

# Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: Entering a new century, do we do better?

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**Background:** Hematopoietic stem cell transplantation remains the only treatment for most patients with severe combined immunodeficiencies (SCIDs) or other primary immunodeficiencies (non-SCID PIDs).

**Objective:** To analyze the long-term outcome of patients with SCID and non-SCID PID from European centers treated between 1968 and 2005.

**Methods:** The product-limit method estimated cumulative survival; the log-rank test compared survival between groups. A Cox proportional-hazard model evaluated the impact of independent predictors on patient survival.

**Results:** In patients with SCID, survival with genotypical donors ( $n = 25$ ) from 2000 to 2005 was 90%. Survival using a mismatched relative ( $n = 96$ ) has improved (66%), similar to that using an unrelated donor ( $n = 46$ ; 69%;  $P = .005$ ).

Transplantation after year 1995, a younger age, B<sup>+</sup> phenotype,

genotypical and phenotypical donors, absence of respiratory impairment, or viral infection before transplantation were associated with better prognosis on multivariate analysis. For non-SCID PID, in contrast with patients with SCID, we confirm that, in the 2000 to 2005 period, using an unrelated donor ( $n = 124$ ) gave a 3-year survival rate similar to a genotypical donor ( $n = 73$ ), 79% for both. Survival was 76% in phenotypical transplants ( $n = 23$ ) and worse in mismatched related donor transplants ( $n = 47$ ; 46%;  $P = .016$ ).

**Conclusion:** This is the largest cohort study of such patients with the longest follow-up. Specific issues arise for different patient groups. Patients with B-SCID have worse survival than other patients with SCID, despite improvements in each group. For non-SCID PID, survival is worse than SCID, although more conditions are now treated. Individual disease categories now need to be analyzed so that disease-specific prognosis may be better understood and the best treatments planned. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

**Key words:** Primary immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, CD40 ligand deficiency, chronic granulomatous disease, hematopoietic stem cell transplantation

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Primary immunodeficiencies (PIDs) are a genetically heterogeneous group of diseases affecting distinct components of innate and acquired immunity including development and function of complement proteins, phagocytes, natural killer (NK) cells, and T and B lymphocytes.<sup>1</sup> Severe combined immunodeficiencies (SCIDs) are the most severe PID, characterized by impaired T-lymphocyte and B-lymphocyte function, normally leading to death within the first year without hematopoietic stem cell transplantation (HSCT).<sup>2</sup> Other T-lymphocyte immunodeficiencies may present later; although prophylaxis improves outcome, recent studies demonstrate that long-term outlook is poor, with many patients dying from infectious or inflammatory-related complications or malignancy in early adulthood.<sup>3,4</sup> Innate immune defects may present in infancy, but prophylaxis has meant that many patients survive until early adulthood.<sup>5,6</sup> HSCT has been shown to be curative since 1968 and remains the only

*Abbreviations used*

|          |                                                            |
|----------|------------------------------------------------------------|
| EBMT:    | European Blood and Marrow Transplantation                  |
| ESID:    | European Society for Immunodeficiency                      |
| GvHD:    | Graft versus host disease                                  |
| HR:      | Hazard ratio                                               |
| HSCT:    | Hematopoietic stem cell transplantation                    |
| NK:      | Natural killer                                             |
| PID:     | Primary immunodeficiency                                   |
| RAG:     | Recombinase activating gene                                |
| SCETIDE: | Stem Cell Transplantation for Immunodeficiencies in Europe |
| SCID:    | Severe combined immunodeficiency                           |
| URD:     | Unrelated donor                                            |
| WAS:     | Wiskott-Aldrich syndrome                                   |

form of treatment for many patients with PID. European centers have been transplanting these patients for over 30 years; previous reports demonstrated an improvement in survival over time.<sup>7</sup> Over that period, HLA-tissue typing methods have been refined, new stem cell sources including umbilical cord blood have become more readily available,<sup>8</sup> and improved methods of isolating hematopoietic stem cells including CD34<sup>+</sup> stem cell selection and CD3<sup>+</sup>/CD19<sup>+</sup> depletion have been developed.<sup>9</sup> More grafts using unrelated donors (URDs) have been performed. Less toxic chemotherapy conditioning regimens have been developed, improving survival in very sick patients.<sup>10</sup> Molecular detection of viral infection has enabled pre-emptive antiviral treatment before organ damage supervenes.<sup>11</sup> Greater awareness of PID among pediatricians has led to earlier diagnosis and referral to specialist centers. With experience of HSCT concentrated in a few centers of excellence, the chance of successful treatment with cure of disease and long-term survival has increased. Common guidelines set out by the European group for Blood and Marrow Transplantation (EBMT) and the European Society for Immunodeficiency (ESID) Inborn Errors Working Party have enabled common treatment protocols to evolve. Patient data are collected in the Stem Cell Transplantation for Immunodeficiencies in Europe (SCETIDE) registry giving data on almost 1500 patients. In this study, long-term results of HSCT in SCID and non-SCID PID, including previous cases of SCID and non-SCID PID reported in 1986, 1990, and 2003, is based on analysis of patients with SCID and non-SCID PID treated in European centers between 1968 and 2005. Because many innovations in HSCT were introduced in the period 2000 to 2005, we explored whether better results were obtained compared with previous periods. The outcome of transplants from HLA-identical (genoidentical) siblings, phenotypically compatible nonsibling relatives (phenoidentical), URDs, and HLA mismatched related donors has been assessed. The large number of cases registered in the database gives sufficient statistical power for assessment of changing trends in outcome over different periods.

**METHODS**

Data were derived from the electronic SCETIDE database established for EBMT/ESID to register HSCT for PID.<sup>7</sup> All centers affiliated to the working party currently undertaking such procedures for SCID and inborn errors were enrolled. Between 1968 and December 31, 2005, thirty-seven centers collected and recorded continuous and systematic relevant data on children undergoing HSCT for SCID and other PIDs gathered on the basis of a questionnaire built up and validated by the European Working Party. Each

center was responsible for quality control of its own data, collated by data managers in the largest centers. Previous definitions of SCID or non-SCID PID, as recently published by the International Union of Immunological Societies,<sup>12</sup> were used for consistency.<sup>7</sup> Data were transmitted to the Department of Biostatistics, Hôpital Necker Enfants Malades, Paris. Three periods have been examined: pre-1995 as a historical period, 1995 to 1999, and 2000 to 2005. The most recent period was analyzed as a distinct interval because many innovations in HSCT were being introduced, as noted.

Donor and recipient HLA matching was determined by serology for the earlier patients and low-resolution class I with high-resolution class II molecular DNA typing in more recent patients; methods were dependent on each center's practice. Genoidentical donors were defined as HLA-identical sibling donors, phenoidentical donors as HLA-identical nonsibling family donors. URDs were mainly HLA-matched, although some were mismatched at 1 or 2 antigens. T-lymphocyte depletion was performed by a number of different methods including E-rosetting with or without soybean agglutination and *in vitro* Campath-1M antibody with complement. Since the late 1990s, CD34<sup>+</sup> stem cell selection rather than T-lymphocyte depletion was used.<sup>9</sup> If given, cytoreductive chemotherapy and graft versus host disease (GvHD) prophylaxis (cyclosporine or tacrolimus) was given in accordance with the EBMT/ESID Inborn Errors Working Party treatment guidelines current at time of transplantation. Broadly, chemotherapy consisted of busulfan-containing regimens; other chemotherapy without busulfan; anti-thymocyte globulin (ATG; Janssen-Cilag, High Wycombe, UK), Alemtuzumab (Genzyme, Cambridge, UK), or muromonab-CD3 (OKT3; Janssen-Cilag, High Wycombe, UK) only; or no chemotherapy. Precautions to reduce the risk of infection were based on reverse isolation, including gnotobiotic isolation, although the exact mechanism used was center-dependent.

**Statistical analysis**

All records available by December 31, 2005, were retained for analysis. Engraftment was evaluated in patients alive 1 month after HSCT. Survival times started from the date of last HSCT. A center effect was explored, and analyses were adjusted for a center effect in the multivariate analysis, comparing centers that transplanted more or less than 50 patients. Differences in observed distributions were analyzed by using the  $\chi^2$  test. Cumulative survival was estimated with the product-limit method. The log-rank test was used to compare survival between different groups. A Cox proportional hazard model with a stepwise forward selection process was retained to evaluate the impact of independent predictors (demographics, comorbidity, transplant characteristics, and therapeutics before HSCT) on patient survival. Hazard ratios (HRs) were provided with their 95% CIs. The SCETIDE database was developed by using Access software (Microsoft Access 2000, Microsoft Corporation, Seattle, WA). Statistical analyses were performed by using the SAS system for Windows (SAS Institute Inc, Cary, NC), and R software for multivariate analyses with the "GLM" and "Survival" libraries.

**RESULTS****Patients with SCID**

Data on 699 patients with SCID were collected. Details of diagnosis are shown (Table I); over the whole period, 49% had B<sup>+</sup> SCID (including T<sup>+</sup> B<sup>+</sup> NK<sup>+</sup> phenotype - common  $\gamma$  chain or janus kinase 3 (JAK3) deficiency, and T<sup>+</sup> B<sup>+</sup> NK<sup>+</sup> phenotype - IL-7 receptor  $\alpha$  deficiency), 29% had B<sup>-</sup> SCID (predominantly T<sup>-</sup> B<sup>-</sup> NK<sup>+</sup> phenotype - recombinaise activating gene [RAG] 1 or 2, or artemis deficiency), and 22% had other forms of SCID, including CD3 subunit deficiency, CD45 deficiency, and other rare molecular defects as well as genetically undefined defects. The proportions of patients presenting with each diagnosis were unchanged over time. More URDs have been used as a proportion of total transplants in successive periods, reflecting establishment of international registries and improved donor selection and harvesting procedures.

**TABLE I.** Type of immunodeficiency according to donor origin, HLA matching, and year of graft

| Diagnosis                       | n   | Percent | Related donor                     |                                    |                       | URD, n |
|---------------------------------|-----|---------|-----------------------------------|------------------------------------|-----------------------|--------|
|                                 |     |         | Genotypically<br>HLA identical, n | Phenotypically<br>HLA identical, n | HLA-<br>mismatched, n |        |
| SCID                            |     |         |                                   |                                    |                       |        |
| Years of graft <1995            |     |         |                                   |                                    |                       |        |
| Total                           | 361 |         | 84                                | 33                                 | 229                   | 15     |
| Reticular dysgenesis            | 11  | 3       | 2                                 | 1                                  | 7                     | 1      |
| ADA deficiency                  | 42  | 12      | 14                                | 1                                  | 25                    | 2      |
| T- B−                           | 105 | 29      | 29                                | 14                                 | 60                    | 2      |
| T- B+                           | 181 | 50      | 34                                | 13                                 | 127                   | 7      |
| Other                           | 22  | 6       | 5                                 | 4                                  | 10                    | 3      |
| Years of graft 1995-1999        |     |         |                                   |                                    |                       |        |
| Total                           | 157 |         | 26                                | 21                                 | 90                    | 20     |
| Reticular dysgenesis            | 3   | 2       | 0                                 | 0                                  | 3                     | 0      |
| ADA deficiency                  | 15  | 10      | 6                                 | 4                                  | 2                     | 3      |
| T- B−                           | 46  | 29      | 3                                 | 11                                 | 25                    | 7      |
| T- B+                           | 80  | 51      | 11                                | 4                                  | 57                    | 8      |
| Other                           | 13  | 8       | 6                                 | 2                                  | 3                     | 2      |
| Years of graft 2000-2005        |     |         |                                   |                                    |                       |        |
| Total                           | 181 |         | 25                                | 14                                 | 96                    | 46     |
| Reticular dysgenesis            | 5   | 3       | 0                                 | 0                                  | 4                     | 1      |
| ADA deficiency                  | 18  | 10      | 5                                 | 1                                  | 4                     | 8      |
| T- B−                           | 55  | 30      | 7                                 | 5                                  | 32                    | 11     |
| T- B+                           | 84  | 46      | 9                                 | 7                                  | 52                    | 16     |
| Other                           | 19  | 11      | 4                                 | 1                                  | 4                     | 10     |
| Non-SCID                        |     |         |                                   |                                    |                       |        |
| Years of graft <1995            |     |         |                                   |                                    |                       |        |
| Total                           | 278 |         | 103                               | 17                                 | 130                   | 28     |
| WAS                             | 85  | 30      | 30                                | 3                                  | 40                    | 12     |
| T-cell deficiencies             |     |         |                                   |                                    |                       |        |
| Omenn syndrome                  | 21  | 8       | 4                                 | 2                                  | 12                    | 3      |
| PNP deficiency                  | 3   | 1       | 1                                 | 1                                  | 1                     | 0      |
| HLA class II deficiency         | 36  | 13      | 13                                | 3                                  | 18                    | 2      |
| CD40 ligand deficiency          | 1   | 0       | 1                                 | 0                                  | 0                     | 0      |
| Other                           | 41  | 15      | 13                                | 1                                  | 25                    | 2      |
| Phagocytic cell disorders       |     |         |                                   |                                    |                       |        |
| Agranulocytosis                 | 5   | 2       | 3                                 | 0                                  | 2                     | 0      |
| Chronic granulomatous disorders | 11  | 4       | 7                                 | 0                                  | 0                     | 4      |
| Leukocyte adhesion deficiency   | 19  | 7       | 6                                 | 1                                  | 11                    | 1      |
| Hemophagocytic syndromes        |     |         |                                   |                                    |                       |        |
| Familial lymphohistiocytosis    | 33  | 12      | 14                                | 1                                  | 16                    | 2      |
| Chédiak-Higashi syndrome        | 15  | 5       | 7                                 | 4                                  | 2                     | 2      |
| XLP (Purtillo)                  | 0   | 0       | 0                                 | 0                                  | 0                     | 0      |
| Griscelli disease               | 2   | 1       | 2                                 | 0                                  | 0                     | 0      |
| Other                           | 6   | 2       | 2                                 | 1                                  | 3                     | 0      |
| Years of graft 1995-1999        |     |         |                                   |                                    |                       |        |
| Total                           | 238 |         | 75                                | 25                                 | 66                    | 72     |
| WAS                             | 34  | 14      | 10                                | 4                                  | 8                     | 12     |
| T-cell deficiencies             |     |         |                                   |                                    |                       |        |
| Omenn syndrome                  | 24  | 10      | 6                                 | 1                                  | 12                    | 5      |
| PNP deficiency                  | 1   | 0       | 1                                 | 0                                  | 0                     | 0      |
| HLA class II deficiency         | 17  | 7       | 4                                 | 7                                  | 5                     | 1      |
| CD40 ligand deficiency          | 18  | 8       | 4                                 | 0                                  | 0                     | 14     |
| Other                           | 65  | 27      | 20                                | 6                                  | 18                    | 21     |
| Phagocytic cell disorders       |     |         |                                   |                                    |                       |        |
| Agranulocytosis                 | 0   | 0       | 0                                 | 0                                  | 0                     | 0      |
| Chronic granulomatous disorders | 9   | 4       | 9                                 | 0                                  | 0                     | 0      |
| Leukocyte adhesion deficiency   | 8   | 3       | 3                                 | 1                                  | 4                     | 0      |
| Other                           | 6   | 3       | 3                                 | 1                                  | 1                     | 1      |

(Continued)

TABLE I. (Continued)

| Diagnosis                       | n   | Percent | Related donor                     |                                    |                       | URD, n |
|---------------------------------|-----|---------|-----------------------------------|------------------------------------|-----------------------|--------|
|                                 |     |         | Genotypically<br>HLA identical, n | Phenotypically<br>HLA identical, n | HLA-<br>mismatched, n |        |
| Hemophagocytic syndromes        |     |         |                                   |                                    |                       |        |
| Familial lymphohistiocytosis    | 33  | 14      | 6                                 | 3                                  | 15                    | 9      |
| Chédiak-Higashi syndrome        | 5   | 2       | 3                                 | 0                                  | 0                     | 2      |
| XLP (Purtillo)                  | 4   | 2       | 2                                 | 0                                  | 0                     | 2      |
| Griscelli disease               | 6   | 3       | 2                                 | 1                                  | 2                     | 1      |
| Other                           | 8   | 3       | 2                                 | 1                                  | 1                     | 4      |
| Years of graft 2000-2005        |     |         |                                   |                                    |                       |        |
| Total                           | 267 |         | 73                                | 23                                 | 47                    | 124    |
| WAS                             | 49  | 18      | 8                                 | 3                                  | 3                     | 35     |
| T-cell deficiencies             |     |         |                                   |                                    |                       |        |
| Omenn syndrome                  | 20  | 8       | 3                                 | 4                                  | 9                     | 4      |
| PNP deficiency                  | 7   | 3       | 0                                 | 2                                  | 2                     | 3      |
| HLA class II deficiency         | 9   | 3       | 2                                 | 0                                  | 5                     | 2      |
| CD40 ligand deficiency          | 17  | 6       | 5                                 | 0                                  | 1                     | 11     |
| Other                           | 46  | 17      | 15                                | 2                                  | 7                     | 22     |
| Phagocytic cell disorders       |     |         |                                   |                                    |                       |        |
| Agranulocytosis                 | 5   | 2       | 0                                 | 0                                  | 0                     | 5      |
| Chronic granulomatous disorders | 21  | 8       | 13                                | 0                                  | 0                     | 8      |
| Leukocyte adhesion deficiency   | 7   | 3       | 4                                 | 0                                  | 3                     | 0      |
| Other                           | 1   | 0       | 1                                 | 0                                  | 0                     | 0      |
| Hemophagocytic syndromes        |     |         |                                   |                                    |                       |        |
| Familial lymphohistiocytosis    | 33  | 12      | 8                                 | 4                                  | 9                     | 12     |
| Chédiak-Higashi syndrome        | 6   | 2       | 1                                 | 2                                  | 1                     | 2      |
| XLP (Purtillo)                  | 15  | 6       | 1                                 | 0                                  | 5                     | 9      |
| Griscelli disease               | 7   | 3       | 3                                 | 2                                  | 0                     | 2      |
| Other                           | 24  | 9       | 9                                 | 4                                  | 2                     | 9      |

ADA, Adenosine deaminase; PNP, purine nucleoside phosphorylase; XLP, x-linked lymphoproliferative disease.

Recipient age at transplantation and the number of procedures undertaken is shown (see this article's Table E1 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). Median age at transplant was slightly lower in 2000 to 2005, but not significantly, which may reflect a trend toward earlier diagnosis and referral or more rapid identification of suitable donors. In 2000 to 2005, a higher percentage of patients was transplanted >18 months of age than in previous periods, a significant increase, which may reflect improvements in supportive care or improved molecular diagnosis picking up older patients with atypical forms of SCID. Ten-year survival in patients with SCID after transplantation has improved over time, although there is no difference in the 2 most recent periods (Table II; Fig 1;  $P = .0003$ ).

Overall, 10-year survival was better with a sibling genodentical donor compared with other types of donor recipient compatibility (Table II; Fig 1;  $P < .0001$ ). For phenodentical donors and URDs, survival improved in the 2 recent periods; however, the numbers per period were low, and the differences did not reach significance (Table E1). Survival using a mismatched relative has improved (Table E1; see this article's Fig E1 in the Online Repository at [www.jacionline.org](http://www.jacionline.org);  $P = .005$ ) with better survival from 1995 to 2005. There was no significant difference in survival using an URD or a mismatched relative in the period 2000 to 2005 (Table E1; see this article's Fig E2 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). Patients transplanted before 6 months of age had better overall survival than those transplanted >12 months old (Table II; see this article's Fig E3 in the Online Repository at [www.jacionline.org](http://www.jacionline.org);  $P = .0008$ ). Survival for patients with  $B^+$  and other forms of SCID remained significantly better than  $B^-$  SCID (Table II;

Fig 2;  $P < .0001$ ). Pre-existing respiratory impairment was associated with a worse outcome (Table II;  $P = .006$ ). Pre-existing septicemia, liver impairment, meningeal infection, and malnutrition were also associated with a worse outcome post-HSCT. The use of chemotherapy conditioning did not significantly affect survival (chemotherapy,  $n = 280$  [61%]; no chemotherapy,  $n = 399$  [63%];  $P = .53$ ; (see "Effect of conditioning on outcome" and Tables E2, E3, and E4 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). Multivariate analysis demonstrated that age at transplant, SCID phenotype, recipient/donor compatibility, pre-existing respiratory infection, protected environment, antibiotic prophylaxis, and the presence or absence of T-lymphocyte depletion were significantly associated with outcome (Table II). There was a weaker significance with the presence or absence of septicemia.

### Patients with other PIDs

Data on 783 patients with non-SCID PID were collected. Details of diagnosis, recipient age at transplantation, and the number of procedures undertaken are shown (Table I; Table E1). After 1995, the numbers and proportion of patients with inborn errors other than Wiskott-Aldrich syndrome (WAS) increased. Of the T-lymphocyte deficiencies, 34% had Omenn syndrome, 6% purine nucleoside phosphorylase deficiency, 32% HLA class II deficiency, 18% CD40 ligand deficiency, and 10% undefined. The proportion of patients with CD40 ligand deficiency markedly increased after 1995, and the proportion of patients with other inborn errors increased in the latest period. Of the phagocytic cell disorders, the proportion of patients with leukocyte adhesion deficiency was greater before 1995 and that of patients with chronic

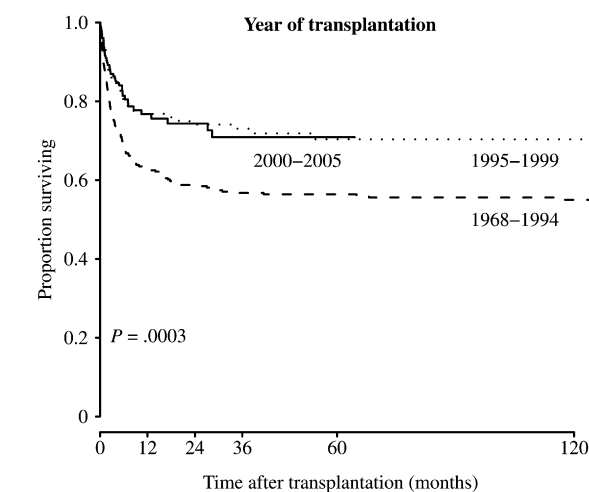
**TABLE II.** Factors affecting outcome after stem cell transplantation

| Outcome factors                  | Univariate analysis         |                           |                             |         | Multivariate analysis |         |
|----------------------------------|-----------------------------|---------------------------|-----------------------------|---------|-----------------------|---------|
|                                  | Absolute number of patients | Absolute number of deaths | 10-Year survival % (95% CI) | P value | Hazard ratio (95% CI) | P value |
| <b>SCID</b>                      |                             |                           |                             |         |                       |         |
| Years of graft                   |                             |                           |                             |         |                       |         |
| 2000-2005                        | 181                         | 41                        | 71 (63-80)*                 | .0003   | 1                     |         |
| 1995-1999                        | 157                         | 40                        | 70 (63-79)*                 |         | 1.0 (0.6-1.7)         | .97     |
| <1995                            | 361                         | 153                       | 56 (51-62)*                 |         | 1.5 (1.0-2.2)         | .06     |
| Age at transplantation (mo)      |                             |                           |                             |         |                       |         |
| <6                               | 289                         | 79                        | 68 (62-74)                  | .0008   | 1                     |         |
| 6-11                             | 253                         | 92                        | 59 (53-67)                  |         | 1.3 (0.9-1.9)         | .11     |
| >12                              | 145                         | 61                        | 51 (42-61)                  |         | 2.4 (1.6-3.5)         | <.0001  |
| SCID phenotype                   |                             |                           |                             |         |                       |         |
| B <sup>+</sup>                   | 345                         | 92                        | 70 (64-76)                  | <.0001  | 1                     |         |
| B <sup>-</sup>                   | 300                         | 128                       | 51 (45-58)                  |         | 2.2 (1.6-2.9)         | <.0001  |
| Other                            | 54                          | 14                        | 71 (58-87)                  |         | 1.2 (0.7-2.2)         | .55     |
| Recipient/donor compatibility    |                             |                           |                             |         |                       |         |
| Related genotypically identical  | 135                         | 20                        | 84 (77-91)                  | <.0001  | 1                     |         |
| Related phenotypically identical | 68                          | 18                        | 64 (52-80)                  |         | 2.6 (1.3-5.3)         | .009    |
| URD                              | 81                          | 23                        | 66 (55-79)                  |         | 4.1 (2.1-8.1)         | .0001   |
| Related HLA-mismatched           | 415                         | 173                       | 54 (48-60)                  |         | 8.9 (4.6-17.2)        | <.0001  |
| Respiratory impairment           |                             |                           |                             |         |                       |         |
| No                               | 379                         | 123                       | 63 (58-69)                  | .006    | 1                     |         |
| Yes                              | 247                         | 102                       | 55 (48-62)                  |         | 1.6 (1.2-2.2)         | .002    |
| Septicemia                       |                             |                           |                             |         |                       |         |
| No                               | 563                         | 197                       | 61 (56-65)                  | .003    | 1                     |         |
| Yes                              | 53                          | 27                        | 46 (33-63)                  |         | 1.8 (1.1-2.8)         | .013    |
| Viral infection                  |                             |                           |                             |         |                       |         |
| No                               | 432                         | 144                       | 63 (58-68)                  | .002    | 1                     |         |
| Yes                              | 191                         | 81                        | 52 (45-61)                  |         | 1.4 (1.0-1.9)         | .041    |
| T-cell depletion                 |                             |                           |                             |         |                       |         |
| Yes                              | 422                         | 160                       | 57 (52-63)                  | .011    | 1                     |         |
| No                               | 266                         | 71                        | 69 (63-76)                  |         | 2.0 (1.3-3.3)         | .004    |
| Protected environment            |                             |                           |                             |         |                       |         |
| Yes                              | 613                         | 199                       | 63 (59-67)                  | .004    | 1                     |         |
| No                               | 55                          | 26                        | 50 (37-66)                  |         | 2.0 (1.2-3.2)         | .005    |
| Prophylaxis <sup>†</sup>         |                             |                           |                             |         |                       |         |
| Yes                              | 503                         | 173                       | 62 (57-67)                  | .021    | 1                     |         |
| No                               | 88                          | 40                        | 54 (44-66)                  |         | 1.9 (1.3-2.8)         | .0007   |
| <b>Non-SCID</b>                  |                             |                           |                             |         |                       |         |
| Years of graft                   |                             |                           |                             |         |                       |         |
| 2000-2005                        | 267                         | 65                        | 69 (60-78)‡                 | .0001   | 1                     |         |
| 1995-1999                        | 238                         | 93                        | 58 (51-65)‡                 |         | 1.7 (1.2-2.5)         | .005    |
| <1995                            | 278                         | 126                       | 54 (49-61)‡                 |         | 1.4 (1.0-2.0)         | .09     |
| Recipient/donor compatibility    |                             |                           |                             |         |                       |         |
| Related genotypically identical  | 251                         | 63                        | 71 (65-78)                  | <.0001  | 1                     |         |
| Related phenotypically identical | 65                          | 24                        | 57 (45-72)                  |         | 1.9 (1.1-3.2)         | .021    |
| URD                              | 224                         | 63                        | 63 (54-74)                  |         | 1.2 (0.8-1.9)         | .29     |
| Related HLA-mismatched           | 243                         | 134                       | 39 (32-47)                  |         | 2.4 (1.7-3.3)         | <.0001  |
| Respiratory impairment           |                             |                           |                             |         |                       |         |
| No                               | 522                         | 176                       | 61 (56-67)                  | <.0001  | 1                     |         |
| Yes                              | 150                         | 76                        | 43 (34-53)                  |         | 1.5 (1.1-2.1)         | .012    |
| Malnutrition                     |                             |                           |                             |         |                       |         |
| No                               | 562                         | 187                       | 62 (57-67)                  | .0004   | 1                     |         |
| Yes                              | 145                         | 74                        | 44 (35-54)                  |         | 1.5 (1.1-2.0)         | .017    |
| Prophylaxis <sup>†</sup>         |                             |                           |                             |         |                       |         |
| Yes                              | 590                         | 204                       | 60 (56-65)                  | <.0001  | 1                     |         |
| No                               | 91                          | 55                        | 33 (23-48)                  |         | 2.4 (1.7-3.3)         | <.0001  |

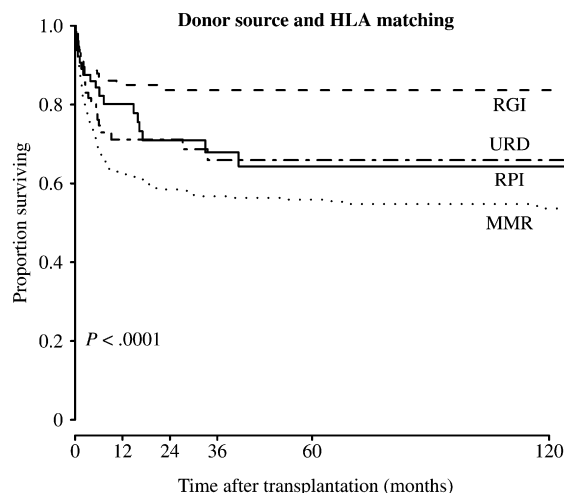
\*5-Year survival is given.

<sup>†</sup>Trimethoprim-sulfamethoxazole.

‡4-Year survival.



| Months                | 0   | 6   | 12  | 24  | 36  | 60  | 120 |
|-----------------------|-----|-----|-----|-----|-----|-----|-----|
| <b>Number at risk</b> |     |     |     |     |     |     |     |
| 1968-1994             | 361 | 245 | 187 | 172 | 166 | 151 | 88  |
| 1995-1999             | 157 | 113 | 95  | 78  | 66  | 40  | 3   |
| 2000-2005             | 181 | 111 | 74  | 49  | 26  | 4   | 0   |

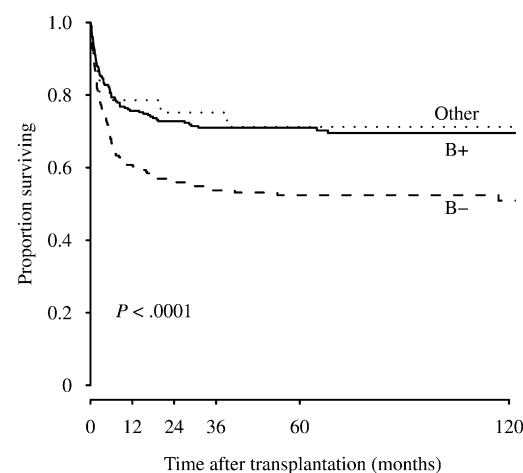


| Months                | 0   | 6   | 12  | 24  | 36  | 60  | 120 |
|-----------------------|-----|-----|-----|-----|-----|-----|-----|
| <b>Number at risk</b> |     |     |     |     |     |     |     |
| RGI                   | 135 | 111 | 77  | 64  | 60  | 50  | 31  |
| RPI                   | 68  | 46  | 36  | 27  | 21  | 16  | 8   |
| URD                   | 81  | 53  | 36  | 33  | 23  | 18  | 6   |
| MMR                   | 415 | 259 | 207 | 175 | 154 | 111 | 46  |

**FIG 1.** Cumulative probability of survival in patients with SCID after HSCT according to the period in which transplanted, donor source (related or URD), and HLA matching. *MMR*, Mismatched related; *RGI*, related genodental; *RPI*, related phenodental.

granulomatous disease much greater in the period 2000 to 2005. Of the hemophagocytic cell disorders, 62% had familial lymphohistiocytosis, 16% Chédiak-Higashi syndrome, 10% Griscelli syndrome, and 12% X-linked lymphoproliferative disease (the proportion of which increased in each of the periods).

The proportion of children >2 years being transplanted was significantly greater after 1995. The 4 year survival showed a marked improvement in 2000 to 2005 (Table II; Fig 3;  $P = .0001$ ), an improvement not seen in the patients with SCID. Survival was better with URDs than phenodental transplants (Table



| Months                | 0   | 6   | 12  | 24  | 36  | 60  | 120 |
|-----------------------|-----|-----|-----|-----|-----|-----|-----|
| <b>Number at risk</b> |     |     |     |     |     |     |     |
| B+                    | 345 | 247 | 195 | 168 | 147 | 111 | 55  |
| B-                    | 300 | 184 | 135 | 109 | 91  | 69  | 33  |
| Other                 | 54  | 38  | 26  | 22  | 20  | 15  | 3   |

**FIG 2.** Cumulative probability of survival in patients with T-B- or T-B+ SCID after HSCT through all periods.

II; Fig 3;  $P < .0001$ ). Survival in the period 2000 to 2005 was better with an URD than a mismatched relative donor, in contrast with patients with SCID (Table E1; see this article's Fig E4 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). Furthermore, survival using a genodental donor was almost the same as that using an URD, a feature not seen in the SCID group. There was a significant improvement over time in survival at 3 years for URD transplants (Table E1;  $P = .027$ ).

Univariate analysis demonstrated that 10-year survival was significantly better for patients with WAS and phagocytic and hemophagocytic disorders than for patients with T-lymphocyte immunodeficiencies (WAS,  $n = 168$  [survival 71%; 95% CI 64-79%]; phagocytic,  $n = 92$  [survival 63%; 95% CI 48-83%]; familial lymphohistiocytosis,  $n = 159$  [survival 58%; 95% CI 49-69%]; T deficiency,  $n = 326$  [survival 47%; 95% CI 41-54%]; Fig 3;  $P < .0001$ ), although this difference was not significant using multivariate analysis.

Pretransplant presence of malnutrition, pulmonary infection, gut infection, or respiratory or liver impairment had a significant deleterious effect on survival (Table II). Multivariate analysis showed that donor type, pre-existing respiratory impairment, or malnutrition and co-trimoxazole prophylaxis during transplant were strongly significantly associated with outcome (Table II).

## DISCUSSION

This is largest cohort study on the outcome of patients undergoing HSCT for PID, with the longest follow-up. Although the data analysis is complex, the large number of patients in the database gives sufficient statistical power to assess outcome trends over different periods. Survival continues to improve over time. Transplantation by using a genodental sibling donor now gives survival of 90% (95% CI, 77% to 100%) for patients with SCID and 79% (95% CI, 69% to 89%) for patients with non-SCID PID—emphasizing how much safer and successful HSCT has become over time. For selected patients with no pre-existing infection, such as newborns with SCID, the outcome is even

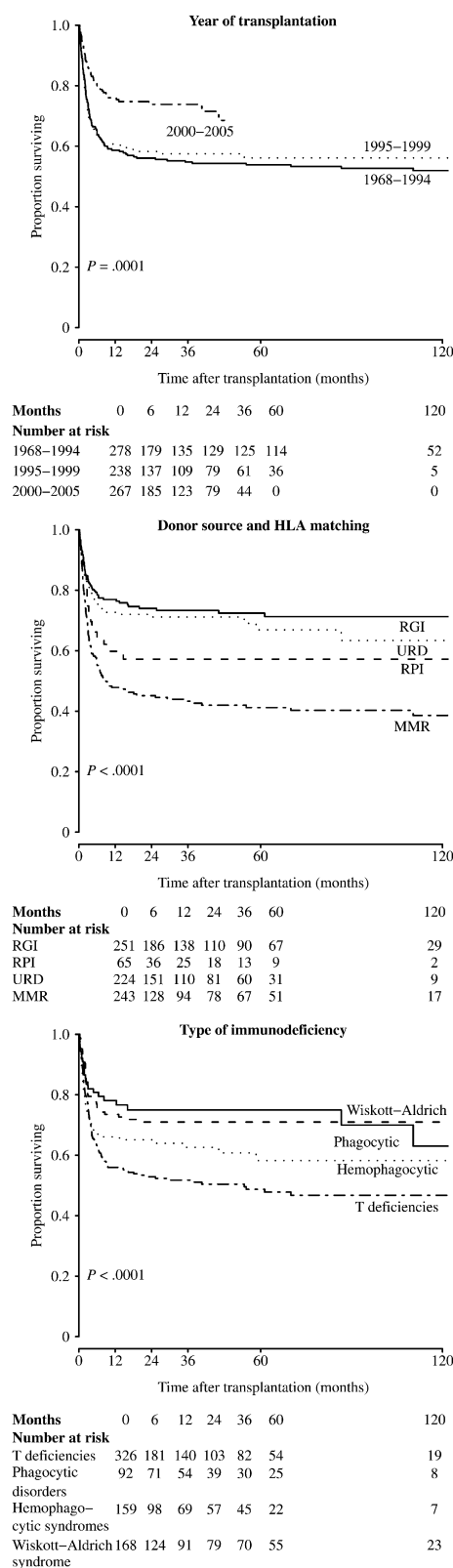


**FIG 3.** Cumulative probability of survival in patients with non-SCID PID after HSCT according to the period in which transplanted, donor source (related or URD), and HLA matching and type of immunodeficiency through all periods. *MMR*, Mismatched related; *RGI*, related genoidential; *RPI*, related phenoidential.

better.<sup>13,14</sup> These data clearly demonstrate an improved outcome when patients are transplanted before 6 months of age. Newborn screening programs are likely to facilitate the early diagnosis of SCID,<sup>15</sup> and thus survival can be expected to improve in the future. Outcome for patients with non-SCID PID is almost as good and continues to improve. As data on long-term outcome of specific PIDs from national and international registries become available,<sup>4,5,16</sup> these data regarding the outcome of HSCT for particular diseases will help inform clinical decisions for optimal treatment of these patients. Simple measures including protected environment and co-trimoxazole prophylaxis during transplantation remain important predictors of outcome. Pre-existing lung and liver damage continues to be associated with a poor outcome, as demonstrated in previous studies.<sup>7,17</sup>

The proportion of HLA-mismatched donor transplants for SCID has diminished over time, likely in part because of the increasing use of URD transplants. Umbilical cord stem cells, particularly suitable for infant recipients, are being used for an increasing number of patients,<sup>8</sup> with 14 cord blood transplants for SCID reported to SCETIDE and 67 to EUROCORD between 1995 and 2005,<sup>18</sup> including genoidential sibling and URD cord blood transplants. A comparative study of unrelated cord blood transplantation versus haploidentical related stem cell transplantation for patients with severe T-cell deficiencies is in preparation with the Eurocord database. A greater use of molecular tissue typing, and hence more accurate identification of HLA matching, is likely to have influenced improved survival for patients receiving stem cells from URDs. The increased use of nonconditioned transplants in patients with SCID receiving genoidential stem cells may lead to a more rapid increase in T-lymphocyte counts than after URD transplantation, and hence faster clearance of infection. Our data, in contrast with previous reports,<sup>19</sup> demonstrate that for patients with SCID, a URD appears to have no significant advantage over a phenoidential or HLA-mismatched donor and may take significantly longer to assess before stem cell donation.

On multivariate analysis, for patients with non-SCID PID, survival is better using an unrelated, rather than phenoidential, donor. The reasons for this are unclear, but there could be a center effect. Related phenoidential donors are a mixed group of genoidential and partially identical donors, but because both phenoidential related and URD recipients receive ATG, Campath, or OKT3 as part of conditioning, these differences are difficult to explain. The accuracy of HLA typing has improved such that URDs are likely to now be a better molecular HLA match than in historic series, thus explaining improvements over time. Survival is almost equivalent to when a genoidential donor is used, in contradistinction to patients with SCID, in whom the outcome using a genoidential donor is better. In the non-SCID group, an URD or other identical relatives show a clear advantage over a haploidentical donor.

Specific issues arise for different patient groups. In the SCID group, after multivariate analysis, patients with  $B^+$  SCID have better survival than those with  $B^-$  SCID, despite improvements in survival in each group over time (data not shown). The effect may be skewed by a large number of artemis-deficient patients in the  $B^-$  SCID group, a defect associated with poorer outcome, possibly because of the associated generalized cellular radiosensitivity, not confined to cells of hematopoietic origin. However, RAG-deficient  $B^-$  SCID also has a poorer outcome than  $B^+$  SCID.<sup>20</sup> Further explanations include a more hostile microthymic environment in some SCID phenotypes because of a later block in

thymocyte development, leading to precursor competition in the thymic niche<sup>21</sup>; predisposition to development of autoreactive T cells after engraftment; or organs that are more susceptible to damage by chemotherapy, leading to more veno-occlusive disease or GvHD, for instance in adenosine deaminase-deficient SCID. In addition, data have not been analyzed with respect to the presence or absence of NK cells, in part because of incomplete ascertainment. Some of the results may therefore be attributable not to the presence of B lymphocytes, but rather to the lack of NK cells, which may favor engraftment over rejection.<sup>22</sup> The lack of improvement in survival over the last period is striking. Patients with SCID are perhaps more difficult to transplant because they are younger at the time of transplant and often have severe opportunistic infection at diagnosis. In addition, physiologically immature organs including lungs and liver may be more susceptible to the effects of veno-occlusive disease or GvHD. The presence of more factors of worse prognosis (eg, more  $T^- B^-$  than  $T^- B^+$  phenotypes, more mismatched than genotypical donors) in patients of the third period was sought to help explain an absence of survival improvement between period 2 and period 3 despite improved diagnostic and therapeutic progress. No difference was found that might substantiate this hypothesis, although the analysis may lack power to show a difference (data not shown).

Survival is similar after transplantation for SCID, whether chemotherapy conditioning is used or not. The role of chemotherapy conditioning in the treatment of SCID is unclear.<sup>23-26</sup> There is not adequate detailed data in SCETIDE to comment about the quality of immunoreconstitution, including production of immunoglobulin and antibody responses to specific protein and polysaccharide antigens associated with the use or absence of chemotherapy. Increasing evidence from other sources suggests that full immunoreconstitution with long-term T and B lymphogenesis requires stem cell engraftment evidenced by donor myeloid chimerism, at least for some SCID phenotypes.<sup>9,20,27-29</sup> The data from SCETIDE need to be interpreted with caution, however, because nonconditioned patients are likely to be the most sick, with end-organ damage, and historically would not have tolerated conventional conditioning regimens. Reduced intensity regimens may enable long-term engraftment and immunoreconstitution, even in patients with significant end-organ damage.<sup>10</sup> Although reduced intensity chemotherapy conditioning is advantageous for patients with significant pre-existing organ damage, the place of fully myeloablative conditioning over reduced intensity chemotherapy is undetermined, and further studies on long-term survival, quality of immunoreconstitution, long-term effects of GvHD, neurodevelopmental outcomes, and fertility need to be addressed.

An increasing range of non-SCID PID conditions is now treated by HSCT. Changes in proportion of disease categories transplanted over time likely reflect improved diagnosis and better care in early childhood leading to survival in later childhood, facilitating transplantation at an older age. Survival is not yet as good as for patients with SCID, perhaps reflecting the perception that patients need to earn the right to transplantation by presenting with significant complications or infections. It is noteworthy that in disease-specific series, outcome is better for younger patients without pre-existing organ damage or infection.<sup>17,30-32</sup> Overall survival for each disease category is improving over time but remains poor for undefined T-lymphocyte immunodeficiencies. This may be because without a clear genetic diagnosis, patients are not offered HSCT, in contrast with those

with a clearly defined clinical and genetic PID. Interestingly, survival was better for patients transplanted at 12 to 47 months rather than <12 or >48 months of age (data not shown). A possible explanation is the inclusion of Omenn syndrome, as well as purine nucleoside phosphorylase and MHC class II deficiencies, in the T-lymphocyte immunodeficiency category. These patients are generally transplanted before 12 months of age. Their outcome is poor, possibly explaining the unexpectedly worse outcome in this younger age group in contradistinction to patients with SCID transplanted at the same age (Fig E3). A separate analysis of the T-lymphocyte deficiency category showed worse outcome for these 3 diagnoses, and the generally poor overall outcome for the T-immunodeficiency group was not skewed by particularly poor results for a specific disease category within the group (see this article's Fig E5 in the Online Repository at [www.jacionline.org](http://www.jacionline.org))—as previously demonstrated in disease-specific series.<sup>33,34</sup> Beyond a year, survival improves as well patients with no or minimal organ damage are treated. Decrease in survival beyond 48 months may reflect treatment of older, sicker patients with diseases such as WAS and CD40 ligand deficiency who have more infection and end-organ damage. This study did not look at donor chimerism. Detailed data regarding mixed and mixed split-cell lineage chimerism are not available from the current database but are important because the quantity of donor chimerism and the cell lineages in which it is found may affect the quality of immune function.<sup>35</sup>

Since the first HSCT for PID in 1968, survival has continued to improve, and the range of disorders for which HSCT is considered is expanding. These data from SCETIDE show continuing improvement in survival in all categories. As survival improves, the long-term quality of immunoreconstitution and other life quality issues become important. Few studies have examined long-term immunoreconstitution. Significant long-term sequelae are now being identified, including thymic failure in patients without stem cell engraftment<sup>20,27</sup>; the appearance of human papilloma virus warts, predominantly in patients with common  $\gamma$  chain or JAK3-deficient SCID<sup>20,36</sup>; and neurocognitive development in patients post-HSCT.<sup>37,38</sup> It is now critical to analyze the long-term outcome for disease-specific groups. The SCETIDE database is now large enough to begin analysis of the outcome of HSCT for different specific genetic defects—for instance, RAG-deficient or artemis-deficient  $T^- B^- NK^+$  SCID—although data may be required in addition to those routinely collected. The next stage will be carefully to analyze individual disease categories so that the prognosis after HSCT for the different genetic conditions may be better understood.<sup>39</sup> Continued careful data collection is required to gain a complete understanding of the outcome for these rare genetic disorders so that the best treatment can be planned, including the different stem cell therapies and gene therapy.<sup>40</sup>

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## Key messages

- Transplantation for primary immunodeficiency before 6 months of age is associated with improved outcome and supports the use of newborn screening programs to facilitate the early diagnosis of SCID.
- Prognosis after HSCT for PID is multifactorial, including molecular defect, disease status, donor, stem cell source, and conditioning regimen, and it is important now to analyze the long-term outcome for disease-specific groups.

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## EFFECT OF CONDITIONING ON OUTCOME

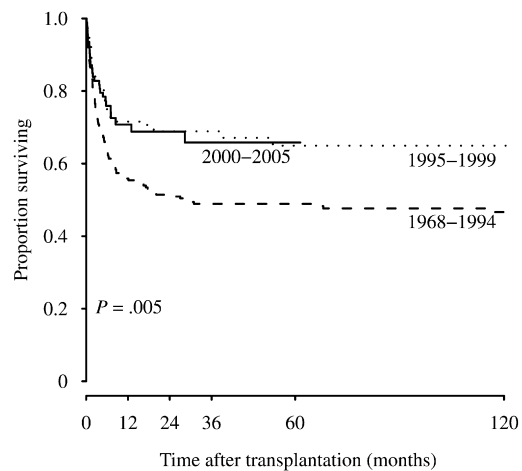
Conditioning was performed in accordance with guidelines current at the time of transplantation.

A complementary analysis is presented considering the conditioning variable composed of 4 classes: no conditioning, busulfan containing, other chemotherapy without busulfan, and ATG, Campath, or OKT3 only (Table E3). Whereas 42% of patients with SCID did not receive conditioning, only 5% of patients with non-SCID PID were not conditioned. The outcome using busulfan was no better than not giving conditioning, although it was close to statistical significance (HR, 1.4; 95% CI, 1.0-2.1;  $P = .05$ ). This result was expected because recipients receiving stem

cells from genotypical donors as well as those with T-B+ PID did not often receive conditioning.

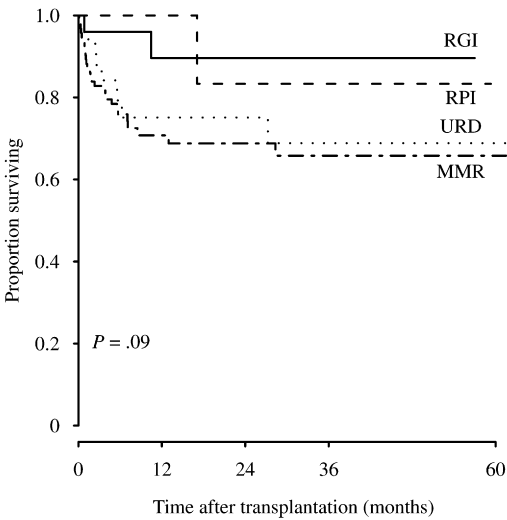
The outcome using busulfan appeared better than using non-busulfan regimens (HR, 2.1; 95% CI, 1.3-3.3;  $P = .002$ ; Table E3). The outcome using busulfan did not appear better than using ATG, Campath, or OKT3 alone (HR, 1.1; 95% CI, 0.5-2.3;  $P =$  nonsignificant), although the number of patients who received ATG, Campath, or OKT3 alone was limited ( $n = 29$ ).

In patients with non-SCID PID, survival after transplantation using busulfan conditioning was not statistically different from using no conditioning, other chemotherapy, or ATG, Campath, or OKT3 alone.



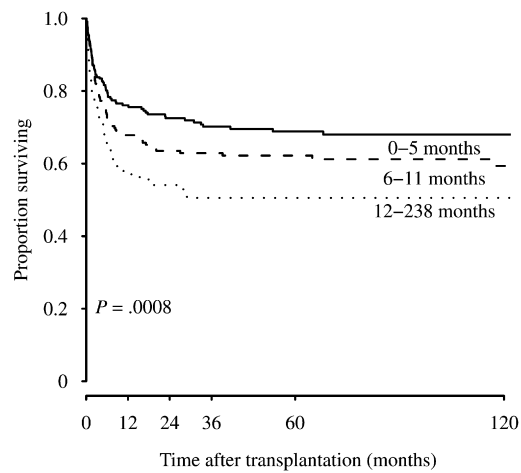
| Months                | 0   | 6   | 12  | 24  | 36 | 60 | 120 |
|-----------------------|-----|-----|-----|-----|----|----|-----|
| <b>Number at risk</b> |     |     |     |     |    |    |     |
| 1968-1994             | 229 | 144 | 113 | 101 | 96 | 86 | 45  |
| 1995-1999             | 90  | 65  | 57  | 49  | 43 | 23 | 1   |
| 2000-2005             | 96  | 50  | 37  | 25  | 15 | 2  | 0   |

**FIG E1.** Cumulative probability of survival in patients with SCID after HSCT according to year at grafting in HLA-mismatched SCID.



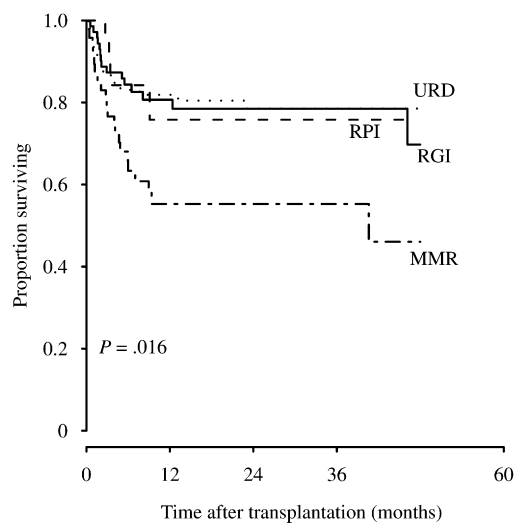
| Months         | 0  | 6  | 12 | 24 | 36 | 60 |
|----------------|----|----|----|----|----|----|
| Number at risk |    |    |    |    |    |    |
| RGI            | 25 | 22 | 12 | 6  | 3  | 0  |
| RPI            | 14 | 9  | 7  | 2  | 1  | 0  |
| URD            | 46 | 30 | 18 | 16 | 7  | 2  |
| MMR            | 96 | 50 | 37 | 25 | 15 | 2  |

**FIG E2.** Cumulative probability of survival in patients with SCID after HSCT according to donor source (related or URD) and HLA matching for the period 2000 to 2005. *MMR*, Mismatched related; *RGI*, related genoidential; *RPI*, related phenoidential.



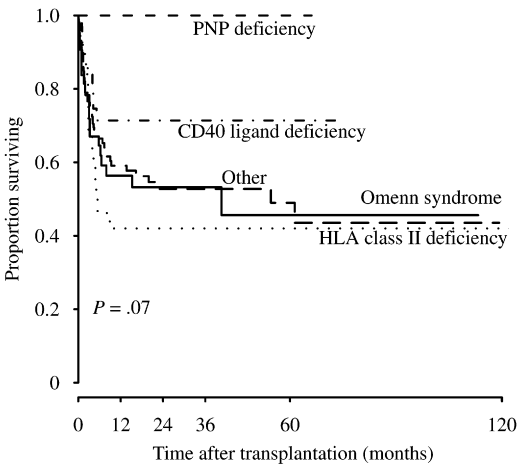
| Months                | 0   | 6   | 12  | 24  | 36  | 60 | 120 |
|-----------------------|-----|-----|-----|-----|-----|----|-----|
| <b>Number at risk</b> |     |     |     |     |     |    |     |
| 0-5 months            | 289 | 210 | 158 | 135 | 118 | 92 | 47  |
| 6-11 months           | 253 | 170 | 134 | 110 | 94  | 70 | 32  |
| 12-238 months         | 145 | 80  | 56  | 48  | 40  | 28 | 12  |

**FIG E3.** Cumulative probability of survival in patients with SCID after HSCT according to age at transplantation through all periods.



| Months         | 0   | 6  | 12 | 24 | 36 | 60 |
|----------------|-----|----|----|----|----|----|
| Number at risk |     |    |    |    |    |    |
| RGI            | 73  | 55 | 37 | 20 | 13 | 0  |
| RPI            | 23  | 14 | 8  | 5  | 2  | 0  |
| URD            | 124 | 88 | 60 | 41 | 21 | 0  |
| MMR            | 47  | 28 | 18 | 13 | 8  | 0  |

**FIG E4.** Cumulative probability of survival in patients with non-SCID PID after HSCT according to donor source (related or URD) and HLA matching for the period 2000 to 2005. *MMR*, Mismatched related; *RGI*, related genoidentical; *RPI*, related phenoidentical.



| Months                       | 0   | 6  | 12 | 24 | 36 | 60 | 120 |
|------------------------------|-----|----|----|----|----|----|-----|
| Number at risk               |     |    |    |    |    |    |     |
| Omenn syndrome               | 44  | 26 | 19 | 11 | 9  | 3  | 0   |
| PNP deficiency               | 8   | 5  | 4  | 2  | 1  | 1  | 0   |
| HLA class II deficiency      | 26  | 11 | 10 | 8  | 4  | 1  | 1   |
| CD40 ligand deficiency donor | 35  | 21 | 17 | 11 | 4  | 3  | 0   |
| Other                        | 111 | 60 | 45 | 28 | 24 | 10 | 0   |

**FIG E5.** Cumulative probability of survival in patients with non-SCID PID after HSCT according to type of T-cell deficiency for the period 1995 to 2005.

**TABLE E1.** Clinical characteristics of patients according to year of graft

| Clinical characteristic               | Related donor                  |                                 |                    | URD            |
|---------------------------------------|--------------------------------|---------------------------------|--------------------|----------------|
|                                       | Genotypically<br>HLA identical | Phenotypically<br>HLA identical | HLA-<br>mismatched |                |
| SCID                                  |                                |                                 |                    |                |
| Years of graft <1995                  |                                |                                 |                    |                |
| Total                                 | 84                             | 33                              | 229                | 15             |
| More than 1 stem cell transplantation | 8                              | 3                               | 43                 | 4              |
| Median age at transplantation (mo)    | 5.8                            | 6.2                             | 7.2                | 13.1           |
| <6                                    | 46                             | 15                              | 87                 | 2              |
| 6-11                                  | 20                             | 17                              | 98                 | 2              |
| 12-18                                 | 8                              | 0                               | 27                 | 6              |
| >18                                   | 8                              | 1                               | 15                 | 5              |
| Year of transplantation               |                                |                                 |                    |                |
| 1968-85                               | 34                             | 14                              | 57                 | 4              |
| 1986-90                               | 27                             | 11                              | 89                 | 0              |
| 1991-94                               | 23                             | 8                               | 83                 | 11             |
| Conditioning                          | 20                             | 12                              | 160*               | 11             |
| Median (range) follow-up (y)          | 8.8 (0.5-27.8)                 | 9.6 (0.5-32.6)                  | 9.3 (0.5-22.3)     | 8.9 (5.3-12.8) |
| 3-Year survival % (95% CI)            | 81 (73-90)                     | 57 (41-78)                      | 49 (43-56)         | 53 (33-86)     |
| Years of graft 1995-1999              |                                |                                 |                    |                |
| Total                                 | 26                             | 21                              | 90                 | 20             |
| More than 1 stem cell transplantation | 3                              | 2                               | 17                 | 2              |
| Median age at transplantation (mo)    | 6.6                            | 4.5                             | 6.9                | 10.1           |
| <6                                    | 12                             | 11                              | 34                 | 6              |
| 6-11                                  | 6                              | 4                               | 40                 | 8              |
| 12-18                                 | 5                              | 2                               | 6                  | 2              |
| >18                                   | 2                              | 3                               | 8                  | 3              |
| Conditioning                          | 7                              | 2                               | 63                 | 15             |
| Median (range) follow-up (y)          | 2.0 (0.4-9.6)                  | 2.5 (0.4-6.2)                   | 4.5 (0.2-10.8)     | 7.1 (0.9-10.4) |
| 3-Year survival % (95% CI)            | 84 (69-100)                    | 80 (62-100)                     | 69 (60-79)         | 68 (48-97)     |
| Years of graft 2000-2005              |                                |                                 |                    |                |
| Total                                 | 25                             | 14                              | 96                 | 46             |
| More than 1 stem cell transplantation | 0                              | 2                               | 23                 | 5              |
| Median age at transplantation (mo)    | 4.9                            | 4.2                             | 7.5                | 9.5            |
| <6                                    | 16                             | 9                               | 33                 | 18             |
| 6-11                                  | 5                              | 2                               | 41                 | 10             |
| 12-18                                 | 2                              | 0                               | 6                  | 7              |
| >18                                   | 2                              | 3                               | 13                 | 11             |
| Conditioning                          | 3                              | 4                               | 78*                | 37             |
| Median (range) follow-up (y)          | 1.0 (0.5-2.1)                  | 1.2 (0.4-4.9)                   | 1.4 (0.2-5.0)      | 1.8 (0.2-5.4)  |
| 3-Year survival % (95% CI)            | 90 (77-100)                    | 83 (58-100)                     | 66 (55-78)         | 69 (54-89)     |
| Non-SCID                              |                                |                                 |                    |                |
| Years of graft <1995                  |                                |                                 |                    |                |
| Total                                 | 103                            | 17                              | 130                | 28             |
| More than 1 stem cell transplantation | 8                              | 2                               | 21                 | 1              |
| Median age at transplantation (mo)    | 30.6                           | 21.9                            | 17.7               | 34.4           |
| <12 mo                                | 29                             | 6                               | 42                 | 5              |
| 12-23 mo                              | 16                             | 3                               | 38                 | 8              |
| 2-3 y                                 | 19                             | 4                               | 27                 | 8              |
| >4 y                                  | 39                             | 4                               | 22                 | 7              |
| Year of transplantation               |                                |                                 |                    |                |
| 1968-85                               | 31                             | 6                               | 21                 | 4              |
| 1986-90                               | 32                             | 6                               | 57                 | 3              |
| 1991-94                               | 40                             | 5                               | 52                 | 21             |
| Conditioning                          | 96*                            | 16                              | 128                | 28             |
| Median (range) follow-up (y)          | 8.6 (0.5-18.6)                 | 9.5 (0.5-14.6)                  | 8.7 (0.1-16.6)     | 9.1 (0.5-13.9) |
| 3-Year survival % (95% CI)            | 72 (63-81)                     | 46 (27-78)                      | 41 (33-51)         | 66 (50-87)     |
| Years of graft 1995-1999              |                                |                                 |                    |                |
| Total                                 | 75                             | 25                              | 66                 | 72             |
| More than 1 stem cell transplantation | 1                              | 6                               | 15                 | 4              |

(Continued)

TABLE E1. (Continued)

| Clinical characteristic                          | Related donor                  |                                 |                    | URD               |
|--------------------------------------------------|--------------------------------|---------------------------------|--------------------|-------------------|
|                                                  | Genotypically<br>HLA identical | Phenotypically<br>HLA identical | HLA-<br>mismatched |                   |
| Median age at transplantation                    | 50.5                           | 19.2                            | 18.2               | 50.1              |
| <12 mo                                           | 19                             | 4                               | 22                 | 10                |
| 12-23 mo                                         | 4                              | 10                              | 18                 | 14                |
| 2-3 years of age                                 | 13                             | 3                               | 10                 | 11                |
| >4 years of age                                  | 39                             | 8                               | 13                 | 37                |
| Conditioning                                     | <b>70*</b>                     | <b>25</b>                       | <b>63</b>          | <b>70</b>         |
| Median (range) follow-up (y)                     | 2.7 (0.2-10.9)                 | 1.8 (0.2-5.5)                   | 2.6 (0.2-10.4)     | 3.8 (0.1-11.2)    |
| 3-Year survival % (95% CI)                       | <b>71 (60-83)</b>              | <b>53 (36-78)</b>               | <b>41 (30-57)</b>  | <b>60 (49-73)</b> |
| Years of graft 2000-2005                         |                                |                                 |                    |                   |
| Total                                            | 73                             | 23                              | 47                 | 124               |
| More than 1 stem cell transplantation            | 6                              | 4                               | 14                 | 17                |
| Median age at transplantation<br>(months of age) | 38.5                           | 24.2                            | 19.7               | 36.5              |
| <12 mo                                           | 19                             | 8                               | 19                 | 23                |
| 12-23 mo                                         | 6                              | 3                               | 9                  | 25                |
| 2-3 years of age                                 | 16                             | 8                               | 9                  | 23                |
| >4 years of age                                  | 31                             | 4                               | 10                 | 52                |
| Conditioning                                     | <b>67*</b>                     | <b>21</b>                       | <b>43</b>          | <b>113</b>        |
| Median (range) follow-up (y)                     | 1.5 (0.0-5.0)                  | 1.2 (0.3-3.9)                   | 2.3 (0.4-5.0)      | 1.4 (0.2-5.0)     |
| 3-Year survival % (95% CI)                       | <b>79 (69-89)</b>              | <b>76 (57-100)</b>              | <b>55 (42-72)</b>  | <b>79 (71-87)</b> |

\*Missing data for 1 patient in this group.

**TABLE E2.** Type of conditioning according to year of transplantation and diagnosis: SCID (1968-2005; N = 699)

|                      | No conditioning<br>(n = 285) | Busulfan contain.<br>(n = 297) | Other chemotherapy<br>(n = 69) | ATG, Campath,<br>or OKT3 only (n = 29) | Other conditioning<br>or n.a. (n = 19) | Stat    |
|----------------------|------------------------------|--------------------------------|--------------------------------|----------------------------------------|----------------------------------------|---------|
| <1995                | 55.09%                       | 44.11%                         | 50.72%                         | 68.97%                                 | 100%                                   | Fisher  |
| 1995-1999            | 24.56%                       | 24.58%                         | 15.94%                         | 10.34%                                 | 0%                                     | 0.00001 |
| 2000-2005            | 20.35%                       | 31.31%                         | 33.33%                         | 20.69%                                 | 0%                                     |         |
| Reticular dysgenesis | 0.7%                         | 3.37%                          | 2.9%                           | 3.37%                                  | 13.79%                                 | Fisher  |
| ADA deficiency       | 14.74%                       | 5.39%                          | 7.25%                          | 5.39%                                  | 13.79%                                 | 0.00001 |
| T-B–                 | 30.88%                       | 29.63%                         | 30.43%                         | 29.63%                                 | 10.34%                                 |         |
| T-B+                 | 49.82%                       | 53.87%                         | 39.13%                         | 53.87%                                 | 48.28%                                 |         |
| Other                | 3.86%                        | 7.74%                          | 20.29%                         | 7.74%                                  | 13.79%                                 |         |
| Geno ident.          | 36.84%                       | 5.05%                          | 11.59%                         | 13.79%                                 | 17.65%                                 | Fisher  |
| Pheno ident.         | 17.54%                       | 2.69%                          | 7.25%                          | 6.9%                                   | 17.65%                                 | 0.00001 |
| URD                  | 6.32%                        | 14.14%                         | 24.64%                         | 13.79%                                 | 0%                                     |         |
| Mismatch             | 39.3%                        | 78.11%                         | 56.52%                         | 65.52%                                 | 64.71%                                 |         |

*contain.*, containing; *n.a.*, not available; *ident.*, identical; *Stat.*, statistic; *Geno.*, genoidential; *Pheno.*, phenoidential; *URD*, unrelated donor.

**TABLE E3.** Type of conditioning according to year of transplantation and diagnosis: non-SCID PID (1968-2005; N = 783)

|           | Conditioning no<br>(n = 40) | Busulfan contain.<br>(n = 499) | Other chemotherapy<br>(n = 116) | ATG, Campath, or<br>OKT3 only (n = 55) | Other conditioning<br>or n.a. (n = 73) | Stat     |
|-----------|-----------------------------|--------------------------------|---------------------------------|----------------------------------------|----------------------------------------|----------|
| <1995     | 22.5%                       | 23.85%                         | 29.31%                          | 81.82%                                 | 100%                                   | $\chi^2$ |
| 1995-1999 | 22.5%                       | 37.47%                         | 31.03%                          | 9.09%                                  | 0%                                     | <0.00001 |
| 2000-2005 | 55%                         | 38.68%                         | 39.66%                          | 9.09%                                  | 0%                                     |          |
| Geno      | 37.5%                       | 31.46%                         | 25%                             | 10.91%                                 | 58.57%                                 | Fisher   |
| Pheno     | 7.5%                        | 9.22%                          | 4.31%                           | 7.27%                                  | 10%                                    | <0.00001 |
| URD Mud   | 32.5%                       | 31.66%                         | 42.24%                          | 7.27%                                  | 0%                                     |          |
| Mismatch  | 22.5%                       | 27.66%                         | 28.45%                          | 74.55%                                 | 31.43%                                 |          |

*contain.*, containing; *n.a.*, not available; *ident.*, identical; *Stat*, statistic; *Geno*, genoidential; *Pheno*, phenoidential; *URD*, unrelated donor.

**TABLE E4.** Outcome of transplantation according to type of conditioning regimen used for patients with SCID and non-SCID PID

| Variable                                  | HR* | 95% CI* | P value* |
|-------------------------------------------|-----|---------|----------|
| SCID                                      |     |         |          |
| Conditioning: no conditioning vs busulfan | 1.4 | 1.0-2.1 | .05      |
| other chemotherapy vs busulfan            | 2.1 | 1.3-3.3 | .002     |
| ATG, Campath, or OKT3 only vs busulfan    | 1.1 | 0.5-2.3 | .84      |
| Non-SCID PID                              |     |         |          |
| Conditioning: no conditioning vs busulfan | 1.4 | 0.7-2.7 | .29      |
| other chemotherapy vs busulfan            | 1.4 | 0.9-2.0 | .12      |
| ATG, Campath, or OKT3 only vs busulfan    | 1.3 | 0.8-2.0 | .33      |

\*Cox proportional hazard model.