Long-term outcome after hematopoietic stem cell transplantation of a single-center cohort of 90 patients with severe combined immunodeficiency

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for severe combined immunodeficiency (SCID). Detailed assessment of the long-term outcome of HSCT, ie, the occurrence of clinical events and the quality and stability of immune reconstitution, is now required. We performed a single-center retrospective analysis of the long-term outcome of HSCT in 90-patient cohort followed for between 2 and 34 years (median, 14 years). Clinical events and immune reconstitution data were collected. Almost half the patients have experienced one or more significant clinical events, including persistent chronic graft-versus-host disease (GVHD), autoimmune and inflammatory manifestations, opportunistic and nonopportunistic infections, chronic human papilloma virus (HPV) infections, and a requirement for nutritional support. With the notable exception of severe HPV infection, these complications tend to become less common 15 years later after HSCT. A multivariate analysis showed that the occurrence of these events correlated with non–genoidentical donors, diagnosis of Artemis SCID, and quality of immune reconstitution. In most cases, HSCT enables long-term survival with infrequent sequelae. However, the occurrence of relatively late-onset complications is a concern that requires specific means of prevention and justifies careful patient follow-up. (Blood. 2009;113:4114-4124)

Introduction

Severe combined immunodeficiency (SCID) disorders comprise a heterogeneous group of genetically determined diseases affecting T-lymphocyte differentiation and are always associated with direct or indirect deficiencies in B-cell immunity.[1,2] In the absence of treatment, the lack of adaptive immunity results in overwhelming infections and death within the first year of life. Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice in these conditions, although enzyme replacement therapy and gene therapy could be an option in selected cases.[3-6] The overall survival rate in patients with SCID having undergone HSCT from a matched sibling donor (MSD) is good, at greater than 80% in patients treated since 1968 and even greater than 90% in those treated since 1996.[7] The survival rate for patients treated with haploidentical T cell–depleted HSCT is not as good, with long-term survival rates ranging from 50% to 78% in various series.[5,7] Over time, results have improved as a result of better management of infections and graft-versus-host disease (GVHD). It has recently been reported that the results of transplantations from matched unrelated donors are satisfactory,[7,8] although concerns on the probability of finding a donor, the time required to do so, and the risk of GVHD must also be considered.

Despite remarkable improvements in survival rates, few data are available on the long-term clinical status and quality of life of patients with SCID who received a transplant. There are some concerns about possible impairment of T-cell function later in life, as a consequence of thymopoiesis exhaustion.[9] A decline in thymus output can result from the inability of a hypoplastic SCID thymus to sustain thymopoiesis over time or absent or poor donor stem cell engraftment in a setting when, in many patients, a myeloablative conditioning regimen (CR) is not used. In the present single-center report, we present a retrospective, in-depth analysis of the clinical and immunologic follow-up of all our patients with SCID having survived for more than 2 years after HSCT. We determined risk factors for occurrence of events at least 2 years after HSCT and poor immune reconstitution in a univariate and multivariate analysis.

Methods

Patients and HSCT characteristics

Between 1972 and 2004, 149 patients with SCID were treated by allogeneic HSCT in the Department of Immuno-Hematology at the Necker Children's

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Hospital (Paris, France). Ninety-four patients were alive 2 years after HSCT (2-year survival rate of 63%). Long-term follow-up data were available in 90 cases and have been included in this retrospective analysis. The patient and HSCT characteristics are given in Table 1. The median follow-up period was 14 years after HSCT (range, 2-34 years). The follow-up period was fewer than 5 years for 12 patients, between 5 and 15 years in 40 patients, and more than 15 years in 38 patients. Note that HSCT from an unrelated donor (URD) and adenosine deaminase (ADA) SCID are underrepresented compared with other series in the literature.[10] The retrospective data were collected in accordance with the ethical committee of Hôpital Necker-Enfants Malades (Paris, France).

Clinical assessment

The patients' clinical events (ie, infections, chronic GVHD [cGVHD], autoimmune manifestations, and the requirement for enteral or parenteral nutritional support) and personal variables (growth, school attendance) were assessed retrospectively with data gathered on a yearly basis at the outpatient clinic. All clinical events present 2 years after HSCT or occurring thereafter were recorded, together with the onset, severity, and outcome of these events. A clinical score was established (Table S1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article). The end time point for analysis was December 31, 2006.

Immunologic investigations and chimerism

T- and B-cell immune functions were assessed on a yearly basis (see the supplementary data). Chimerism on total blood or sorted cell lineages was determined by XY-fluorescent in situ hybridization (FISH) or by polymerase chain reaction amplification of short tandem repeats. For each cell lineage, mixed chimerism was defined as the presence of 10% to 90% of donor-derived cells.

Statistical analysis

Factors associated with occurrence of clinical events were searched for by univariate analysis with the use of Poisson regression and Cox proportional hazard models. Then multivariate Poisson model was built with variables that were statistically significant ($P < .05$) in the univariate analysis and was reduced by a stepwise procedure. Relations between late and early immune reconstitution were studied by logistic and linear regression models, including a continuous time variable. A clinical score was built and compared over time between groups of patients with the use of a covariance analysis. Statistical analyses were performed with Stata/SE 8 software (StataCorp, College Station, TX) and Prism 5 (GraphPad Software, San Diego, CA).

Results

Correction of the immunodeficiency

T- and B-cell immune functions, assessed on a regular basis up to last follow-up (median, 11 years; range, 2-28 years) are given in Table 2. We showed that $CD4^+$ T-cell counts 1 and 2 years after HSCT were highly predictive of late immune T-cell reconstitution (Table 3; Figure 1A; data not shown) and of late thymic output (Figure 1B; data not shown). Interestingly, specific analysis of $CD3^+$ and $CD4^+$ T-cell counts in the 16 patients with a follow-up period of more than 20 years did not show a decline in those T-cell subsets 10 years and more after HSCT (Figure 1C; data not shown), suggesting that there is no long-term decline in T-cell immunity in this cohort of patients. All patients had T cells of donor origin. Data on myeloid chimerism were available for 70 patients. Twenty-seven (41%) had significant myeloid engraftment (donor-derived granulocytes ≥ 10%), compared with 43 (59%) with myeloid cells of recipient origin. Engraftment of donor-derived myeloid cells, associated with use of full myeloablative conditioning regimen

Table 1. Patients and HSCT characteristics

Characteristics	No. of patients (%)
Molecular diagnosis	
IL2RG (γc)	22 (24.5)
RAG-1/2	20 (22)
JAK3	16 (18)
DCLRE1C (*Artemis*)	12 (13)
IL7RA	6 (6.5)
Unknown	6 (7)
Reticular dysgenesis	4 (4.5)
ADA	3 (3.5)
CD3E	1 (1)
Median age at diagnosis: 4 mo	
≤ 3 mo	35 (39)
> 3 mo	55 (61)
Sex	
Male	55 (61)
Female	35 (39)
Symptoms at diagnosis	
None	16 (18)
Infections	60 (67)
Failure to thrive	40 (44)
Omenn syndrome	8 (9)
Maternofetal engraftment	12 (13)
Age at HSCT	
≤ 3.5 mo	23 (25)
> 3.5 mo	67 (75)
Donor origin	
Matched sibling (MSD)	22 (24.5)
Pheno-related (PRD)	15 (16.5)
Unrelated (URD)	2 (2)
Mismatched-related (MMRD)	51 (57)
No. of HSCTs/patient*	
One	80 (89)
Two	7 (8)
Three	3 (3)
Conditioning regimen†	
None	46 (51)
Immunosuppression only	5 (5.5)
Bu 8/Cy 200 mg/kg	22 (24.5)
Bu 16/Cy 200 mg/kg	17 (19)
GVHD prophylaxis	
T depletion	52 (58)
E-Rosetting	25
In vitro monoclonal anti–T-cell antibodies	8
$CD34^+$ selection	19
Cyclosporin A	32 (35)
Acute GVHD	
Grade ≥ 2	31 (34)
Grade 2	18
Grade 3	12
Grade 4	1
Chronic GVHD, < 2 y	24 (27)
Severe events after HSCT, < 2 y	
Persistent diarrhea, > 1 y	
With GVHD	20 (22)
Without GVHD	9 (10)
Autoimmunity	6 (7)

IL2RG indicates interleukin-2 receptor γ; γc, common γ-chain deficiency; *JAK3*, Janus kinase-3; *RAG-1/2*, recombination activating gene −1/−2; *DCLRE1C*, DNA cross-link repair protein 1C; *IL7RA*, interleukin-7 receptor α; *ADA*, adenosine deaminase; *CD3E*, CD3 ε; Bu, busulfan; and Cy, cyclosporine.

*Patients who presented engraftment failure (defined as absence of donor T lymphocytes 6 months after HSCT) received at least 2 HSCTs. In these recipients data are analyzed from the last HSCT.

†Conditioning regimen follows the European Society for Immunodeficiency/European Bone Marrow Transplantation guidelines for HSCT in SCID.

Table 2. Immunologic abnormalities during follow-up

	1 y after HSCT, n (%)	2 y after HSCT, n (%)	Last follow-up, n (%)	
			5-15 y	> 15 y
Low $CD3^+$*	19/79 (24)	20/83 (24)	8/35 (23)	4/32 (12.5)
Low $CD4^+$†	25/79 (31.6)	22/83 (26)	8/35 (23)	4/32 (12.5)
Low $CD8^+$‡	17/79 (21.5)	17/83 (20)	3/35 (9)	1/32 (3)
Low naive $CD4^+$ (< 200/μL)	ND	ND	11/25 (44)	17/30 (56)
Low NK cell (< 50/μL)	ND	ND	10/30 (33)	9/31 (29)
Low T-cell function§	9/79 (11)	7/83 (8.5)	5/35 (14)	2/32 (6)
Immunoglobulin substitution	46/90 (51.1)	35/90 (39)	13/40 (32.5)	4/38 (12.5)

ND indicates not done.
*Low $CD3^+$ T-cell counts: 1 year, < 1000 lymphocytes/μL; 2 years, < 1400/μL; 5-15 years, < 1000/μL; > 15 years, < 800/μL.
†Low $CD4^+$ T-cell counts: 1 year, < 500/μL; 2 years, < 650/μL; 5-15 years, < 450/μL; > 15 years, < 300/μL.
‡Low $CD8^+$ T-cell counts: 1 year, < 300/μL; 2 years, < 400/μL; 5-15 years, < 300/μL; > 15 years, < 200/μL.
§Proliferative response to mitogens: < 30 000 cpm and/or response to antigen: < 10 000 cpm.

(CR; data not shown), correlated with higher $CD4^+$ T-cell counts 1 and 2 years after HSCT and at last follow-up, and with higher naive CD4 T-cell counts and normal natural killer (NK) cell counts at last follow-up (Figure 2A-C; Table 3; data not shown). Donor or mixed myeloid chimerism was also associated with good B-cell reconstitution (independence of immunoglobulin substitution; $P = .03$; Table 3). At last follow-up, 65 of the 82 alive patients were off immunoglobulin substitution. All had normal IgG, 2 had low IgM, and 10 had low IgA. Antigen-specific antibody responses to tetanus toxoid and polio were available in 60 patients; these responses were fully complete in 54 of them and partial in 6 without clinical relevance (all with γc/Jak3 deficiency). NK cell counts were low ($< 50/mm^3$) in 19 of the 59 patients (33%) evaluated more than 5 years after HSCT. All but 3 of these patients had a γc or JAK3 deficiency, and 14 had very low NK cell counts ($< 15/mm^3$). Molecular diagnosis correlated with immunoglobulin substitution requirement (Table 3) but not with T-cell immune reconstitution (CD4 T-cell count 1 and 2 years after HSCT or at last follow-up) (Figure S1A; data not shown). However, of the patients who did not receive a full myeloablative CR, naive $CD4^+$ $CD45RA^+$ T-cell counts were significantly higher in patients with γc/Jak3/Il7Rα deficiencies than in patients with Rag-1/2 and Artemis deficiencies (Figure 2D). Finally, donor origin had no overall influence on CD4 T-cell counts both 1 and 2 years after HSCT (Figure S1B) and later (not shown).

Table 3. Factors associated with poor immune reconstitution at last follow-up

Variables	Crude OR* (95% CI)	P†
CD4 T-cell count		
Host chimerism	5.4 (1.1-27)	.04
Low $CD4^+$ T-cell count 1 y after HSCT	15.9 (3.8-66)	< .001
Low $CD4^+$ T-cell count 2 y after HSCT	11 (3.2-41)	< .001
Immunoglobulin substitution		
Molecular diagnosis		.05
Rag-1/2 deficiency	1	
Artemis deficiency	13 (1.2-129)	.03‡
γ c/Jak3 deficiency	12 (1.5-99)	.02‡
Others	1.8 (0.1-32)	.7‡
Host chimerism	5.6 (1.2-86)	.03
Immunoglobulin substitution 2 y after HSCT	22 (5.6-86)	< .001

OR indicates odds ratio; and 95% CI, 95% confidence interval.
*Odds ratio calculated with a logistic regression model (with continuous variable of time).
†Wald test.
‡Wald test for each category.

Occurrence of clinical events 2 years and later after HSCT

A total of 43 patients (48%) presented 106 events during the follow-up period (Table 4). Twenty-one patients experienced more than 1 event (2 events, n = 9; > 2 events, n = 12). Fifty-three of these events (50%) were already present 2 years after HSCT, whereas half occurred de novo at a median time after HSCT of 6 years (range, 2.5-22 years). The frequency of occurrence of events tended to decrease over time, except for severe HPV infection (Figure 3A,B).

Chronic GVHD. Ten patients had persistent cGVHD symptoms (11%) and required immunosuppressive treatment 2 years after HSCT, whereas none of the patients had a de novo diagnosis of GVHD later than 2 years. There were 6 recipients of mismatched-related donor (MMRD) HSC transplants (10%), 2 recipients of a pheno-related donor (PRD) HSC transplant (13%), 1 of 2 URD HSC transplant, and 1 from a matched sibling donor (MSD) HSC transplant (5%). Chronic GVHD was disseminated in 6 patients (2 organs, n = 3; 3 organs, n = 3). Skin was involved in 7 patients, digestive tract in 6, and liver in 4. In 5 patients, the symptoms of cGVHD had normalized, and immunosuppressive drugs had been withdrawn 3 to 6 years after HSCT, whereas 2 patients were still on immunosuppression at the time of writing (4 and 18 years after HSCT, respectively). Three patients died of cGVHD and related infectious complications.

Autoimmune and inflammatory complications. Twelve patients displayed autoimmune or inflammatory complications. Onset was before 2 years after HSCT in 6 patients (2-20 months after HSCT) and later than this time point in 6 (2.5-14 years after HSCT). Autoimmune hemolytic anaemia (AIHA) and autoimmune myositis occurred in 6 and 2 patients, respectively. One patient had psoriasis, alopecia, and vitiligo. Three patients had an ill-defined chronic inflammatory disease with recurrent episodes of fever of noninfectious origin, associated with intermittent blood cytopenia. One patient presented disseminated granulomatous disease involving the liver, spleen, lungs, and kidneys. Liver biopsy showed portal, lobular, and sinusoidal inflammation with granuloma and CD8 T lymphocyte infiltrates. These autoimmune/inflammatory complications required immunosuppressive treatment for 1.5 to 17 years (median, 4 years). Outcome was poor, because 5 patients died of autoimmunity/inflammation or related complications, 4 were still on immunosuppressive therapy at the time of writing, and 3 were in remission without treatment.

Requirement for nutritional support. Eighteen patients (20%) had persistent digestive symptoms (diarrhea, anorexia, or both) requiring prolonged nutritional support 2 years after HSCT. Seven

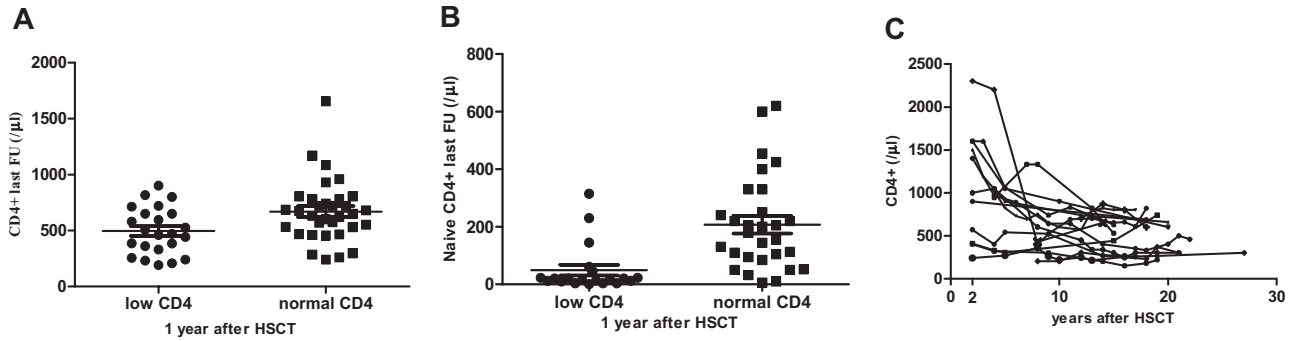

Figure 1. Early immune reconstitution is predictive of late immune reconstitution and late thymic output. FU denotes follow-up. (A,B) Early CD4$^+$ T-cell counts are predictive of late CD4$^+$ and naive CD4$^+$ T-cell counts. Patients with follow-up $>$ 5 years were divided in 2 groups according to their CD4$^+$ T-cell count 1 year after HSCT. CD4$^+$ T-cell counts and naive CD4$^+$ T-cell counts at last follow-up were significantly higher in patients with a normal CD4$^+$ T-cell count 1 year after HSCT ($P \leq .001$ using a linear regression model). (C) Individual CD4$^+$ T-cell counts in patients with follow-up of 20 years or longer, showing no decline in CD4$^+$ T cells 10 years or more after HSCT.

patients needed parenteral nutrition, and 11 patients received enteral feeding. The onset of digestive symptoms and nutritional support occurred within 2 years of HSCT in all cases. Twelve of these patients had GVHD, and the condition persisted until 2 years after HSCT in 5 patients. The median duration of nutritional support was 3 years (range, 2.5-15 years). Persistent cGVHD, autoimmune/inflammatory complications, and a requirement for nutritional support were found to be partially overlapping events (Figure 3C).

Infections. Significant infectious complications occurred in 10 patients 2 to 17 years after HSCT (11%) (median, 8 years). Three patients with low T- and B-cell reconstitutions presented opportunistic infections, consisting of pulmonary and sinus aspergillosis associated with chronic bronchopneumopathy, hepatic cryptosporidiosis, and *Pneumocystis jiroveci* pneumonia, respectively. Five patients on immunoglobulin substitution therapy (with an absence of B-cell function but normal T-cell reconstitution) presented mild chronic sinusitis, chronic bronchopneumopathy, or both as a consequence of recurrent respiratory tract infections. Viral encephalitis occurred in 1 patient 2.5 years after HSCT. Significantly less-intense respiratory tract infections (as defined by the occurrence of one episode of pneumonia per year requiring oral or intravenous antibiotics over 2 consecutive years of follow-up) occurred in 2 patients with normal B-cell function.

Chronic HPV infections. Twenty-three patients presented with HPV infection (26%). Nine previously described patients with γc (n = 3) or Jak3 deficiencies (n = 6) developed severe HPV infection,[11] as defined by the persistence of multiple lesions ($>$ 30) for more than 2 consecutive years of the follow-up period. The median age at onset in this group was 7 years (range, 4-15 years). All patients were intensely treated by various combinations of topic treatments (retinoic acid, imiquimod) systemic (cidofovir, interferon α, retinoic acid), and surgery (abrasion). At the time of writing, 3 patients were in remission after treatment. Fourteen patients developed mild HPV infection, as defined by the presence of fewer than 20 lesions over 2-year periods during follow-up. The molecular diagnoses were mainly cases of γc deficiency (n = 8) and Jak3 deficiency (n = 2); 2 patients had a RIL7α deficiency. The median time to onset was 10 years (range, 5-19 years). The lesions resolved in 11 patients, remained stable in 3, and progressed in 1 patient with RIL7α deficiency.

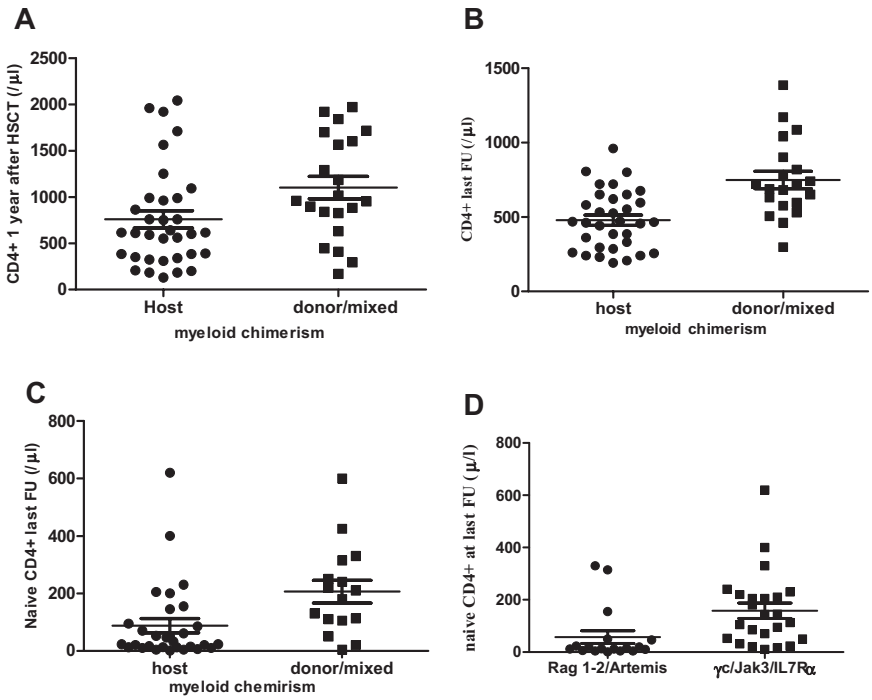

Figure 2. Engraftment of donor-derived myeloid cells correlates with a higher CD4$^+$ T-cell count (1 year after HSCT and at last follow-up) and higher naive CD4 T-cell counts. FU denotes follow-up. Patients were separated into 2 groups according to their myeloid chimerism: group 1 with host myeloid chimerism and group 2 with donor or mixed myeloid chimerism. (A,B) CD4$^+$ T-cell counts 1 year after HSCT and at last follow-up were significantly higher in the group with donor or mixed myeloid chimerism ($P < .001$ using a Mann-Whitney nonparametric test and $P = .03$ using a linear regression model). (C) Naive CD4$^+$ T-cell counts at last follow-up were significantly higher in the group with donor or mixed myeloid chimerism ($P = .04$ using a linear regression model). (D) Relation between naive CD4$^+$ T-cell counts at last follow-up and at diagnosis. Patients who did not receive a fully myeloablative CR were separated into 2 groups according to their genetic defect: group 1 includes Rag1/2/Artemis-deficient patients and group 2 includes γc/Jak3/IL7Rα deficiencies. Naive CD4$^+$ T-cell counts were significantly higher in group 2 ($P = .01$ using a linear regression model).

Table 4. Clinical events more than 2 years after HSCT

Clinical events	No. of patients (%)
Overall	43 (48)
Persistent cGVHD	10 (11)
Autoimmune/inflammatory events	12 (13)
AIHA	6
Myositis	2
Psoriasis, vitiligo, alopecia	1
Ill-defined inflammatory disease	3
Disseminated granulomatous disease	1
Severe or recurrent infection	11 (12)
Opportunistic infection	3
Recurrent LRTI	2
Chronic sinusitis and/or chronic bronchopneumopathy	6
Viral encephalitis	1
Chronic HPV infection	23 (25)
Severe HPV infection	9
Mild HPV infection	14
Nutritional support	18 (20)
Enteral feeding	11
Parenteral nutrition	7
Boost	11 (12)
Growth insufficiency (weight and/or height less than the third percentile)	16 (18)
Obesity	3 (3)
Psychosocial disabilities	6 (7)
Myelodysplasia*	2 (2)
Late-onset mortality	8 (9)

AIHA indicates autoimmune hemolytic anaemia; and LRTI, lower respiratory tract infection.

*Patients with reticular dysgenesis.

Boost transplantation. Twelve patients (12%) received 1 or 2 boosts 2.5 to 15 years after the first HSCT (Table S2) In 7 patients, the reason for the boost was poor T- or B-cell reconstitution. This subgroup of 7 patients received 9 boosts (median time after the first procedure, 3.5 years; range, 2-10.5 years) from 7 MMRD and 2 PRD. CR was given twice (busulfan [Bu] 8 mg/kg and cyclophosphamide [Cy]200 mg/kg = 1; Bu 16 mg/kg and Cy 200 mg/kg = 1). Five patients had a clinical benefit associated with T- and B-cell immunity improvement. Two patients died of poor immune reconstitution despite 2 boosts each. Another 2 patients received a non–T-cell–depleted boost for extensive HPV infection (from a MSD in 1 and a PRD in the other) without previous CR, respectively 16 and 14 years after the first procedure. It was partially efficient in one case. One patient without B-cell reconstitution received a boost without CR from a PRD 4.5 years after the first HSCT. It was inefficient. Finally, 2 patients with reticular dysgenesis underwent a second MMRD HSCT with full myeloablative CR for myelodysplasia in a setting of split chimerism (ie, T lymphocytes of donor origin and myeloid cells of host origin after HSCT with incomplete myeloablative CR 3 and 6 years after the first HSCT). The boost failed in one patient (who died of acute myeloid leukemia of host origin) and led to cure in the other.

Late mortality. Eight patients died 2.5 to 11 years (median, 5 years) after transplantation, corresponding to a late-onset mortality rate of 9% (Table S3). Poor immune reconstitution, chronic GVHD, and related complications (such as autoimmune/inflammatory events) were the main causes of death (n = 6; Figure 1C). One patient died of the neurologic sequelae of a pre-HSCT viral meningoencephalitis, and one patient with reticular dysgenesis died of myelodysplasia complicated by acute myeloid leukemia. No other cancers occurred.

Growth and development. Sixteen patients (15%) presented growth failure with a weight and height below 2 standard deviations (SDs) at some point in their follow-up longer than 2 years after HSCT. All except 1 patient presented concomitant significant clinical events, such as autoimmune and inflammatory complications or chronic GVHD (Figure 1C). Seven of these patients died. Growth failure improved with resolution of concomitant clinical events in the others except in one who remained low for height 2 years after normalization of autoimmunity and cessation of immunosuppressive therapy. Endocrine explorations were not performed on a systematic basis for the whole cohort, but all patients with growth failure who survived were explored. No growth hormone deficiency was found, whereas thyroid hormone deficiency was identified in 2 patients currently on substitutive therapy. Of the patients aged older than 15 (n = 39), adult weight or height were low (≤ -2 SD) in 3, and obesity developed in 3 patients. All patients aged 15 and older have completed clinically normal pubertal development. Two patients who did not receive chemotherapy before transplantation have given birth to, respectively, 1 and 2 children; a further patient who had received a CR with 8 mg/kg busulfan and 200 mg/kg cyclophosphamide total dose was pregnant but had an abortion for a nonmedical reason. One patient developed exocrine pancreatic insufficiency 4 years after HSCT.

Psychosocial disabilities. One patient presented severe mental retardation and epilepsy as a consequence of pre-HSCT severe metabolic disturbances, another developed schizophrenia in adulthood, 3 patients had mild psychologic problems that required transient psychotherapy, and 1 has developed hyperactivity in childhood. Among 62 patients older than 10 years, 58 (88%) had school performances within the normal range (0-2 years of delay in primary and secondary school program) and suggest that cognitive development is fairly good, in accordance with the recent report of Titman et al[12] for patients negative for ADA SCID. Together, 7 patients did not reach any level of graduation. The social life of patients with severe HPV infections was impaired, in view of the resulting aesthetic handicap.

At present, 58 (71%) of the 82 living patients do not require any form of treatment. Seventeen patients need infection prophylaxis via immunoglobulin substitution, antibiotic treatment, or both. Six patients require enteral feeding for anorexia. Immunosuppressive drugs for cGVHD and/or autoimmunity/inflammation were given to 4 patients. Two patients received thyroid hormone replacement therapy. Pancreatic enzymes and neuroleptic and antiepileptic drugs are each used by one patient. Combined medical and surgical treatments are still required for 5 patients with severe HPV infections.

Factors associated with the long-term outcome of HSCT

We used univariate and multivariate analyses to search for factors associated with the occurrence of clinical events 2 to 34 years after HSCT, including pre-HSCT variables (clinical condition, age at transplantation, molecular diagnosis), HSCT characteristics (type of donor, use of CR, use of T depletion, type of T depletion) early after HSCT events (occurrence of GVHD) quality of immune reconstitution, myeloid chimerism, and time of transplantation ($<$ 1988, n = 31; between 1989 and 1997, n = 31; $\geq$ 1998, n = 28). Severe HPV infections, probably related to extrahematopoietic consequences of γc and JAK3 deficiencies,[11] were excluded from these analyses. Results are given in Table 5.

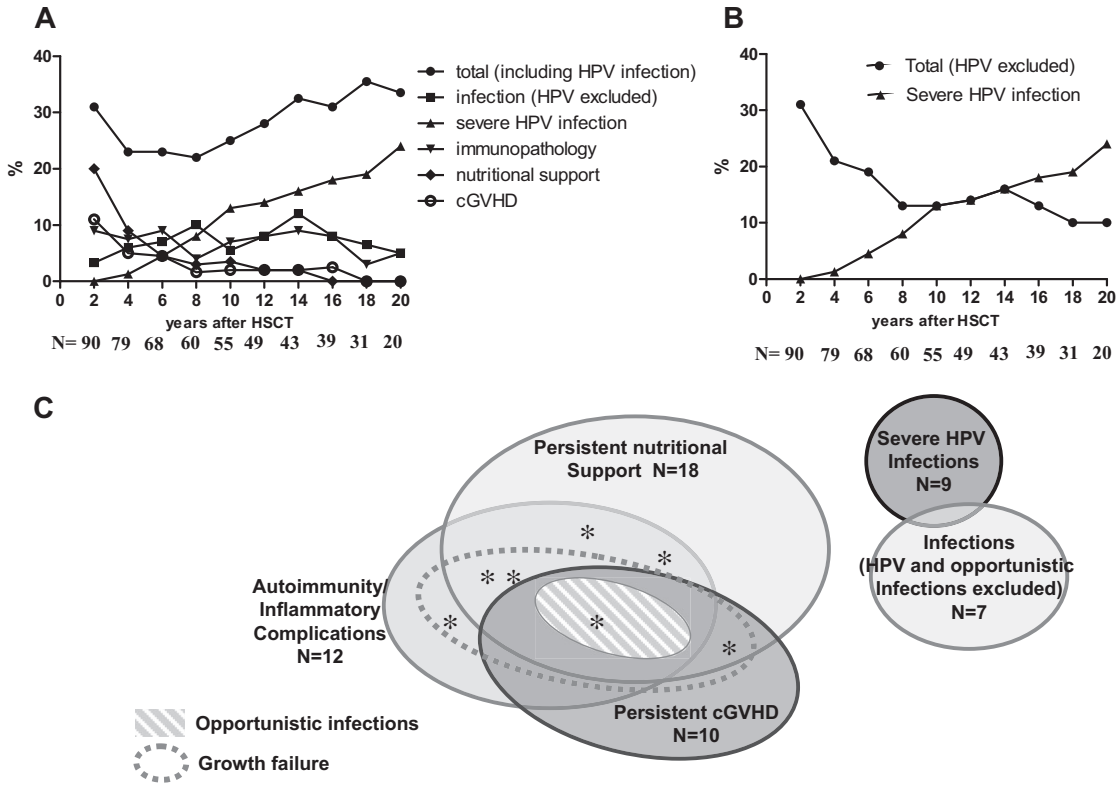

Figure 3. Proportion of patients with events, over time and aggregation of these events. (A) The frequency of events over time is represented. Numbers of patients for each time point are given under the x-axis. (B) The frequencies of severe HPV infections and all events other than HPV infections are plotted separately, showing a decreased incidence of events over time and a progressive increase in severe HPV infections. Numbers of patients for each time point are given under the x-axis. (C) Aggregation of clinical events: nutritional support, autoimmunity/inflammation, persistent cGVHD, and opportunistic infection: n = 3; persistent nutritional support and autoimmunity/inflammation: n = 4; autoimmunity/inflammation and persistent cGVHD: n = 1; persistent nutritional support and persistent cGVHD: n = 2. Severe HPV infections and nonopportunistic infections: n = 2; growth failure: n = 15. *Death (individual cases).

Events as a function of donor origin. Donor origin and occurrence of acute GVHD (aGVHD) were heavily associated with clinical outcome in univariate analysis (Table 5). Occurrence of aGVHD, directly related to donor origin, was associated to outcome in multivariate Poisson analysis. MSD HSC transplant recipients had the best 15-year event-free survival (EFS) rate, compared with recipients of PRD/URD HSC transplant and MMRD HSC transplant (Cox model; Figure 4A). Over time, the frequency of patients experiencing events tends to decrease in all patient groups (Figure 4B). Occurrence of

Table 5. Factors associated with clinical events (severe HPV infection excluded)

Variables	Crude IRR (95% CI)*	*P*	Adjusted IRR (95% CI)†	*P*
Donor origin				
Matched sibling	1	< .001	1	.2
Mismatched related	3.7 (1.6-8.6)		1.4 (0.6-3.4)	
Pheno-related and unrelated	4.8 (2.3-9.9)		2.1 (0.9-5.4)	
GVHD (acute) myeloid chimerism	2.7 (1.8-4.0)	< .001	2.1 (1.3-3.2)	.002
Mixed or donor origin	1	.03		
Recipient	1.7 (1.0-2.8)			
Molecular diagnosis				
RAG 1/2	1	< .001	1	.03
Artemis	6.0 (3.0-12)		1.9 (0.8-4.5)	
γc, JAK3, IL7Rα	1.8 (0.9-3.5)		0.9 (0.4-2.1)	
Others	1.5 (0.7-3.5)		1.4 (0.5-3.5)	
Immune reconstitution				
Low $CD4^+$ T-cell counts	2.7 (1.8-4.2)	< .001	1.8 (1.1-2.8)	.02
Immunoglobulin substitution	4.6 (2.9-7.2)	< .001	2.8 (1.5-5.3)	.002

Because of strong colinearity between donor origin and occurrence of acute GHVD, 2 multivariate Poisson models were built (1 with donor origin, 1 with GVHD). Similarly, myeloid chimerism was not included in multivariate analysis because of colinearities. Negative factors in univariate analysis are not represented in the table (clinical condition and age at diagnosis, age at transplantation presence of maternofetal engraftment, use of conditioning regimen, degree of myeloablation [busulfan 8 or 16 mg/kg total dose]) and time of transplantation (before 1988, between 1989 and 1997, and after 1998).

IRR indicates incidence risk ratio.

*Calculated by univariate survival analysis with a Poisson model.

†Calculated by multivariate survival analysis with a Poisson model.

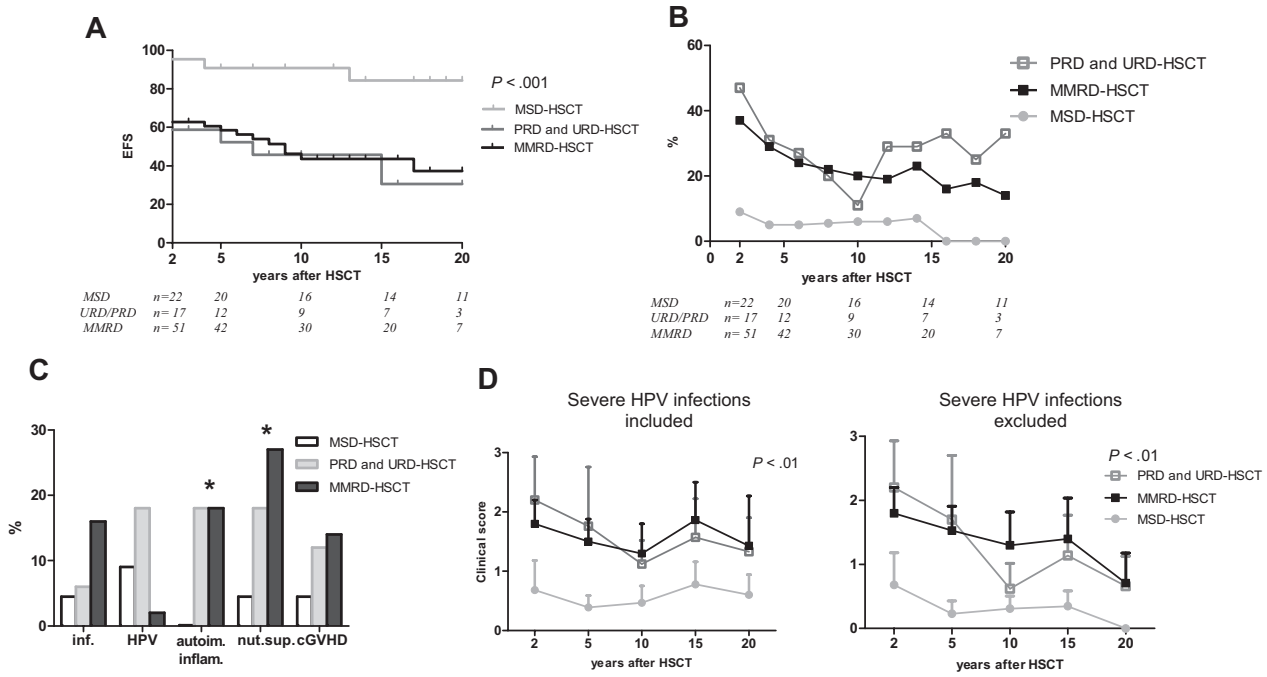

Figure 4. Clinical events as a function of donor origin. (A) Event-free survival (EFS; apart from severe HPV infections). (B) Frequency of all clinical events over time (apart from severe HPV infections). (C) Prevalence of each event (inf. denotes infections other than HPV; autoim. inflam., autoimmunity and inflammatory events; nut.sup., persistent nutritional support). *A significant difference ($P < .05$) between recipients of a MSD HSC transplant and others according to Poisson regression model. (D) Change over time in the clinical score (mean clinical score and standard deviation for each category of patients are given in the y-axis), taking in account severe HPV infections or not.

autoimmune/inflammatory complications and a prolonged requirement of nutritional support were significantly higher in PRD/URD and MMRD HSC transplant recipients, compared with MSD HSC transplant recipients (Figure 4C). The clinical score was significantly higher in PRD/URD and MMRD HSC transplant recipients than in MSD HSC transplant recipients (Figure 4D). Of note, there was no difference between PRD/URD HSCT and MMRD HSCT in terms of long-term outcome (EFS, incidence of clinical events, clinical score).

Clinical events as a function of molecular diagnosis. The SCID diagnosis was also associated with outcome in univariate and multivariate Poisson analysis (Table 5). Given the strong influence of donor origin, patients with MSD HSCT were excluded from this analysis. Of the 68 patients who received PRD/URD or MMRD HSC transplants, those with Artemis deficiency had the poorest outcome, compared with γc/Jak3/RIL7α- and Rag-1/2–deficient patients (Cox analysis) (Figure 5A). Clinical events lasted longer in Artemis-deficient patients (Figure 5B), and all complications (other than severe HPV infections) were more frequent in these patients (Figure 5C). They also had the highest clinical score throughout the follow-up (Figure 5D).

Events as a function of immune reconstitution. Because $CD4^+$ T-cell counts 1 and 2 years after HSCT best predicted late immune reconstitution (Figure 1), this variable was used to assess associations with the clinical outcome. Early T-cell reconstitution was strongly associated with outcome (Table 5). EFS of patients with low $CD4^+$ T-cell counts 1 and 2 years after HSCT were significantly poorer than for patients with normal $CD4^+$ T-cell counts (Figure 6A; data not shown). Autoimmune/inflammatory events and cGVHD were significantly more frequent in the group of patients with poor T-cell immune function (Figure 6B,C). $CD4^+$ T-cell counts 1 and 2 years after HSCT correlated well with the overall clinical score (Figure 6D; data not shown). Naive CD4 T-cell count at last follow-up did not correlate to outcome (data not shown).

The quality of B-cell reconstitution was also associated with outcome in univariate and multivariate Poisson analysis (Table 5). Patients with poor B-cell reconstitution (defined as the persistence of immunoglobulin substitution 2 years after HSCT) presented significantly more clinical events during follow-up, as shown by an EFS analysis (Figure 6E). The effect of early B-cell reconstitution persisted over time (Figure 6F). With the exception of severe HPV infections, all categories of clinical events were significantly more frequent in patients with poor B-cell reconstitution (Figure 6G). Similarly, the clinical score was significantly higher in this latter group (Figure 6H).

We also analyzed the correlation between outcome and NK cell reconstitution in patients who had a NK(−)SCID. The incidence of clinical events was similar in patients with low ($< 50/\mu L$; n = 18) or normal ($> 50/\mu L$; n = 16) NK cell counts at the last follow-up session (data not shown). In particular, HPV infection occurred in 10 of the 18 patients with a low NK cell count (mild, n = 8; severe, n = 2) and in 8 of the 16 with a normal NK cell count (mild, n = 2; severe, n = 7). Patients with very low NK cell count ($< 15/\mu L$) did not exhibit more frequent or more severe clinical complications (data not shown).

Discussion

Here, we report on our detailed analysis of the long-term outcome of HSCT performed in a series of 90 patients with SCID, based on a yearly assessment of the latter's clinical and immunologic status. Although this work confirms that the majority of patients do well with limited or no disease- and HSCT-related sequelae up to 34 years after transplantation,[5,7,8,13,14] it also points to the fact that clinically significant events are not rare, with half occurring or

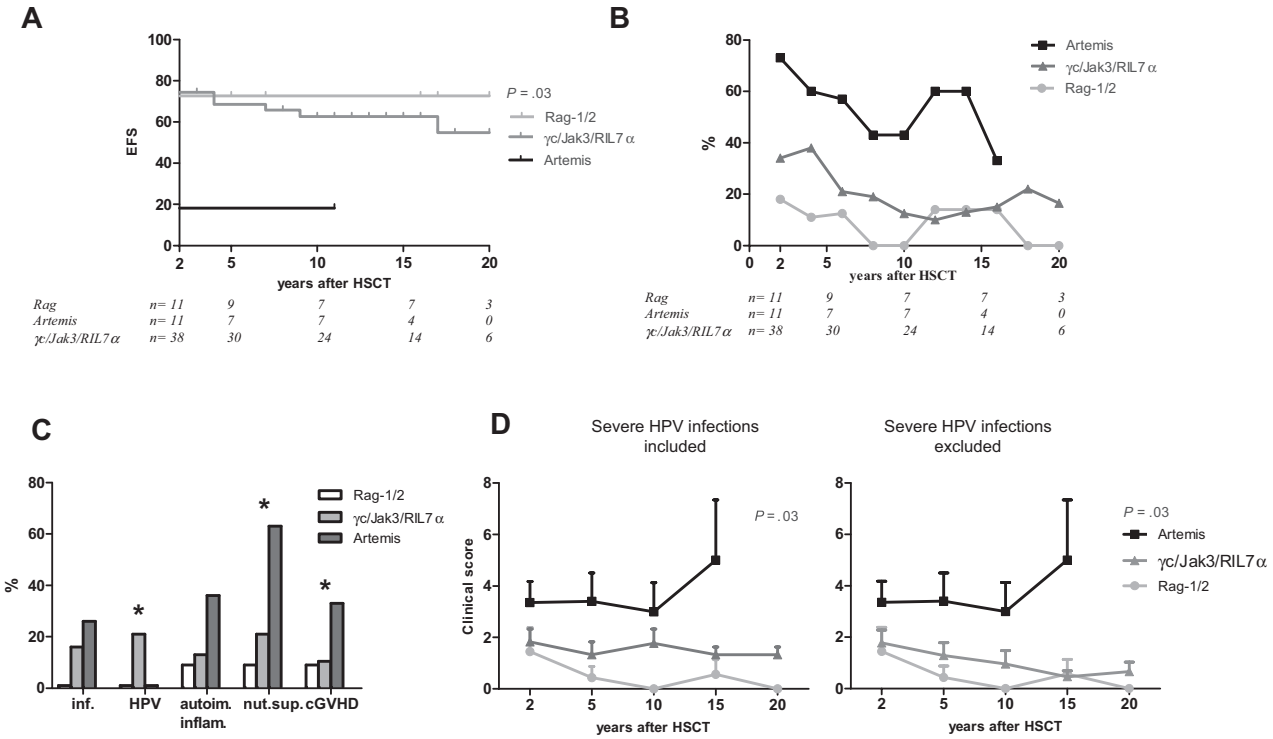

Figure 5. Clinical events as a function of the molecular diagnosis for recipients of PRD/URD and MMRD HSC transplants. (A) Event-free survival (EFS; apart from severe HPV infections). (B) Frequency of all events (apart from severe HPV infections) over time. (C) Prevalence of each event (inf. denotes infections other than HPV; autoim. inflam., autoimmunity and inflammatory events; nut.sup., persistent nutritional support). *A significant difference ($P < .05$) between the 3 groups according to Poisson regression model. (D) Change over time in the clinical score (mean clinical score and standard deviation for each category of patients are given in the y-axis).

persisting more than 2 years after HSCT. Data may not necessarily reflect the overall outcome of patients with SCID because of the rarity of ADA deficiency and URD transplants. Complications may be severe, because the mortality rate is not negligible (8 of 90 patients). It is therefore crucial to try to understand the underlying mechanisms of these complications. As shown in Figure 1C, there are 3 groups of patients who develop late complications: a large group affected by cGVHD, autoimmune/inflammatory manifestations, and/or requiring continuous nutritional support; a second characterized by the occurrence of recurrent, nonopportunistic infections; and a third characterized by the occurrence of severe chronic HPV infection.[11] Hence, these 3 groups deserve separate comment.

It appears that the aggregate of events encompassing persistent cGVHD (≥ 2 years), autoimmunity/inflammation, requirement for some form of long-term nutritional support, opportunistic infections, and growth failure in some patients is more frequently found in (1) recipients of HSC transplants from donors other than HLA-identical siblings and (2) patients with an Artemis deficiency with SCID. The first observation also fits with previously reported data showing reduced survival in recipients of PRD and MMRD HSC transplants, compared with HSCT from HLA identical siblings.[5,7] Together with the results of the statistical analysis, these data clearly indicate that GVHD can have long-term consequences on the outcome of HSCT in SCID, both directly through its clinical consequences and indirectly by affecting the quality of the T(+B)–cell immunodeficiency correction.[15,16] This is indeed the case, because occurrence of the above-mentioned events correlates with a sustained T- and B-cell immunodeficiency in this series. In fact, GVHD-induced thymic lesions probably favor T-cell immunodeficiency and may also affect the control of self-reactivity because of defective negative selection in the thymus, reduced regulatory T-cell development and function, or both.[17] It is also possible that the use of T-cell depletion to prevent GVHD in the setting of MMRD HSCT could affect the quality of T(+B)–cell immunodeficiency correction, because the overall number of transplanted hematopoietic progenitors is lower than in nonmanipulated HSCT. In any case, these observations, based on long-term assessment of HSCT in patients with SCID, justify all possible efforts to prevent GVHD after HSCT from donors other than siblings. They emphasize that PRD HSCT is not the same as MSD HSCT and that reinforcement of GVHD prophylaxis should be envisaged when an HLA-identical parent is chosen as a donor. It is unclear whether donor age or other factors account for this striking difference.

Another finding is the high frequency of the same constellation of complications in Artemis SCID recipients of non-HLA genoidentical HSC transplant. This is particularly striking relative to Rag-1/2 SCID, because the arrest in T- and B-cell development is identical in both cases.[18] Although this difference does not seem to affect survival (C. Schultz et al, manuscript in preparation), it indicates that the Artemis deficiency has additional effects that affect HSCT outcome. Artemis is ubiquitously expressed and is a key element of the non–homologous end-joining (NHEJ) process involved in double-strand DNA break repair.[19,20] One can then reasonably imagine that tissue lesions caused by chemotherapy, infection, and GVHD may be more severe in the context of a defect in a DNA repair pathway. To some extent, this is reminiscent of the known poorer prognosis for HSCT in Fanconi anemia[21] and DNA ligase IV.[22] Confirming these findings will require more data on the long-term outcome of greater numbers of patients with SCID Artemis who received a transplant.[23] Further efforts should thus be made to design an appropriate strategy or perhaps consider an alternative approach, such as gene therapy.[24]

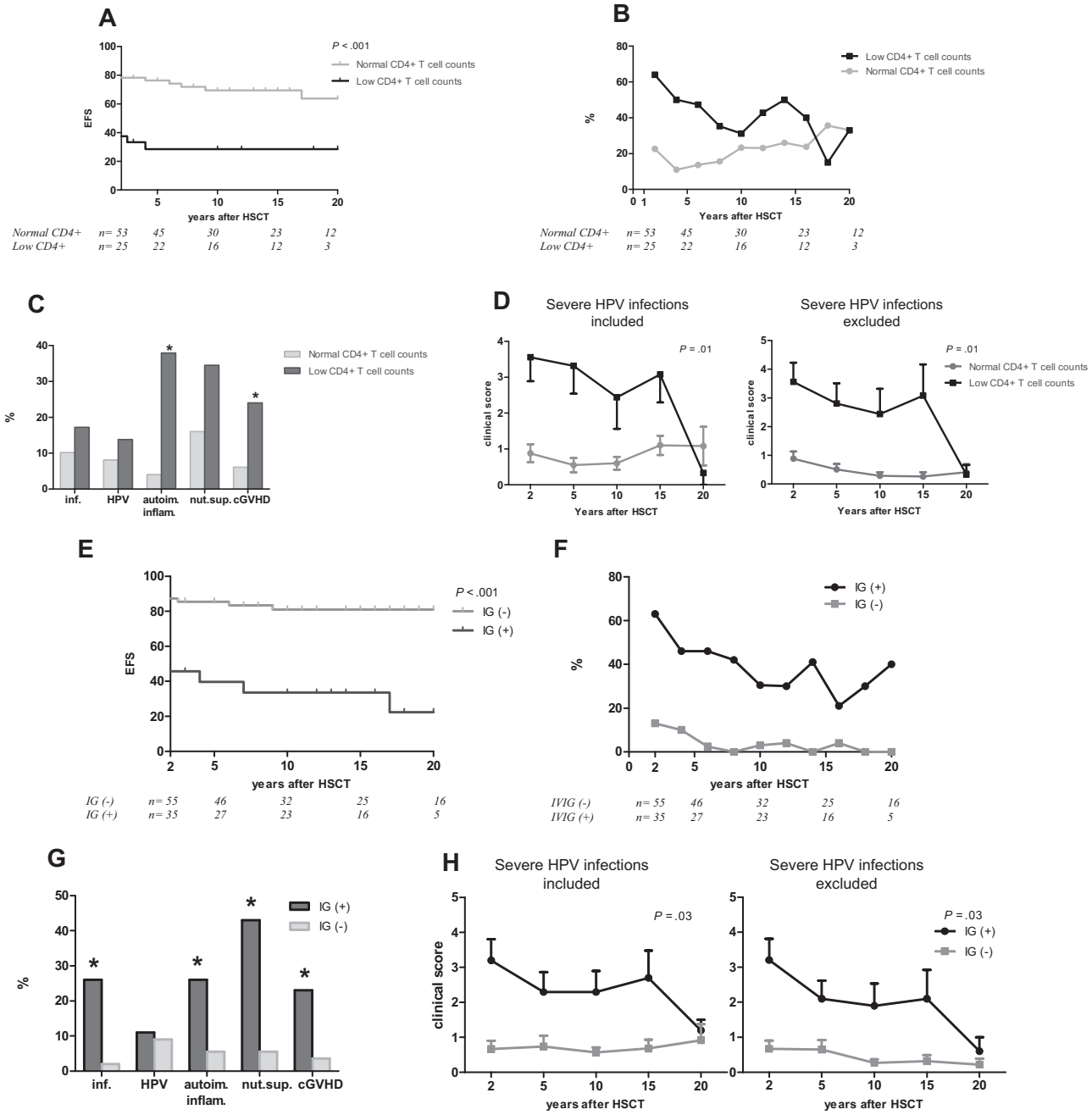

Figure 6. Clinical events as a function of T- and B-cell function. Events as a function of $CD4^+$ T counts 1 year after HSCT (A-D) and as a function of immunoglobulin substitution 2 years after HSCT (E-H). (A,E) Event-free survival (EFS; apart from severe HPV infections). (B,F) Frequency of all events over time (apart from severe HPV infections). (C,G) Prevalence of each event (inf. indicates infections other than HPV; autoim. inflam., autoimmunity and inflammatory events; nut.sup., persistent nutritional support). *A significant difference ($P < .05$) according to Poisson regression model. (D,H) Change over time in the clinical score (mean clinical score and standard deviation for each category of patients are given in the y-axis).

The 2 other groups of long-term complications, ie, recurrent, nonopportunistic infections and chronic HPV disease, have been previously reported.[5,10,11,13,14,25] Both are known to result from defective B-cell function and extra hematopoietic disorders in γc and Jak3 deficiencies, respectively.[5,10,13,25] In our experience, infectious complications related to poor B-cell engraftment, poor B-cell function in γc and Jak3 SCID, or both, in a setting of normal T-cell immunity, are infrequent and mild. It is important to note that the kinetics of the occurrence of complications differ strikingly; immunologic and infectious complications tend to decrease over time (Figure 1), whereas the probability of severe HPV infection increases at least up to 20 years after HSCT. This strongly suggests that a distinct mechanism is at work, as discussed elsewhere.[11,26]

Clearly, the quality of the long-term correction of the immunodeficiency is a major issue in the treatment of SCID. Our study provides long-term confirmation of earlier reports that the assessment of T-cell immunity by various means (T-cell subset counts, particularly CD4 T cells, detection of naive T cells, T-cell function, etc) at 1 and 2 years after HSCT predicts the long-term outcome of T-cell immune responses.[13,27] The determining factor is primarily the rate of early T-cell production, which gives rise to T cells with a long life span. The fact that patients with SCID leading to a

complete absence of thymocytes (eg, γc, Jak3, and IL7Rα deficiencies) exhibit better thymopoiesis than those with SCID associated with the presence of early thymocytes (eg, Rag-1/2 and Artemis deficiencies)[1,2] (see Figure 2D) suggests that competition in thymic niches can influence long-term T-cell immunity. The initially described irrevocable decline in thymopoiesis in all patients[9] has not been confirmed by Borghans[13] or us.[28] In our cohort, we failed to observe an association between thymic function and late-onset complications. It is worth noting that several patients with few naive T cells continue to do well up to 30 years after HSCT.

It has been debated whether use of myeloablative CR in MMRD HSCT could favor better immune reconstitution and clinical outcome. In our study, no effect of CR (mostly used in patients with NK(+) SCID) was observed on the clinical outcome of the whole cohort or of a subgroup of patients who received a MMRD HSC transplant (data not shown). However, use of myeloablative CR was associated with donor or mixed chimerism that more often led to a better T- and B-cell immune reconstitution.

As previously discussed,[29,30] long-term B-cell function depends on the presence of donor B cells or functional host B cells (IL7Rα, CD3 deficiencies). B-cell deficiency can result in recurrent lower respiratory tract infections. It is noteworthy that dependence on immunoglobulin substitution tends to resolve in some patients over time, suggesting that the occurrence of complications (such as cGVHD, autoimmunity, etc) that progressively disappear affects B-cell function independently of chimerism and SCID diagnosis. Of note, no decline in B-cell functions based on detection of memory B cells and antibody titers was observed in the long term. Finally, this long-term survey indicates that defective NK cell recovery in many patients with NK(−) SCID (ie, γc and JAK3) does not have clinical consequences and, notably, is not associated with more frequent infections (including HPV[31]).

This report provides an overview of a large series of patients with SCID, with more than 20 years of follow-up after HSCT in many cases. With the exception of chronic HPV disease, the frequency of ongoing clinical events is low. T-cell counts and functions are stable; there is no indication of a decline in T-cell immunity or the late onset of opportunistic infection or autoimmune conditions, regardless of the donor hematopoietic stem cell status (as indirectly determined by an analysis of myeloid cells chimerism). This clearly shows the previously postulated long life span of T cells. Further studies in these patients, including analysis of telomere length,[32] should tell us how long this favorable setting could persist. Finally, the sequelae of SCID disease manifestations and the HSCT procedure and their implications are limited. Most patients, as described in the smaller series,[10,14] enjoy a good quality of life, with infrequent psychosocial consequences. However, this statement should be qualified, because this series does not include many patients with ADA deficiency, a condition known to be associated with a risk of late-onset psychologic or neurologic impairment or both.[6,33]

In conclusion, this large, retrospective survey provided information that could help refine the further development of HSCT for patients with SCID. Prevention of GVHD is a priority for patients receiving an HSC transplant from donors other than HLA-identical siblings. Gene therapy (an approach that avoids the risk of GVHD has been proven to be successful in 2 types of SCID[4,34,35] but has not yet been proven to be totally safe[36]) could be considered as an alternative. The long-term outcome differs as a function of SCID diagnosis and thus justifies the search for specific approaches. Finally, a boost should be recommended rapidly in cases of poor early T-cell reconstitution (ie, 1-2 years after HSCT), because the likelihood of success is much reduced for late boosts probably because of loss of thymic function.[37] It is essential to continue assessing the status of patients with SCID who received a transplant over the long term, because this is likely to provide further information of clinical interest to the field of HSCT in general. Collaborative studies that not only assess survival[7] but also detail clinical and immunologic status and quality of life will be necessary if we are to more accurately define the many complex issues governing the outcome over the entire life span of patients with SCID.

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Authorship

Contribution: B.N. coordinated the management of the study, collected and analyzed the data, participated in the writing of the report, and contributed to patients' clinical care; S.L. conducted statistical analysis; H.D. helped in collecting data; F.L.D. and C.P. performed immunologic investigations; D.M., N.M., M.D., S.B., and J.-L.C. contributed to patients' clinical care; L.D.C., S.H.-B., and M.C.-C. directed the processing and quality of stem cell transplantation; Y.M. participated in statistical analysis; G.d.S.B. and J.-P.d.V. performed gene analysis; and A.F. contributed to study design, data analysis, writing of the report, and patients' clinical care.

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