# Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: report of the European experience 1968–99

*Corinne Antoine, Susanna Müller, Andrew Cant, Marina Cavazzana-Calvo, Paul Veys, Jaak Vossen, Anders Fasth, Carsten Heilmann, Nicolas Wulffraat, Reinhard Seger, Stéphane Blanche, Wilhelm Friedrich, Mario Abinun, Graham Davies, Robert Bredius, Ansgar Schulz, Paul Landais, Alain Fischer, for the European Group for Blood and Marrow Transplantation and the European Society for Immunodeficiency*

## Summary

**Background** Transplantation of allogeneic haemopoietic stem cells can cure several primary immunodeficiencies. This European report focuses on the long-term results of such procedures done between 1968 and December, 1999, for primary immunodeficiencies.

**Methods** The report includes data from 37 centres in 18 countries, which participated in a European registry for stem-cell transplantation in severe combined immunodeficiencies (SCID) and in other immunodeficiency disorders (non-SCID). 1082 transplants in 919 patients were studied (566 in 475 SCID patients, 512 in 444 non-SCID patients; four procedures excluded owing to insufficient data). Minimum follow-up of 6 months was required.

**Findings** In SCID, 3-year survival with sustained engraftment was significantly better after HLA-identical than after mismatched transplantation (77% *vs* 54%; p=0·002) and survival improved over time. In HLA-mismatched stem-cell transplantation, B(–) SCID had poorer prognosis than B(+) SCID. However, improvement with time occurred in both SCID phenotypes. In non-SCID, 3-year survival after genotypically HLA-matched, phenotypically HLA-matched, HLA-mismatched related, and unrelated-donor transplantation was 71%, 42%, 42%, and 59%, respectively (p=0·0006). Acute graft versus host disease predicted poor prognosis whatever the donor origin except in related HLA-identical transplantation in SCID.

**Interpretation** The improvement in survival over time indicates more effective prevention and treatment of disease-related and procedure-related complications—eg, infections and graft versus host disease. An important factor is better prevention of graft versus host disease in the HLA-non-identical setting by use of more efficient methods of T-cell depletion. For non-SCID, stem-cell transplantation can provide a cure, and grafts from unrelated donors are almost as beneficial as those from genetically HLA-identical relatives.

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*See Commentary page 541*

**Service de Biostatistique et Service d'Immunologie et d'Hématologie Pédiatrique, Hôpital Necker Enfants Malades, Paris, France** (C Antoine MD, M Cavazzana-Calvo MD, S Blanche MD, P Landais MD, A Fischer); **Universitäts-Kinderklinik, Ulm, Germany** (S Müller MD, W Friedrich MD, A Schulz MD); **Department of Paediatric Immunology, Newcastle General Hospital, Newcastle upon Tyne, UK** (A Cant MD, M Abinun MD); **Departments of Immunology and Bone Marrow Transplantation, Great Ormond Street Hospital, London, UK** (P Veys, G Davies MD); **Department of Paediatrics, Academisch Ziekenhuis, Leiden, Netherlands** (J Vossen MD, R Bredius MD); **Queen Silvia Children's Hospital, Göteborg, Sweden** (A Fasth MD); **Department of Paediatrics, Rigshospitalet, Copenhagen, Denmark** (C Heilmann MD); **Wilhelmina Kinderziekenhuis, Utrecht, Netherlands** (N Wulffraat MD); **and Division of Immunology/Haematology, University Children's Hospital, Zurich, Switzerland** (R Seger MD)

**Correspondence to:** Dr Alain Fischer, Service d'Immunologie et d'Hématologie Pédiatrique, Hôpital Necker, 149 rue de Sèvres, 75743 Paris, France.
(e-mail: fischer@necker.fr)

## Introduction

Primary immunodeficiencies are inherited disorders characterised by impairment of innate or adaptive immunity, commonly leading to lethal complications. Transplantation of allogeneic haemopoietic human stem cells can cure most of the lethal forms of immunodeficiencies,[1] including severe combined immunodeficiencies (SCID), several T-cell immunodeficiencies, Wiskott-Aldrich syndrome, phagocyte disorders such as leucocyte adhesion deficiency and chronic granulomatous diseases, haemophagocytic syndromes such as familial lymphohistiocytosis, Chediak-Higashi syndrome, Griscelli's disease, and X-linked lymphoproliferative syndrome. At first, only HLA-identical relatives were used as donors, but the introduction of T-cell depletion of bone marrow in 1981 allowed efficient prevention of graft versus host disease and thus the successful treatment of SCID by transplantation of HLA-mismatched stem cells.[2] The greater availability of unrelated donors has led to more transplants from unrelated donors.[3]

In this study, data gathered in the SCETIDE (Stem Cell Transplantation for Immunodeficiencies) registry were analysed to give the long-term results of human haemopoietic stem-cell transplantations in primary immunodeficiencies in Europe since 1968. The outcome of transplants from donors of various origins—ie, HLA-identical siblings, phenotypically compatible parents, HLA-matched unrelated donors, and HLA-haploidentical family donors—has been assessed. Previous analyses in 1986,[4] in 1990 for SCID (n=183),[5] and in 1994 for other forms of immunodeficiencies (n=149)[6] helped to define prognostic factors related to disease conditions, patients' status before stem-cell transplantation, donor origin, and the transplant procedure. This report, including the previous cases (SCID and non-SCID), is based on the analysis in the long term of a total of 919 patients treated in 37 European centres between 1968 and 1999. The large number of cases registered in the database gives sufficient statistical power for assessment of changing trends in outcome over different periods.

## Methods

### *Patients*

The European Group derived all data from the SCETIDE register, established for the European Group for Blood

and Marrow Transplantation and the European Society for Immunodeficiency. The electronic database was developed to register haemopoietic stem-cell transplantation for primary immunodeficiency. All the centres affiliated to the European Working Party currently undertaking such procedures for SCID and inborn errors were enrolled. Between 1968 and December, 1999, 37 centres in 18 European countries recorded relevant data. Centres included data on children presenting with an immunodeficiency and undergoing haemopoietic stem-cell transplantation. Data collection was continuous and systematic in each centre. Information was gathered on the basis of a questionnaire built up and validated by the European Working Party. Each centre was in charge of the quality control of its own data, undertaken by data managers in the largest centres. The data were then transmitted to the Department of Biostatistics, Hôpital Necker Enfants Malades, Paris, which did an additional assessment of coherence of the data before the analysis.

Of the 1082 transplantations, 566 were done in 475 SCID patients and 512 in 444 non-SCID patients. During the inclusion period, insufficient data were recorded for four procedures (two in SCID, two in non-SCID), which were therefore excluded from this report. The median follow-up after transplantation was 9 years for SCID and 7 years for non-SCID.

### *Procedures*

Marrow was used as the source of haemopoietic stem cells in 88% of transplants, peripheral stem cells in 12%, and cord blood in 0·7%. Of the SCID patients, 107 with HLA-identical related donors, 87 with HLA-mismatched donors, and 11 with unrelated donors did not receive any conditioning regimen. For the other SCID patients, the conditioning regimen consisted of busulphan (8 mg/kg) and cyclophosphamide (200 mg/kg) in most cases, in accordance with the recommendations of the European Group for Blood and Marrow Transplantation and European Society For Immunodeficiency working group.

For non-SCID patients, all but ten received a conditioning regimen consisting of busulphan (16–20 mg/kg) and cyclophosphamide (200 mg/kg). T-cell depletion was used in 91% of HLA-mismatched cases and in 41% of unrelated marrow samples. Methods of T-cell depletion included E-rosetting, soybean agglutination, monoclonal antibodies, or (since 1996) positive selection of CD34-positive cells. In 1986, the group agreed that in non-HLA-identical transplantation, the graft should contain no more than $5\times10^5$ T cells per kg after T-cell depletion. This threshold was changed to $1\times10^4$ T cells/kg in 1998. In-vivo immunosuppression (anti-LFA1 with or without CD2, Campath IG, monoclonal antibodies, or antithymocyte globulin) was given to most non-SCID patients who received an unrelated or an HLA-mismatched graft.

In non-SCID patients, prophylaxis against graft versus host disease after HLA-identical stem-cell transplantation consisted of methotrexate (before 1983) or ciclosporin with or without a short course of methotrexate. No prophylaxis against graft versus host disease was used in SCID patients after an HLA-identical transplantation. All patients who received a graft of haemopoietic stem cells that was depleted of T cells by either monoclonal antibodies or rosetting were treated with ciclosporin A for at least 2 months. Recipients of CD34-selected cells were not given any prophylaxis. Graft versus host disease was graded according to standard criteria.[7,8] Various techniques were used to study chimerism, including karyotyping, assessment of red-blood-cell antigens, immunoglobulin allotypes, HLA typing, and more recently Southern-blot hybridisation or PCR analysis with microsatellite probes as well as FISH, and allele-specific antibodies to HLA.

The development of T and B lymphocytes and their function were analysed by standard methods (T-cell and B-cell markers, in-vitro T-cell proliferation induced by lectin or antigen, serum immunoglobulin concentrations, and serum antibodies after immunisation).

| | Number (% of category) | Related donor | | | Unrelated |
|---|---|---|---|---|---|
| | | Genotypically HLA identical | Phenotypically HLA identical | HLA mismatched | |
| **SCID** | | | | | |
| Total | 475 | 104 | 49 | 294 | 28 |
| Reticular dysgenesis | 12 (3%) | 2 | 1 | 8 | 1 |
| ADA deficiency | 51 (11%) | 19 | 2 | 26 | 4 |
| Low T and low B | 137 (29%) | 32 | 23 | 77 | 5 |
| Low T | 217 (46%) | 39 | 15 | 154 | 9 |
| Other | 58 (12%) | 12 | 8 | 29 | 9 |
| **Non SCID** | | | | | |
| Total | 444 | 148 | 40 | 176 | 80 |
| Wiskott-Aldrich syndrome | 103 (23%) | 33 | 5 | 45 | 20 |
| T-cell deficiencies | | | | | |
| Omenn syndrome | 43 (10%) | 9 | 6 | 20 | 8 |
| PNP deficiency | 4 (1%) | 2 | 1 | 1 | 0 |
| HLA class II deficiency | 52 (12%) | 17 | 10 | 22 | 3 |
| CD40 ligand deficiency | 11 (2%) | 3 | 0 | 0 | 8 |
| Other | 76 (17%) | 19 | 4 | 36 | 17 |
| Phagocytic-cell disorders | | | | | |
| Agranulocytosis | 5 (1%) | 3 | 0 | 2 | 0 |
| Chronic granulomatous disorders | 17 (4%) | 13 | 0 | 0 | 4 |
| Leucocyte adhesion deficiency | 26 (6%) | 9 | 2 | 14 | 1 |
| Haemophagocytic syndromes | | | | | |
| Familial lymphohistiocytosis | 62 (14%) | 19 | 4 | 29 | 10 |
| Chediak-Higashi syndrome | 20 (4%) | 10 | 4 | 2 | 4 |
| XLP (Purtillo) | 2 (1%) | 0 | 0 | 0 | 2 |
| Griscelli's disease | 6 (1%) | 3 | 1 | 1 | 1 |
| Other | 17 (4%) | 8 | 3 | 4 | 2 |

ADA=adenosine deaminase; PNP=purine nucleoside phosphorylase; X-linked hypoproliferative disease.

Table 1: **Type of immunodeficiency, according to donor origin and HLA matching**

### Statistical analysis

Data available as of Dec 1, 1999, with a minimum follow-up of 6 months, were retained for analysis. Engraftment was examined only in patients alive 1 month after transplantation of haemopoietic stem cells. Analysis of acute graft versus host disease was restricted to patients who showed engraftment and were alive 1 month after transplantation. For chronic graft versus host disease, only patients who showed engraftment and were alive 3 months after transplantation were included. Survival times started from the date of the last procedure. The number of previous transplants was introduced as a covariate in multivariate analyses. A centre effect was explored in terms of the number of transplants (50 or more, large centre; less than 50, small centre).

Differences in observed distributions were analysed by $\chi^2$ test. Variables affecting the development of T-cell and B-cell function 6 months after transplantation and acute graft versus host disease were sought with a logistic regression model. Survival was considered when evidence for sustained engraftment was present associated with an improvement of the immunodeficiency condition (labelled as survival in the text). The cumulative survival was estimated by the product-limit method. The log-rank test and Wilcoxon's rank-sum test were used to compare cumulative survival between groups. A Cox's proportional-hazard model was used to assess the affect of independent predictors (demographics, comorbidity, transplant characteristics, and therapy before transplantation) on survival of patients. The SCETIDE database was developed by use of Access software (version 2000). Statistical analyses were done with SAS (version 6.12) and R software for multivariate analyses. GLM and Survival 5 libraries were used.[9,10]

### Role of the funding source

The study had European community support of the database, data collection, and meetings, and support from the European Group for Blood and Marrow Transplantation for meetings.

## Results

Details of diagnosis are shown in table 1 as well as the origin of stem-cell donors. Information on recipient's age at transplantation, number of procedures per patient, and number of procedures undertaken as a function of time is presented in table 2.

### SCID patients

3-year survival with evidence of sustained engraftment and improvement of the immunodeficiency disorder was significantly better for HLA-identical than for HLA-mismatched transplantation (77% *vs* 54%; p=0·002; figure 1). Within the HLA-identical group, 3-year survival after transplantation from genotypically or phenotypically identical related or unrelated donors did not differ significantly (81%, 72%, and 63%, respectively). Significant improvements have occurred over time in survival after both HLA-identical (p=0·04) and non-identical (p=0·0007) stem-cell transplantation (figure 1). SCID phenotype also had an effect on survival after non-HLA-identical stem-cell transplantation (table 3); B(-) SCID had a poorer prognosis than B(+) SCID, confirming and extending a previous observation.[11] Survival rates improved in both SCID phenotypes (data not shown). In the non-HLA-identical setting, use of a myeloablative conditioning regimen had a positive effect on survival in the B(-) SCID group, but it did not reach significance compared with the other SCID groups. For patients with adenosine deaminase deficiency, 3-year survival was 81% for HLA-matched and 29% for HLA-mismatched transplantation. For reticular dysgenesis, 3-year survival was 75% and 29%, respectively.

In Cox's regression multivariate analysis, only age at transplantation and the use of trimethoprim-sulphamethoxazole prophylaxis had a significant effect on survival after related HLA-identical transplantation (table 3). Independent predictors of mortality for SCID patients after a related HLA-mismatched graft are given in table 3. The most powerful predictors of death were B(-) SCID phenotype, the absence of protected environment,

| | Related donor | | | Unrelated donor |
|---|---|---|---|---|
| | Genotypically HLA identical | Phenotypically HLA identical | HLA mismatched | |
| **SCID patients** | | | | |
| Total | 104 | 49 | 294 | 28 |
| More than one stem-cell transplantation | 11 | 4 | 54 | 6 |
| Median age at transplantation (months) | 5·6 | 6·2 | 7·2 | 9·1 |
| <6 | 57 | 23 | 110 | 12 |
| 6–11 | 28 | 20 | 131 | 5 |
| 12–18 | 10 | 1 | 33 | 6 |
| >18 | 9 | 5 | 20 | 5 |
| Year of transplantation | | | | |
| 1968–85 | 36 | 17 | 56 | 4 |
| 1986–90 | 28 | 11 | 91 | 0 |
| 1991–95 | 27 | 10 | 98 | 13 |
| 1996–99 | 13 | 11 | 49 | 11 |
| Median (range) follow-up (years) | 11 (1·0–29) | 11 (2·5–28) | 10 (1·1–30) | 6 (2·2–22·5) |
| **Non-SCID patients** | | | | |
| Total | 148 | 40 | 176 | 80 |
| More than one stem-cell transplantation | 13 | 8 | 33 | 9 |
| Median age at transplantation | 34·6 | 18·3 | 17·5 | 40·7 |
| <12 months | 42 | 11 | 58 | 11 |
| 12–23 months | 20 | 13 | 52 | 17 |
| 2–3 years | 24 | 7 | 32 | 16 |
| ⩾4 years | 62 | 9 | 34 | 36 |
| Year of transplantation | | | | |
| 1968–85 | 31 | 6 | 21 | 4 |
| 1986–90 | 33 | 6 | 53 | 3 |
| 1991–95 | 46 | 10 | 58 | 26 |
| 1996–99 | 38 | 18 | 44 | 47 |
| Median (range) follow-up (years) | 9 (8·8–23) | 5 (0·7–20) | 9 (1·0–18) | 4 (1·5–27) |

Table 2: **Clinical characteristics of SCID and non-SCID patients**

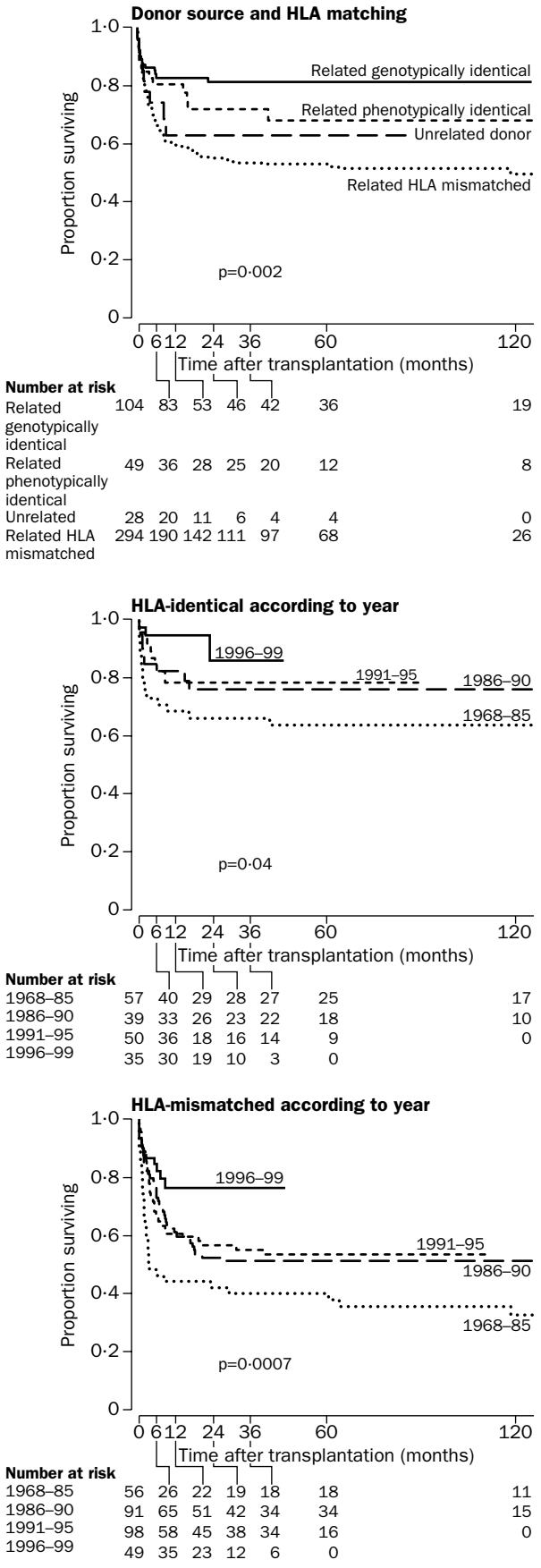



Figure 1: **Cumulative probability of survival in SCID patients, according to donor source (related or unrelated donor) and HLA matching, and year of transplantation**

and the presence of pulmonary infection before transplantation. The probability of survival for the subgroups stratified according to these criteria varied from 74% (all positive criteria) to zero (all negative criteria). A centre size effect was explored by segregation of data from experienced centres (50 or more procedures). In these centres, survival was better for non-HLA-identical transplantation (57% *vs* 43%; p=0·009) and no differences were evident in other types of transplant. The occurrence of acute graft versus host disease (grade 2 or higher) led to poorer survival in related HLA-mismatched transplantation (52% *vs* 77%; p=0·004). No effect was apparent for chronic graft versus host disease, possibly because of lack of statistical power. The frequency of acute graft versus host disease decreased over time after haploidentical transplantation, from 35–40% before 1996 to 22% thereafter (p<0·001), possibly because more stringent methods of T-cell depletion were used. This factor could partly account for the observed better survival with time. The main reported causes of death were infections (56%), graft versus host disease (25%), and B-cell lymphoproliferative syndrome (5%).

The rate of sustained engraftment after HLA-identical stem-cell transplantation was 96% compared with 90% after HLA-non-identical transplantation (odds ratio 2·7, 95% CI 1·2–7·4). In the latter group, only age at transplantation affected the engraftment rate, with a cut-off at 6 months (97% *vs* 86%, patients younger *vs* older than 6 months; odds ratio 5·0 95% CI 1·4–16·7). No significant differences were noted in relation to the use of a conditioning regimen or the SCID phenotype. Engraftment was 88% in SCID B(-), 93% in SCID B(+), and 91% in adenosine deaminase deficiency.

Detailed analysis of the quality of immune reconstitution was beyond the scope of this study and the information provided by the database. Nevertheless, data were analysed at last follow-up. Positive T-cell function was defined as a T-cell count of $1{\cdot}0\times10^9$/L and positive T-cell response to antigens. Positive B-cell function was defined by the absence of intravenous immunoglobulin replacement therapy. There were differences between B(+) and B(-) SCID patients (table 4). T-cell reconstitution arose in most recipients of HLA-identical stem-cell transplantation, but after non-HLA-identical transplantation it arose in a smaller proportion of B(-) SCID than B(+) SCID patients. Similarly, reconstitution of B-cell function was more common both after HLA-identical transplantation and after non-identical transplantation in B(+) SCID than in B(-) SCID.

### *Non-SCID patients*

Figure 2 shows the probability of survival with evidence for sustained engraftment and improvement of the immunodeficiency condition, according to donor origin, in non-SCID patients. Survival was significantly better after HLA-matched than after HLA-mismatched transplantation. 3-year survival after genotypically HLA-matched, phenotypically HLA-matched, HLA-mismatched related, or unrelated-donor transplantation was 71%, 42%, 42%, and 59%, respectively (p=0·0006). No difference in survival between genotypically HLA-identical and unrelated-donor transplantation was noted. 75% of patients with unrelated donors were HLA identical to the donors. An increased risk of death was associated with phenotypically HLA-identical donor transplantation (hazard ratio 2·23, 95% CI 1·3–2·8) and related HLA-mismatched transplantation (2·18, 1·5–3·2) compared with genotypically HLA-identical transplantation. By contrast with SCID, there was no evidence

| | Univariate analysis | | | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | Patients | Deaths | 3-year survival, % (95% CI) | p | Hazard ratio (95% CI) | p |
| **After HLA-identical transplantation** | | | | | | |
| Age at transplantation (months) | | | | | | |
| <6 | 92 | 12 | 85 (77–93) | 0·0004 | 1 | .. |
| 6–11 | 50 | 12 | 73 (59–86) | | 2·2 (0·9–5·6) | 0·12 |
| ⩾12 | 31 | 14 | 53 (35–71) | | 8·3 (2·7–25·4) | 0·0002 |
| Prophylaxis* | | | | | | |
| Yes | 93 | 14 | 79 (72–87) | 0·024 | 1 | |
| No | 35 | 12 | 62 (47–78) | | 3·9 (1·7–9·3) | 0·002 |
| **After related HLA-mismatched transplantation** | | | | | | |
| SCID phenotype | | | | | | |
| B(+) | 159 | 53 | 64 (57–72) | 0·0001 | 1 | |
| B(–) | 107 | 65 | 36 (26–45) | | 2·0 (1·3–2·9) | 0·0007 |
| Protected environment | | | | | | |
| Yes | 258 | 104 | 57 (50–63) | 0·0001 | 1 | |
| No | 20 | 17 | 15 (1–30) | | 5·1 (3·0–8·8) | 0·0001 |
| Pulmonary infection (before transplant) | | | | | | |
| No | 151 | 58 | 59 (51–67) | | 1 | |
| Yes | 106 | 61 | 38 (28–48) | 0·004 | 2·2 (1·5–3·2) | 0·0001 |

*Trimethoprim-sulfamethoxazole.

Table 3: **Factors affecting outcome in SCID patients after HLA-identical or after related HLA-mismatched stem-cell transplantation**

of improvement in survival in non-SCID patients since 1985, whatever the donor origin or the HLA compatibility (figure 3).

In univariate analysis, a moderate effect of the type of immunodeficiency on survival was noted. 3-year survival for phagocytic-cell disorders, haemophagocytic syndromes, Wiskott-Aldrich syndrome, and T-cell deficiencies was 70%, 59%, 62%, and 43% (p=0·02). The cumulative probability of survival did not differ significantly among the groups of immunodeficiencies in separate analyses of genotypically HLA-identical and HLA-mismatched transplants (table 5). There was a tendency toward a poorer outcome for T-cell deficiencies after both types of transplants. HLA class II immunodeficiency within the T-cell-deficiency group seemed to carry a poor prognosis after HLA non-identical transplantation; only 32% of patients survived to 1 year. There was a significant difference in survival between identical and haploidentical transplantation only for patients with Wiskott-Aldrich syndrome (table 5).

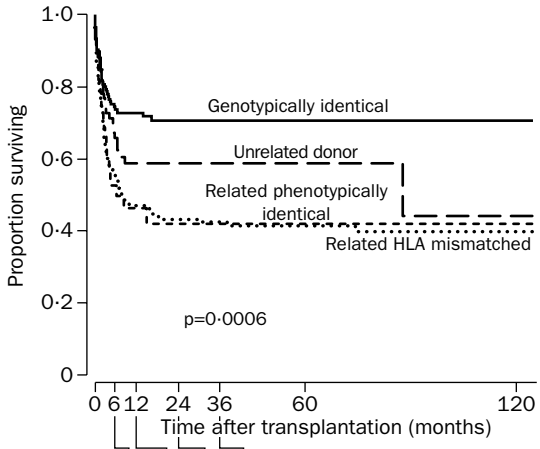
By the Cox's proportional-hazards model, no risk factor was identified after genotypically HLA-identical transplantation or after non-HLA-identical transplantation. No centre effect was apparent in non-SCID patients.

Acute graft versus host disease (grade 2 or higher) indicated poor prognosis whatever the donor origin. Chronic graft versus host disease was not associated with a poor outcome; moreover, the frequency of this complication was low overall (14–32% according to subgroup). The main causes of death were infections (70%; pneumonia in a third of cases), graft versus host disease (9%), toxic effects of the conditioning regimen (9%), B-lymphocyte proliferative syndrome (5%), and rejection (3%).

| | % with reconstitution | | |
|---|---|---|---|
| | B(–) | B(+) | p |
| **HLA-identical transplantation** | (n=48) | (n=34) | |
| T-cell function | 81 | 88 | 0·31 |
| B-cell function | 63 | 88 | 0·017 |
| **Non-HLA-identical transplantation** | (n=39) | (n=79) | |
| T-cell function | 67 | 90 | 0·002 |
| B-cell function | 44 | 66 | 0·02 |

Table 4: **Immunological reconstitution, according to SCID phenotype**

The rate of sustained engraftment after related genotypically HLA-identical transplantation was 99% compared with 81%, 79%, and 75%, respectively, after related phenotypically HLA-identical, unrelated-donor, and related HLA-mismatched transplantation (p=0·001). In the latter group, the engraftment rate was significantly affected by the period during which transplantation was done (53%, 77%, 77%, and 85% in 1968–85, 1986–90, 1991–96, and 1996–99, respectively) from the earlier to the more recent period, indicating improvement in the effect of the immunosuppressive conditioning used to achieve engraftment. No significant difference was noted according to the type of immunodeficiency. Altogether, disease was classified as cured or improved in 94% of patients for whom engraftment was present 6 months or longer after transplantation.




| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Related genotypically identical | 148 | 103 | 69 | 58 | 42 | 31 | 11 |
| Related phenotypically identical | 40 | 20 | 13 | 9 | 7 | 5 | 1 |
| Unrelated | 80 | 48 | 31 | 23 | 18 | 8 | 1 |
| Related HLA mismatched | 176 | 88 | 65 | 54 | 48 | 31 | 9 |

Figure 2: **Cumulative probability of survival in non-SCID patients, according to donor source (related or unrelated donor) and HLA matching**

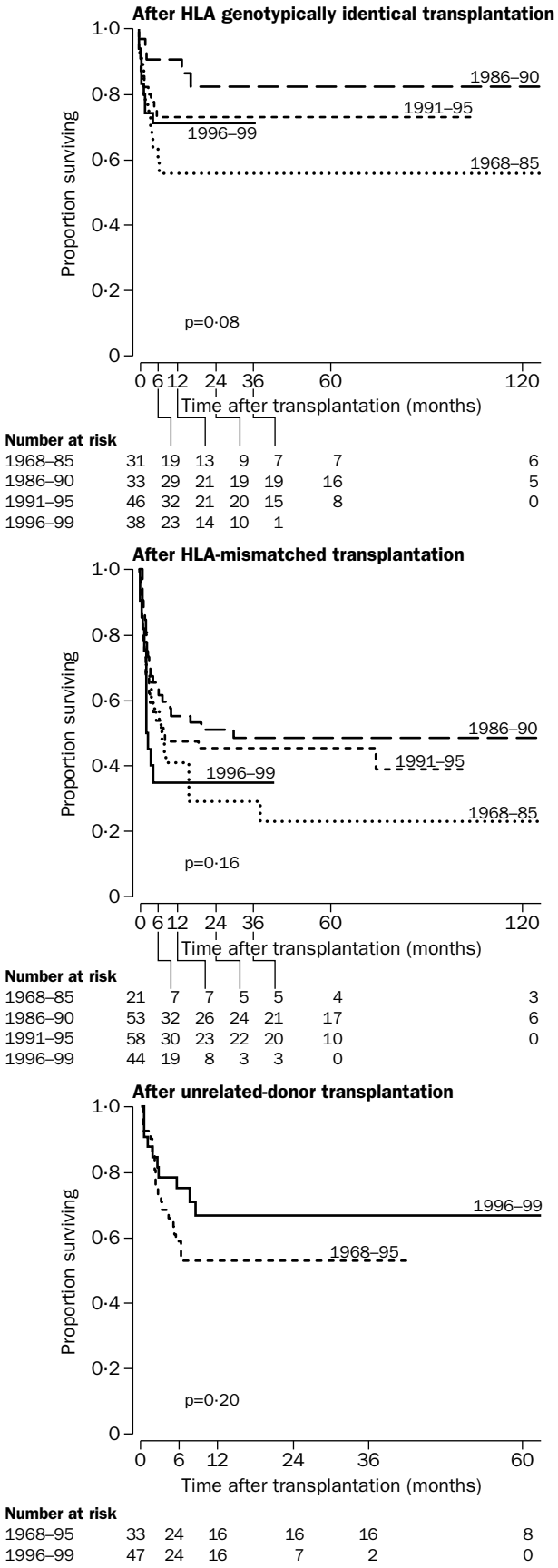



Figure 3: **Cumulative probability of survival in non-SCID patients, according to year of transplant**

| | Genotypically identical | | Related HLA-mismatched | |
|---|---|---|---|---|
| | n | % survival (95% CI) | n | % survival (95% CI) |
| **Disorder** | | | | |
| Phagocytic-cell disorders | 23 | 70 (49–91) | 14 | 69 (44–95) |
| Wiskott-Aldrich syndrome | 32 | 81 (67–94) | 43 | 45 (30–60)* |
| Haemophagocytic syndrome | 32 | 68 (48–87) | 28 | 49 (30–67) |
| T-cell deficiency | 47 | 63 (50–77) | 72 | 35 (24–46) |

*p<0·001 for difference between genotypically identical and related, mismatched transplants.

Table 5: **3-year survival in non-SCID patients, according to primary disease and donor–recipient compatibility**

## Discussion

This study on the outcome of haemopoietic stem-cell transplantation in patients with primary immunodeficiencies is based on the largest cohort of immunodeficient patients treated by transplantation reported so far. This type of analysis is complex because of the array of different immunodeficiency diseases presenting distinct problems both in terms of transplantation procedures and specific risks of complications. For simplicity, patients were classified as having SCID or non-SCID disorders.

The analysis shows that the results of transplantation for SCID have improved over time, as reported by Buckley and colleagues from a single centre.[12] Which factors might account for this improvement? Earlier diagnosis, resulting in healthier patients at the time of transplantation,[13] does not seem to account for better survival in the later years because frequencies of pretransplantation complications and age at transplantation have not changed over time. An improvement in engraftment rate is not the cause, since it remained constant and fairly high over time. Therefore, the observed better event-free survival most likely indicates more effective prevention or treatment of disease-related and transplantation-procedure complications, notably infections and graft versus host disease. An important factor for improved survival is better prevention of graft versus host disease in the non-HLA-identical setting by use of more efficient methods of T-cell depletion (combination of E-rosetting and soybean agglutination and, more recently, positive selection of CD34-positive cells).

Despite incomplete or possibly declining immune function observed late after transplantation in a proportion of SCID patients,[14] very few late deaths were observed. A careful analysis of long-term T-cell and B-cell function is required to assess the risk of late complications. Overall, the outcome of B(+) SCID was significantly better than that of B(-) SCID. Both survival and quality of immune reconstitution were better in B(+) SCID patients, particularly after non-HLA-identical transplantation. These findings extend conclusions drawn from a previous analysis.[11,15] The likely scenario is that several factors account for the survival difference, including lower engraftment rates in B(-) SCID possibly caused by the residual natural-killer-cell activity detectable in most patients with B(-) SCID as well as a higher rate of severe post-transplantation complications.[15,16] Future analysis should focus on the possible relation between SCID variants as defined by mutation analysis and outcome of transplantation, because the genetic causes of most SCID phenotypes have now been identified.[17] For instance, B(-) SCID, characterised by increased cell sensitivity to radiation secondary to mutations of the *DCLRE1C* (Artemis) gene, could carry a poorer prognosis because of defective repair of DNA breaks, occurring around the time of

transplantation, from the effects of chemotherapy, infections, and graft versus host disease.[15,18] Therefore, we cannot yet draw conclusions about the effects of different transplantation strategies—eg, whether myeloablation should be used or not—because results could differ according to the underlying molecular defect.

The use of grafts of stem cells from matched unrelated donors has overall benefited patients who lack an HLA-identical related donor.[3] This benefit may not apply for SCID patients because the outcome of such transplants does not differ from that of non-HLA-identical transplantation done during the same period. The reason may be that engraftment is rarely a problem in SCID patients who require less or no myeloablation and immunosuppression, and graft versus host disease can be efficiently prevented.

An effect of centre size has been noticed, on the outcome of non-HLA-identical transplantation in SCID (but not in other immunodeficiencies). This finding suggests that experience in the care of rare medical disorders benefits the patients. However, experienced centres tend to transplant more difficult cases and this fact might decrease the differences with smaller centres in non-SCID disorders. These findings should be balanced against the need to preserve specialised units in countries with small populations.

Non-SCID immunodeficiency syndromes carry diverse medical problems, including distinct infections (of bacterial, fungal, or viral origin), autoimmunity, and lymphoproliferation. Nevertheless, the study showed that transplantation can provide a cure in all of these disorders, with grafts from unrelated donors being almost as beneficial as genetically HLA-identical grafts. In non-SCID patients, 75% of transplants from unrelated donors were HLA identical. Although this conclusion should certainly take into account the effect of age[3] and clinical condition, it is practically relevant, since it indicates that a search for an unrelated donor is worthwhile (except for SCID as discussed earlier) before consideration of transplantation from a haploidentical donor. Indeed, results for the latter group have not improved over time in the European registry, despite successful engraftment in most cases. Since the numbers of transplants with a haploidentical donor have increased over time, the absence of improvement in survival rate could merely indicate an expansion of transplantation indications to less favourable clinical conditions.

Analysis of results of haemopoietic stem-cell transplantation according to disease does not show obvious disease-specific findings, with the exception of the T-cell immunodeficiency associated with defective expression of HLA class II molecules.[19] In this setting, haploidentical transplantation carries a poor prognosis caused by a mixture of high rate of failure of engraftment and infectious deaths. Of note, no patient older than age 4 years was successfully treated by haploidentical transplantation. In future, a cautious appraisal of transplantation indications in older patients with this disorder is needed.

Analysis of the long-term outcome of transplantation, for non-SCID immunodeficiencies provides good news because no late rejections associated with disease relapses have occurred, with follow-up reaching 20 years and more. This key observation holds true for a vast array of immunodeficiency conditions treated by transplantation, from T-cell immunodeficiency to chronic granulomatous disease and familial haemophagocytic lymphohistiocytosis. A detailed analysis of chimerism and of sequelae caused by disease consequences or transplantation procedures was beyond the scope of this study, but specific studies derived from the European database will be undertaken to address these questions.

Altogether, a retrospective report of the results of a specific procedure has some limitations. Nevertheless, our study provides a picture of what has been achieved so far and what progress has been made. It also permits focus of interest on specific questions to be addressed in selected subsets of patients in the future.

*Contributors*

C Antoine contributed to data analysis and interpretation and writing of the report. S Müller, A Cant, M Cavazzana-Calvo, P Veys, and J Vossen were involved in study design, data collection, and review of the report. A Fasth, C Helman, N Wulffraat, R Seger, S Blanche, M Abinum, G Davies, R Bredius, and A Schultz were involved in data collection and review of the report. W Friedrich contributed to study design, data collection and interpretation, and review of the report. P Landais and A Fischer contributed equally to coordination of study design, data analysis and interpretation, and writing of the report.

*Conflict of interest statement*

None declared.

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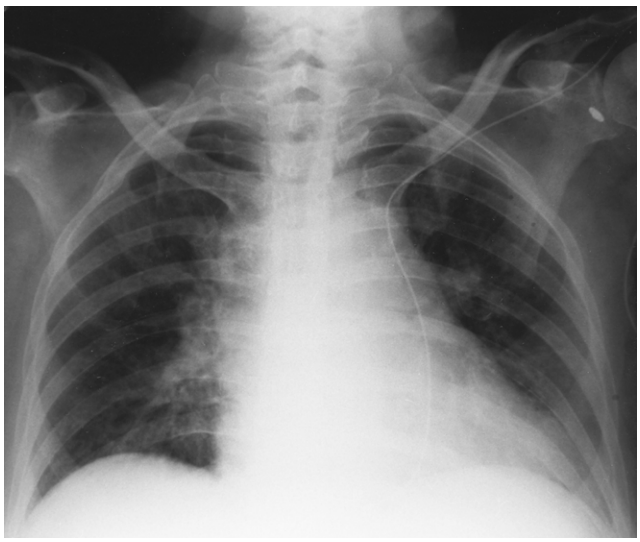
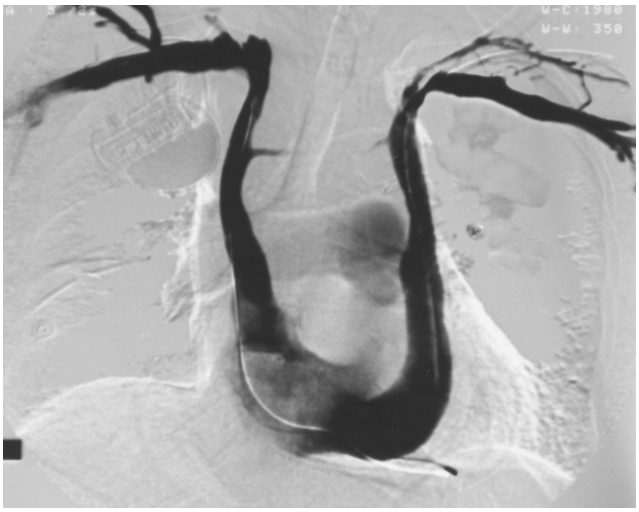
# Clinical picture

## Persistent left superior vena cava

*Hans-Ulrich Schulz, Rene Mantke, Jutta Freitag, Hans Lippert*





A 69-year-old woman was scheduled to undergo cardiac pacemaker implantation because of a sick sinus syndrome. A cardiac stimulation electrode was inserted via the left subclavian vein. Although the intervention was performed under fluoroscopic control, passage to the right in the direction of the superior vena cava was not possible. Instead, the pacemaker electrode took an unusual left-sided downward course crossing to the right at the level of the coronary sinus. This was most likely due to a persistent left superior vena cava that was confirmed by phlebography with injection of contrast medium simultaneously via the right and left cubital veins done after successful cardiac pacemaker electrode placement via the right subclavian vein. Clinicians should be aware of the possibility of a persistent left superior vena cava when placing a central venous line or a cardiac pacemaker electrode. In general, this rare condition does not prevent successful placement of central venous lines or cardiac pacemaker leads.

**Department of Surgery** (H U Schulz, R Mantke, Prof H Lippert) **Magdeburg University Hospital, D-39120, Magdeburg, and Department of Radiology** (Prof J Freitag)**, Schoenebeck County Hospital, D-39218, Schoenebeck, Germany**