# B-cell reconstitution for SCID: Should a conditioning regimen be used in SCID treatment?

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**Bone marrow transplantation has resulted in life-saving sustained T-cell reconstitution in many infants with severe combined immunodeficiency (SCID), but correction of B-cell function has been more problematic. At the annual meeting of the Primary Immunodeficiency Treatment Consortium held in Boston, Massachusetts, on April 27, 2012, a debate was held regarding the use of pretransplantation conditioning versus no pretransplantation conditioning in an effort to address this problem. Reviews of the literature were made by both debaters, and there was agreement that there was a higher rate of B-cell chimerism and a lower number of patients who required ongoing immunoglobulin replacement therapy in centers that used pretransplantation conditioning. However, there were still patients who required immunoglobulin replacement in those centers, and therefore pretransplantation conditioning did not guarantee development of B-cell function. Dr Rebecca H. Buckley presented data on B-cell function according to the molecular defect of the patient, and showed that patients with IL-7 receptor α, ADA, and CD3 chain gene mutations can have normal B-cell function after transplantation with only host B cells. Dr Elie Haddad presented a statistical analysis of B-cell function in published reports and showed that only a conditioning regimen that contained busulfan was significantly associated with better B-cell function after transplantation. The question is whether the risk of immediate and long-term toxicity with use of busulfan is justified, particularly in patients with SCID with DNA repair defects and in very young newborns with SCID who will be detected by using newborn screening.**
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***Key words:*** *Severe combined immunodeficiency, conditioning regimen, hematopoietic stem cell transplantation, B-cell function, immunoglobulin therapy*

Although bone marrow transplantation has resulted in life-saving sustained T-cell reconstitution in most infants with severe combined immunodeficiency (SCID),[1] correction of B-cell function has been more problematic.[2] It has been suggested that the need for posttransplantation immunoglobulin replacement is due to a lack of donor B-cell engraftment, leading some centers to use pretransplantation chemoablative conditioning in an effort to achieve this. However, data to support the efficacy of achieving donor B-cell engraftment with conditioning have been far from clear. Few studies have been published regarding long-term B-cell function in patients with SCID who have received bone marrow transplants.[3-15] A review by Dr Rebecca H. Buckley of 19 reports from Europe and the United States published over the past 2 decades found that the percentage of survivors with B-cell chimerism, function, or both was higher and the percentage requiring immunoglobulin replacement was lower at those centers that used pretransplantation conditioning.[2] However, there were substantial numbers of patients requiring immunoglobulin replacement at all centers, and therefore pretransplantation conditioning does not guarantee development of B-cell function.[3,16] More importantly, survival rates were higher when neither pretransplantation conditioning nor posttransplantation immunosuppressive drugs were used for graft-versus-host disease (GvHD) prophylaxis.[2,17,18] In most of the reviewed reports, there was incomplete information about the underlying molecular defects that caused SCID in those subjects.

This article contains the substance of a debate held at the annual meeting of the Primary Immunodeficiency Treatment Consortium (PIDTC) in April 2012, where Dr Buckley was the proponent of no conditioning and Dr Elie Haddad was the proponent of conditioning, and the arguments posed within are given in the order they were presented.

## NO CONDITIONING

Dr Buckley and her colleagues have recently published the results of a longitudinal study on B-cell function in 125 surviving patients with SCID according to their molecular type who received bone marrow transplants without pretransplantation chemotherapy or posttransplantation GvHD immunosuppressive drugs at her center over a 28-year period.[19] Only 17 of the survivors received HLA-identical marrow, whereas the other 108 received rigorously T cell–depleted haploidentical parental marrow. Table I[19] shows the numbers and percentages with donor B-cell chimerism and the numbers and percentages of patients with disease of each molecular type who currently require intravenous immunoglobulin (IVIg) treatment. The molecular defects

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*Abbreviations used*
CR: Conditioning regimen
GvHD: Graft-versus-host disease
HSCT: Hematopoietic stem cell transplantation
IL-7Rα: IL-7 receptor α
IVIg: Intravenous immunoglobulin
Jak3: Janus kinase 3
OR: Odds ratio
PIDTC: Primary Immunodeficiency Treatment Consortium
RAG: Recombination-activating gene
SCID: Severe combined immunodeficiency

with the highest percentages of donor B-cell chimerism were X-linked SCID, of which 21 (36%) cases had donor B cells, and ADA-deficient SCID, of which 6 (33%) cases had donor B-cell chimerism, with smaller percentages of donor B-cell chimerism found among the other molecular types. Eighty-nine (71%) of the patients do not have donor B-cell chimerism. Nevertheless, only 61 (48.8%) of the 125 survivors require immunoglobulin replacement therapy. Thus 28 of the survivors without B-cell chimerism do not require immunoglobulin replacement. Sixty-two percent of those requiring immunoglobulin replacement had X-linked SCID; 38 of the 58 patients with X-linked SCID are currently receiving it, and 37 of them do not have B-cell chimerism. Other molecular types with a high percentage receiving immunoglobulin replacement had recombination-activating gene (RAG)–deficient SCID (83%) and autosomal recessive SCID of unknown molecular type (73%). By contrast, only 1 (6%) of the 17 patients with IL-7 receptor α (IL-7Rα)–deficient SCID, 4 (22%) of the 18 patients with ADA-deficient SCID, and none of the patients with CD3-deficient SCID require immunoglobulin replacement. Only 1 of the 17 patients with IL-7Rα–deficient SCID, 6 of the 18 patients with ADA-deficient SCID, and none of the patients with CD3 chain–deficient SCID have donor B-cell chimerism. Thus host B cells appear to be able to cooperate with donor T cells and function normally in patients with these particular SCID defects.

A number of studies were performed to examine the reason that B-cell function did not occur in patients with some types of SCID despite the presence of T-cell chimerism.[19] These included blood immunoglobulin measurements; antibody titers to standard vaccines, blood group antigens, and bacteriophage ΦX174; flow cytometry to examine for markers of immaturity, memory, switched memory B cells, and B cell–activating factor of the TNF family receptor expression; B-cell chimerism; B-cell spectratyping; and B-cell proliferation. One of the most significant findings was the inability of the B cells in patients with X-linked and Janus kinase 3 (Jak3)–deficient SCID to isotype switch in response to immunization with bacteriophage ΦX174, whereas this happened normally in patients with the other types of SCID who were immunized with this neoantigen (Fig 1).[20]

We were also able to assess the percentage of switched memory B cells in 55 of the patients (Table II).[19] As can be seen, the molecular types of SCID resulting in the lowest percentages of switched memory B cells are the X-linked SCIDs in patients who are still receiving immunoglobulin therapy ($P \leq .001$), the autosomal recessive SCIDs of unknown molecular type ($P \leq .001$), the ADA-deficient SCIDs ($P = .0017$), and the CD45-deficient SCIDs. The percentages of switched memory B cells are normal for all of the other molecular types except the RAG-deficient, Artemis-deficient, and cartilage-hair hypoplasia patients (not listed) who do not have any B cells.

In summary, these studies found that the most important factor determining whether B-cell function develops in SCID T-cell chimeras is the underlying molecular defect. In some types, host B cells function normally, and therefore there is no need to use ablative measures to ensure donor B-cell chimerism. In those molecular types in which host B-cell function did not develop, donor B-cell chimerism was necessary to achieve B-cell function. However, donor B-cell chimerism developed in 36 (29%) of the 125 patients despite no pretransplantation chemotherapy, and 21 of the 36 had X-linked SCIDs, the most common molecular type of SCID and also the most problematic in terms of B-cell reconstitution.

Now that newborn screening has been recommended by the US Secretary of Health and Human Services, it will be important that infants with SCID who received diagnoses at birth be treated as soon as possible after birth before they become infected with viruses that are difficult to treat.[21] The often-quoted 94% survival rate if patients with SCID undergo transplantation before 3.5 months of life was based on results at Dr Buckley's institution, where none of the SCIDs received pretransplantation conditioning.[14,17,18] The fact that many centers use chemotherapy before transplantation in infants with SCID presents a concerning situation when it comes to treating SCIDs detected by using newborn screening. It will be important that they avoid pretransplantation chemotherapy, particularly myeloablative conditioning, if at all possible because chemotherapy is most toxic in the neonatal period. Omitting toxic chemoablative agents before bone marrow transplantation in patients with SCID allows the patients to avoid later infertility, veno-occlusive disease, and damage to the lungs, endocrine organs, or brain.[22-24]

## FOR CONDITIONING

The optimal outcomes of hematopoietic stem cell transplantation (HSCT) for the treatment of SCID are not only survival but also for patients to lead normal lives without the need for further treatment. Retrospective studies conducted with large cohorts have taught us that this outcome is indeed possible.[8,13,25-28] However, the same retrospective studies have shown that many patients do not have normal B-cell function and still require IVIg substitution therapy. Neven et al[8] have shown, using multivariate Poisson analysis, that abnormal B-cell function was associated with poor outcomes in a retrospective study of 90 long-term SCID survivors of HSCT. Therefore even if the development of normal B-cell function is not required in terms of survival, it remains a logical goal for which to strive in patients with HSCT-treated SCID.

The main goal of HSCT in patients with SCID is to establish T-cell engraftment and normal T-cell function, and the question of the use of a conditioning regimen (CR) versus no CR with regard to B-cell reconstitution is interesting because it has not been proved that the CR influences T-cell reconstitution and survival despite data showing that the use of a CR is associated with better survival in patients with $B^-$ SCID.[25,26]

A review of the literature that addressed B-cell immune reconstitution in long-term survivors was performed. Considering only studies in which at least 5 patients in a group of interest were

**TABLE I.** B-cell chimerism and need for immunoglobulin treatment*

| Group† | No. (%) with donor B-cell chimerism | No. (%) receiving immunoglobulin treatment |
|---|---|---|
| X-linked (n = 58) | 21 (36) | 38 (66) |
| Jak3 deficient (n = 8) | 2 (25) | 3 (38) |
| IL-7R deficient (n = 17) | 1 (6) | 1 (6) |
| ADA deficient (n = 18) | 6 (33) | 4 (22) |
| CD3 chain deficient (n = 3) | 0 | 0 |
| RAG1/2 deficient (n = 6) | 1 (17) | 5 (83) |
| Autosomal recessive (n = 11) | 3 (27) | 8 (73) |
| CD45 deficient (n = 1) | 0 | 1 (100) |
| Artemis (n = 1) | 1 (100) | 0 |
| CHH (n = 1) | 0 | 1 (100) |
| Unknown (n = 1) | 1 (100) | 0 |
| Totals (n = 125) | 36 (29) | 61 (49) |

*CHH*, Cartilage-hair hypoplasia.
*Reproduced with permission from Buckley et al.[19]
†The distribution of the 17 HLA-identical transplants is as follows: 5 among the X-linked, 5 among the ADA-deficient, 3 among the autosomal recessive, 2 among the Jak3-deficient, 1 among the IL-7Rα–deficient, and 1 among the RAG2-deficient groups.

analyzed, 14 publications were reviewed, and data on normal B-cell function as a function of the CR and B-cell chimerism were extracted and presented in Tables III to V.[2,3,6-13,25,27-29] Of these, 2 references were excluded, those of Antoine et al[25] and Neven et al,[8] because the data required for the assessment were not included in these reports. In some studies the data on normal B-cell function as a function of the CR and B-cell chimerism were simply extracted and used as is, whereas for other studies, the data contained in the tables and the bodies of the articles required reanalysis. Patients were considered to have normal B-cell function if they were off IVIg replacement therapy. CRs used among the studies were very heterogeneous. Because a part of the question debated here concerns the necessity or not of using a myeloablative CR to obtain B-cell engraftment and B-cell function, it was decided that patients who received a CR that did not contain busulfan were grouped with patients who did not receive any CR. Pooled odds ratios (ORs; standard and Peto OR) as association estimates were calculated by using a random effects model with inverse variance weighting according to the method of DerSimonian and Laird.[30] Statistical analyses used Stata/SE 11 software (StataCorp, College Station, Tex).

## Analysis of the literature

The question of the use of a CR versus no CR should only be debated in the absence of an HLA-identical related donor because survival in that situation without a CR can be as high as 100%, with most patients having normal B-cell function and an engraftment of donor B cells in 40% to 50% (Table III).

The pertinent issue is the need for using a CR versus no CR for B-cell reconstitution in patients with SCID with donors other than HLA-identical related donors. On this matter, there are several key questions.

## Is normal B-cell function more frequent if a busulfan-containing CR has been used?

This question is indeed crucial, and there are no published data that specifically address it. Nevertheless, compilation of data in the literature seems to show that use of a CR is associated with a higher frequency of normal B-cell function in long-term survivors (Table IV). Indeed, in 7 published studies one can find that in the presence of a busulfan-containing CR, B-cell function was found to be normal in 85% of 139 patients overall (Table IV), ranging from a high of 96% (26/27)[7] to a low of 44% (4/9),[3] whereas in the absence of a CR (or with a non–busulfan-containing CR), B-cell function was found to be normal in a much lower percentage of patients: 33% of 57 patients overall, ranging from a high of only 50% (4/8 and 5/10, respectively) for 2 of the 8 studies[3,9] to a low of 0% (0/1 and 0/2, respectively) in 2 studies.[11,27] Normal B-cell function was thus significantly associated with the use of a busulfan-containing CR (pooled OR, 7.9; 95% CI, 3.0-21.0; $P < .0001$). In a study by Buckley et al,[13] which included the largest cohort of patients who did not receive any CR but that was not considered in the primary analysis because HLA-identical related HSCTs were mixed with other HSCTs, 37% (27/72) of patients had normal B-cell function. Also, in the multicenter study by Haddad et al,[28] 48% (13/27) of patients who did not receive any CR had normal B-cell function, whereas B-cell function was normal in 64% (57/89) of patients who received a CR, although data from this study, retrieved from personal notes from the author, were not included either. Even when these 2 studies with large cohorts were taken into account in the analysis (Table IV), there was a doubling in the percentage of patients with normal B-cell function (77% [175/228]) who had received a CR compared with those patients who had not received a CR (38% [59/156]), and the data remained significant (pooled OR, 3.7; 95% CI, 2.0-6.0; $P < .0001$).

## Is it possible to have normal B-cell function in the absence of B-cell engraftment?

To answer this question, data from 9 studies presented in Table V were evaluated. In the absence of a CR, of a total of 54 evaluable patients, 46 (85%) did not achieve B-cell engraftment, and of these, only 24% (11/46) had normal B-cell function, whereas among the 15% (8/54) of patients with B-cell engraftment, 88% (7/8) had normal B-cell function. B-cell engraftment was thus significantly associated with normal B-cell function in the absence of a CR (pooled OR, 6.2; 95% CI, 1.3-30.9; $P = .02$). In the presence of a CR, the percentage of patients who did not have any B-cell engraftment was greatly reduced to 29% (40/139), yet of these, 53% had normal B-cell function, and among the 71% of patients (99/139) with B-cell engraftment, 96% (84/87 evaluable patients) had normal B-cell function. Thus B-cell engraftment was also significantly associated with normal B-cell function in the presence of a CR (pooled OR, 8.8; 95% CI, 3.1-24.5; $P < .0001$). Therefore it is possible to have normal B-cell function in the absence of B-cell engraftment that can occur both in the absence or presence of a CR, but it is much more likely to occur in the presence of B-cell engraftment (pooled OR, 13.3; 95% CI, 5.6-31.6; $P < .0001$).

## Does a CR induce B-cell engraftment more frequently?

The data in Table V shows that B-cell engraftment increased from 15% (8/54) of patients without a CR to 71% (99/139) of patients who received a CR. If we compare the individual studies, this ranged from a high of 89%[7] to a low of 53%,[11] with the

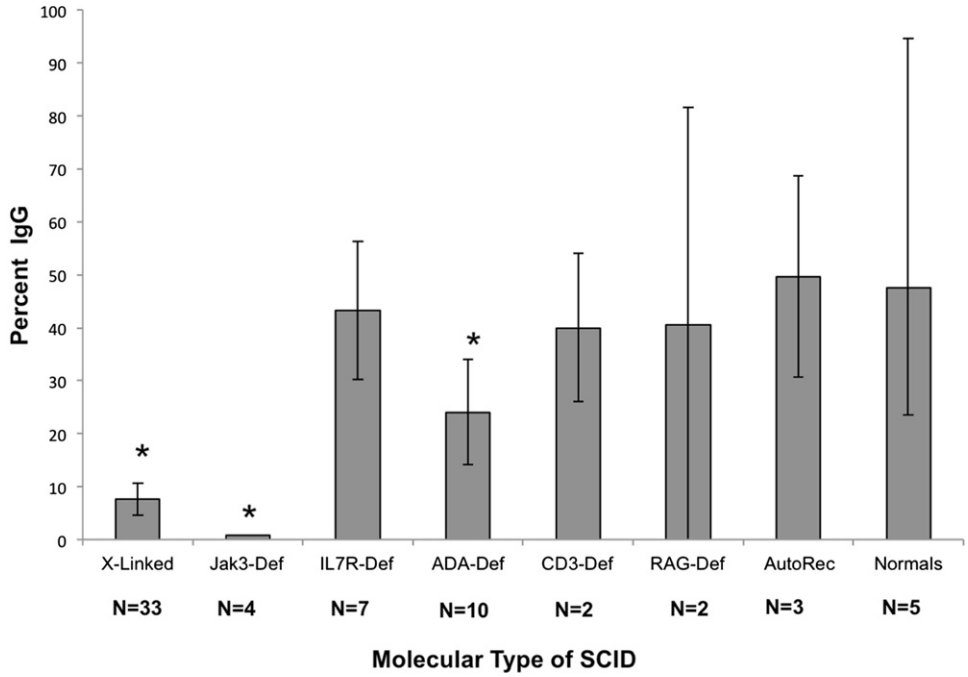



**FIG 1.** Antibody responses to bacteriophage ΦX174 in all 61 patients with SCID immunized with this vaccine after transplantation. The mean percentages of IgG antibody made after the second immunization were significantly (*) lower than normal values in patients with Jak3-deficient ($P < .0001$) and X-linked ($P < .0001$) SCIDs and those with ADA-deficient ($P = .0475$) SCID. Those with Jak3-deficient SCID had an even lower mean percentage of IgG antibody than those with X-linked SCID ($P = .0156$). All other comparisons were not significantly different from healthy control subjects.[20] All patients have donor T cells and good T-cell function.

**TABLE II.** Percentages* of switched memory B cells†

| Molecular type of SCID | No. | Mean | SD | SEM |
|---|---|---|---|---|
| ADA deficient | 6 | 27.67‡ | 10.60 | 4.33 |
| CD3 chain deficient | 2 | 56.75 | 1.85 | 1.31 |
| IL-7Rα deficient | 8 | 48.79 | 12.41 | 4.39 |
| Autosomal recessive | 4 | 11.05§ | 3.69 | 1.85 |
| CD45 deficient | 1 | 8.40 | NA | NA |
| Jak3 deficient | 3 | 30.87 | 13.99 | 8.08 |
| X-linked receiving immunoglobulin | 21 | 11.41§ | 11.16 | 2.44 |
| X-linked not receiving immunoglobulin | 10 | 34.68 | 22.26 | 7.04 |

*NA*, Not applicable for statistics because there is only 1 patient of this type.
*Normal adult mean % and range: 51.4 (32.3-70.5).
†Reproduced with permission from Buckley et al.[19]
‡$P = .0017$.
§$P < .0001$.

exception of one study[3] (11% [1/9 patients]) in which, interestingly, only patients with $B^+$ SCID were analyzed.

This analysis of the literature clearly shows that the use of a CR is associated with a greater chance that the patient will have B-cell engraftment and function. It is true that these data also show that a CR does not guarantee B-cell engraftment. In addition, patients undergoing transplantations without a CR do not receive any GvHD prophylaxis.[2] However, there are no data demonstrating or suggesting that T-cell reconstitution occurs more rapidly in the absence of a CR.

## Issues to consider for the use of a CR

Despite the fact that some of the combined published study data are statistically significant, one should consider these numbers with caution because individual study data taken from the analyzed articles were shown not to be significant for the questions raised in this article for the following reasons: (1) the cohorts studied were too small to reach any significance; (2) only 1 CR strategy was used (CR or no CR) at 1 center, making any comparison impossible; (3) this was not the objective of the study, and B-cell function as a function of the CR was not analyzed; or (4) HLA-identical related HSCTs were mixed together with other HSCTs. Another difficulty is the fact that CRs differed between and also within studies. Should we consider that patients receiving an 8 mg/kg total dose of busulfan be analyzed together with those receiving a total dose of 16 mg/kg? Interestingly, the studies in which the percentage of patients with normal B-cell function was higher[7,27] were those in which patients received 16 mg/kg busulfan and 200 mg/kg cyclophosphamide (Bu16Cy200).

Furthermore, all patients with SCID should not be analyzed in the same way. Indeed, B-cell engraftment and B-cell function could be different in different molecular types of SCID. Unfortunately, the information given in the literature did not allow us to separate the data for the different SCID groups at the clinical or molecular levels.

The higher number of infants with SCID who receive diagnoses early will force us to address whether we should consider the use of a CR in this patient population. Myers et al[14] have shown that for 21 neonatal infants with SCID who received an HLA-identical related bone marrow transplant (n = 2) or a T cell–depleted HLA-haploidentical bone marrow transplant (n = 19) without any CR, survival was 95%. Only 7 of the 20 long-term survivors did not require IVIg. Therefore one could consider that a CR would be

**TABLE III.** B-cell chimerism and B-cell function after HLA-identical related HSCT in patients with SCID

| Reference | No. | B-cell chimerism* | Normal B-cell function | Percentage (no.) of normal B-cell function |
|---|---|---|---|---|
| Haddad et al[3] | 5 | 1 D | 1/1 | 60% (3) |
| | | 4 R | 2/4 | |
| Grunebaum et al[27] | 12† | 3 D | 3/3 | 90% (11) |
| | | 9 R | 8/9 | |
| Mazzolari et al[7] | 8‡ | 3 D | 3/3 | 100% (8) |
| | | 5 R | 5/5 | |
| Friedrich et al[29] | 6 | 6 D | 5/6 | 80% (5) |
| Patel et al[9] | 5 | 1 D‖ | 3 | 60% (3) |
| Patel et al[10] | 5§ | 3 D | 3/3 | 80% (4) |
| | | 2 R | 1/2 | |
| Buckley et al[13] | 12 | 5 D | ND | ND |
| | | 7 R | | |
| O'Marcaigh et al[6] | 6 | 1 D | 1/1 | 17% (1) |
| | | 5 R | 0/5 | |
| Total | 59 (CR = 9) | 23/55 (42%) D | 17/18 (94%)¶ | 74% (35/47) |
| | | 32/55 (58%) R | 16/25 (64%)¶ | |

*D*, Donor; *ND*, no data; *R*, recipient.

*For B-cell chimerism, in most studies it was reported that B cells were of recipient or donor type, whereas in others it was reported in terms of "mixed," in which case we considered that there was an engraftment, or "traces," in which case we considered that there was no engraftment. When a percentage was given, all patients with donor percentages of greater than 10% were included in the category "Donor" in Tables III and V.

†Three of 12 patients received a CR.

‡One of 8 patients received a CR.

§Five of 5 patients received a CR.

‖Only 1 of 5 patients was evaluated for B-cell chimerism.

¶For the 43 patients in whom both B-cell function and B-cell chimerism data were available, 94% of those with B-cell engraftment had normal B-cell function compared with 64% of these with host B cells (pooled Peto OR, 13.2; 95% CI, 1.5-117.5; $P = .02$). However, this association could be ascribed to data from only 1 study in Athabascan subjects with SCIDs in which B-cell function was absent in all 5 (probably Artemis SCID) patients without B-cell engraftment.[6]

**TABLE IV.** Influence of CR on B-cell function in patients with SCID with donors other than HLA-identical related donors

| | No CR (or no myeloablative CR) | | CR (containing Bu) | |
|---|---|---|---|---|
| Reference | No. | Normal B-cell function, % (n) | No. | Normal B-cell function, % (n) |
| Haddad et al[3] | 8 | 50% (4) | 9 | 44% (4) |
| Grunebaum et al[27]* | 1 | 0% (0) | 43 | 95% (41) |
| Mazzolari et al[7] | 5 | 20% (1) | 27 | 96% (26) |
| Slatter et al[11] | 2 | 0% (0) | 32 | 78% (25) |
| Friedrich et al[29] | 12 | 33% (4) | 13 | 92% (12) |
| Patel et al[9] | 10 | 50% (5) | ND | ND |
| Patel et al[10] | ND | ND | 12 | 67% (8) |
| Dvorak et al[12] | 10 (nma) | 40% (4) | ND | ND |
| O'Marcaigh et al[6] | 9 (nma) | 11% (1) | 3 | 67% (2) |
| Buckley et al[13] | 72 | 37%† (27) | ND | ND |
| Haddad et al[28]‡ | 27 | 45%† (13) | 89* | 64%* (57) |
| Total 1† | 57 | 33% (19) | 139 | 85% (118) |
| Total 2† | 156 | 37% (59) | 228 | 77% (175) |

*ND*, No data; *nma*, nonmyeloablative CR.

*The information regarding the dose of busulfan used in the CR was obtained by directly contacting the first author of this article.

†Total 1 does not include the data from Buckley et al[13] and Haddad et al,[28] whereas total 2 includes the data from all references.

‡The information on B-cell function as a function of the CR was unpublished data from Dr Haddad.

unnecessary for these patients. On the other hand, it is also possible that this high survival rate was due to the good clinical condition in which these neonates underwent transplantation, and therefore a CR could potentially be used without causing GvHD or mortality but rather induce better long-term B-cell function. However, the use of a CR in neonates is further complicated by the fact that little is known regarding the pharmacokinetics of busulfan in neonates.

Altogether, from a clinical standpoint, we can consider that the literature provides information that tends to show that a CR is beneficial in terms of B-cell reconstitution for patients with SCID and that perhaps the use of a fully myeloablative CR (ie, with Bu16) is the best strategy to adopt to obtain the greatest chance for B-cell reconstitution. One might question whether a CR or the intensity of a CR should be discussed according to the molecular type of SCID. Certainly, in patients with SCID who have abnormal DNA repair, such as Artemis, one could question the long-term toxicity of a myeloablative CR. Also, one should await upcoming retrospective studies that will specifically address the long-term severe neurologic and developmental side effects in patients with DNA repair abnormalities and whether these long-term complications are associated with the use of a CR or more specifically a myeloablative CR.

These questions and hypotheses should be addressed in well-designed retrospective studies by using registries with enough patients to ask precise questions, such as which type of CR is better for a given type of SCID instead of the global question posed in this debate (ie, CR vs no CR in SCID) that, even with statistically significant data, does not allow one to choose the best strategy for a given patient.

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**TABLE V.** B-cell function and B-cell chimerism in patients with SCID with donors other than HLA-identical related donors

| | No busulfan | | | Busulfan | | |
|---|---|---|---|---|---|---|
| **Reference** | **No.** | **B-cell chimerism*** | **Off IVIg** | **No.** | **B-cell chimerism*** | **Off IVIg†** |
| Haddad et al[3] | 8 | 2 D<br>6 R | 2/2 D<br>2/6 R | 9 | 1 D<br>8 R | 1/1 D<br>3/8 R |
| Grunebaum et al[27] | 1 | 0 D<br>1 R | 0/1 R | 43 | 35 D<br>8 R | 23/23 D<br>2/2 R |
| Mazzolari et al[7] | 5 | 0 D<br>5 R | 1/5 R | 27 | 24 D<br>3 R | 23/24 D<br>3/3 R |
| Slatter et al[11] | 2 | 0 D<br>2 R | 0/2 R | 32 | 17 D or M<br>15 R (5 T) | 17/17 D<br>8/15 R |
| Friedrich et al[29] | 12 | 2 D<br>10 R | 2/2 D<br>2/10 R | 13 | 11 D<br>2 R | 11/11 D<br>1/2 R |
| Patel et al[9] | 7 | 3 D (90-12-11‡)<br>4 R | 2/3 D<br>2/4 R | ND | ND | ND |
| Patel et al[10] | ND | ND | ND | 12 | 9 D (100-45-29-19‡)<br>3 R | 7/9 D<br>1/3 R |
| Dvorak et al[12] | 10 | 1 D<br>9 R (or T) | 1/1 D<br>3/9 R | ND | ND | ND |
| O'Marcaigh et al[6] | 9 | 0 D<br>9 R | 1/9 R | 3 | 2 D<br>1 R | 2/2 D<br>0/1 R |
| Total | 54 | 8 D (15%)<br>46 R (85%) | 7/8 (88%)<br>11/46 (24%) | 139 | 99 D (71%)<br>40 R (29%) | 84/87 (97%)<br>18/34 (53%) |

*D*, Donor; *M*, mixed; *ND*, no data; *R*, recipient; *T*, traces.

*For B-cell chimerism, see the legend of Table III.

†For many patients, the information was not available in the articles, explaining the discrepancy sometimes observed between the number of patients with a given chimerism and the number of patients for whom B-cell function (off IVIg replacement) was given.

‡Corresponds to the chimerism of B cells given in percentage in the article each time for a patient.

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