with IEIs.

Acknowledgments

The authors thank Nicolas Garcelon and Vincent Benoit from the Data Science Platform at Imagine Institute.

CEREDIH uses the European Society for Immunodeficiencies (ESID) registry platform to collect patient data. CEREDIH receives unrestricted grants from pharmaceutical companies LFB Biomédicaments, Takeda, Grifols, CSL Behring, Binding Site, and Octapharma, and from the following patients' associations: IRIS and AT Europe. The study was financially supported by Institut National de la Santé et de la Recherche Médicale (INSERM), l'Association pour la Recherche contre le Cancer (ARC), and Université Paris Cité. E.C.M. is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Authorship

Contribution: M.C., E.C.M., F.S., N.M., S.B., and T.A.F. conceptualized and supervised the study and wrote the manuscript; M.C. and T.A.F. provided data and data analysis; M.A., O.B., M.C., N.M., and F.S. performed statistical analysis; all authors except M.A. and O.B. provided clinical care for the patients described; M.C. obtained funding; all authors edited and approved the final version of the paper; and M.C., E.C.M., F.S., N.M., S.B., and T.A.F. were responsible for the final version of the manuscript.

Conflict-of-interest disclosure: M.C. received research grants from Servier and is a recipient of a grant from l'Association pour la Recherche Contre le Cancer (ARC). The remaining authors declare no competing financial interests.

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Footnotes

Submitted 27 January 2022; accepted 11 July 2022; prepublished online on *Blood* First Edition 10 August 2022. https://doi.org/10.1182/blood.2022015482.

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The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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REFERENCES

1. Pai SY, Logan BR, Griffith LM, et al. Transplantation outcomes for severe combined immunodeficiency, 2000–2009. *N Engl J Med*. 2014;371(5):434-446.
2. Heimall J, Logan BR, Cowan MJ, et al. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: a PIDTC natural history study. *Blood*. 2017;130(25):2718-2727.
3. Ghosh S, Köstel Bal S, Edwards ESJ, et al. Extended clinical and immunological phenotype and transplant outcome in CD27 and CD70 deficiency. *Blood*. 2020;136(23):2638-2655.
4. Dimitrova D, Nademi Z, Maccari ME, et al. International retrospective study of allogeneic hematopoietic cell transplantation for activated PI3K-delta syndrome. *J Allergy Clin Immunol*. 2022;149(1):410-421.e7.
5. Haddad E, Logan BR, Griffith LM, et al. SCID genotype and 6-month posttransplant CD4 count predict survival and immune recovery. *Blood*. 2018;132(17):1737-1749.
6. Lankester AC, Neven B, Mahlaoui N, et al. Hematopoietic cell transplantation in severe combined immunodeficiency: the SCETIDE 2006-2014 European cohort. *J Allergy Clin Immunol*. 2021;149(5):1744-1754.e8.
7. Burns S, Morris EC. How I use allogeneic HSCT for adults with inborn errors of immunity. *Blood*. 2021;138(18):1666-1676.
8. Hacein-Bey Abina S, Gaspar HB, Blondeau J, et al. Outcomes following gene therapy in patients with severe Wiskott-Aldrich syndrome. *JAMA*. 2015;313(15):1550-1563.
9. Notarangelo LD, Fleisher TA. Targeted strategies directed at the molecular defect: toward precision medicine for select primary immunodeficiency disorders. *J Allergy Clin Immunol*. 2017;139(3):715-723.
10. Morris EC, Fox T, Chakraverty R, et al. Gene therapy for Wiskott-Aldrich syndrome in a severely affected adult. *Blood*. 2017;130(11):1327-1335.
11. Albert MH, Hauck F, Wiebking V, et al. Allogeneic stem cell transplantation in adolescents and young adults with primary immunodeficiencies. *J Allergy Clin Immunol Pract*. 2018;6(1):298-301.e2.
12. Ferrua F, Galimberti S, Courteille V, et al; SCETIDE, PIDTC, EBMT & ESID IEWP. Hematopoietic stem cell transplantation for CD40 ligand deficiency: results from an EBMT/ESID-IEWP-SCETIDE-PIDTC study. *J Allergy Clin Immunol*. 2019;143(6):2238-2253.
13. Ngwube A, Hanson IC, Orange J, et al. Outcomes after allogeneic transplant in patients with Wiskott-Aldrich syndrome. *Biol Blood Marrow Transplant*. 2018;24(3):537-541.
14. Booth C, Gilmour KC, Veys P, et al. X-linked lymphoproliferative disease due to SAP/SH2D1A deficiency: a multicenter study on the manifestations, management and outcome of the disease. *Blood*. 2011;117(1):53-62.
15. Nademi Z, Slatter MA, Dvorak CC, et al. Hematopoietic stem cell transplant in patients with activated PI3K delta syndrome. *J Allergy Clin Immunol*. 2017;139(3):1046-1049.
16. Slatter MA, Engelhardt KR, Burroughs LM, et al. Hematopoietic stem cell transplantation for CTLA4 deficiency. *J Allergy Clin Immunol*. 2016;138(2):615-619.e1.
17. Barzaghi F, Amaya Hernandez LC, Neven B, et al; Primary Immune Deficiency Treatment Consortium (PIDTC) and the Inborn Errors Working Party (IEWP) of the European Society for Blood and Marrow Transplantation (EBMT). Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: an international multicenter retrospective study. *J Allergy Clin Immunol*. 2018;141(3):1036-1049.e5.
18. Jones LBKR, McGrogan P, Flood TJ, et al. Special article: chronic granulomatous disease in the United Kingdom and Ireland: a comprehensive national patient-based registry. *Clin Exp Immunol*. 2008;152(2):211-218.
19. Aydin SE, Kilic SS, Aytekin C, et al; inborn errors working party of EBMT. DOCK8 deficiency: clinical and immunological phenotype and treatment options – a review of 136 patients. *J Clin Immunol*. 2015;35(2):189-198.
20. Wehr C, Gennery AR, Lindemans C, et al; Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation and the European Society for Immunodeficiency. Multicenter experience in hematopoietic stem cell transplantation for serious complications of common variable immunodeficiency. *J Allergy Clin Immunol*. 2015;135(4):988-997.e6.
21. Soncini E, Slatter MA, Jones LBKR, et al. Unrelated donor and HLA-identical sibling haematopoietic stem cell transplantation cure chronic granulomatous disease with good long-term outcome and growth. *Br J Haematol*. 2009;145(1):73-83.
22. Chiesa R, Wang J, Blok HJ, et al. Hematopoietic cell transplantation in chronic granulomatous disease: a study of 712 children and adults. *Blood*. 2020;136(10):1201-1211.
23. Güngör T, Teira P, Slatter M, et al; Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation. Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. *Lancet*. 2014;383(9915):436-448.
24. Dimitrova D, Gea-Banacloche J, Steinberg SM, et al. Prospective study of a novel, radiation-free, reduced-intensity bone marrow transplantation platform for primary immunodeficiency diseases. *Biol Blood Marrow Transplant*. 2020;26(1):94-106.
25. Fox TA, Chakraverty R, Burns S, et al. Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency. *Blood*. 2018;131(8):917-931.
26. Albert MH, Sirait T, Eikema D-J, et al. Hematopoietic stem cell transplantation for adolescents and adults with inborn errors of immunity: an EBMT IEWP study. *Blood*. 2022;140(14):1635-1649.
27. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. *Blood*. 2014;124(3):344-353.
28. Lankester AC, Albert MH, Booth C, et al; Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation and the European Society for Immune Deficiencies, and European Reference Network on Rare Primary Immunodeficiency Autoinflammatory Autoimmune diseases (RITA). EBMT/ESID inborn errors working party guidelines for hematopoietic stem cell transplantation for inborn errors of immunity. *Bone Marrow Transplant*. 2021;56(9):2052-2062.
29. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106(8):2912-2919.
30. Thakar MS, Broglie L, Logan B, et al. The Hematopoietic Cell Transplant Comorbidity Index predicts survival after allogeneic transplant for nonmalignant diseases. *Blood*. 2019;133(7):754-762.
31. Ghosh D, Lin DY. Nonparametric analysis of recurrent events and death. *Biometrics*. 2000;56(2):554-562.

32. Tong X, Zhu L, Sun J. Variable selection for recurrent event data via nonconcave penalized estimating function. *Lifetime Data Anal*. 2009;15(2):197-215.

33. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Stat*. 1982;10(4):1100-1120.

34. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008;14(6):641-650.

35. Cheminant M, Mahlaoui N, Desconclois C, et al. Lymphoproliferative disease in patients with Wiskott-Aldrich syndrome: analysis of the French Registry of Primary Immunodeficiencies. *J Allergy Clin Immunol*. 2019;143(6):2311-2315.e7.

36. Tesch VK, Abolhassani H, Shadur B, et al; Inborn Errors, Clinical, and Registry Working Parties of the European Society for Blood and Marrow Transplantation and the European Society for Immunodeficiencies. Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score. *J Allergy Clin Immunol*. 2020;145(5):1452-1463.