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Induction of Remission of Severe and Refractory Rheumatoid Arthritis by Allogeneic Mixed Chimerism

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This report describes the first allogeneic hematopoietic stem cell transplantation (HSCT) performed for the indication of rheumatoid arthritis (RA). We used nonmyeloablative allogeneic HSCT to treat a 52-year-old woman who had treatment-refractory RA and a poor prognosis (24 swollen and 38 involved joints). She was treated with fludarabine, cyclophosphamide, CAMPATH-1H, and CD34-selected HSCT (8 million CD34+ donor cells/kg); the donor was the patient's HLA-matched, rheumatoid factor–negative sister. One year post-HSCT, the patient has had no infection except dermatomal varicella-zoster virus infection and no acute or chronic graft-versus-host disease (GVHD). Her RA has remained in remission with no immunosuppressive or immunomodulatory medications. The patient is a mixed chimera, with 55% donor T (CD3+) cells and 70% donor myeloid (CD33+) cells. This is the first published report of allogeneic HSCT performed for the indication of RA. Mixed chimerism has resulted in marked amelioration of RA, without GVHD.

Hematopoietic stem cell transplantation (HSCT) for the treatment of autoimmune diseases has been overwhelmingly autologous, due to safety reasons. Four hundred ninety-five autologous HSCTs, but no allogeneic HSCTs, for the treatment of autoimmune disease have been reported to the European Bone Marrow Transplant international registry database in Basel, Switzerland (Passweg J: personal communication). Results of autologous HSCT have varied according to the disease and the conditioning regimen used. For patients with rheumatoid arthritis (RA), use of a regimen of cyclophosphamide (200 mg/kg) and antithymocyte globulin has resulted in marked clinical improvement, although the majority of patients experience a relapse within 1–2 years after autologous HSCT (1–3). The regimen has been well tolerated, with no mortality reported in >70 patients with RA who underwent HSCT (4).

Because the long-desired goal of curing RA remains elusive with the current autologous HSCT regimens, we initiated a nonmyeloablative allogeneic HSCT protocol for patients with severe and refractory RA. The protocol is designed to minimize both conditioning regimen–related toxicity and graft-versus-host disease (GVHD) by using nonmyeloablative stem cell transplantation (NST) and a CD34-selected (i.e., lymphocyte-depleted) HLA-matched sibling graft, respectively. The goal of the treatment is to determine the effect of mixed chimerism, in which donor and recipient hematopoiesis coexists in patients with RA.

Case reports of allogeneic HSCT performed for a hematologic indication such as aplastic anemia in patients with coexistent RA have described a drug-free and durable complete remission in the majority of patients who were available for long-term followup (5,6). In those cases in which relapse occurred after allogeneic HSCT, the donor's rheumatoid factor (RF) status either was not reported, or the donor was RF positive (7,8). Despite their potential for being curative, allogeneic HSCTs are traditionally associated with a high risk of mortality, attributable to both the conditioning regimen and GVHD. Because of these toxicities, conventional allogeneic HSCT has not been considered appropriate for patients with RA (9). However, newer, less intensive methods of allogeneic stem cell transplantation (so-called nonmyeloablative transplantation) have been introduced in order to reduce morbidity and mortality

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(10). We used strategies that minimize the risk of both conditioning regimen–related toxicity and GVHD to achieve mixed chimerism, and now present the first published report of allogeneic HSCT using an HLA-matched sibling donor, for the indication of RA.

CASE REPORT

The patient was a 52-year-old woman in whom prior autologous HSCT using a conditioning regimen of cyclophosphamide (200 mg/kg) and equine antithymocyte globulin (90 mg/kg) had failed 4 years earlier. Thereafter, she underwent treatment with infliximab, methotrexate, leflunomide, prednisone, and oral and intravenous cyclophosphamide, which subsequently failed. The patient then underwent NST with 8 million CD34+ donor cells/kg obtained from her HLA-matched, RF-negative sister. The donor graft was mobilized with granulocyte colony-stimulating factor (G-CSF; 10 μg/kg/day) for 6 consecutive days. Stem cell apheresis was performed on days 4, 5, and 6 of treatment with G-CSF. The total pre- and postselection CD34+ hematopoietic stem cell counts were 11.3×10^6/kg and 8.0×10^6/kg, respectively, and the pre- and postselection CD3+ T cell counts were 10.3×10^8/kg and 4.5×10^4/kg, respectively.

The protocol was approved by the US Food and Drug Administration under the Investigational New Drug number 10175 and by the Institutional Review Board. Inclusion criteria were as follows: 1) an established clinical diagnosis of RA according to the American College of Rheumatology (ACR) revised criteria (11), 2) >12 swollen joints from active RA, 3) >20 involved joints (swelling, tenderness, deformity, pain on motion, or decreased motion) despite treatment with methotrexate and/or leflunomide and a tumor necrosis factor α inhibitor, and 4) availability of an RF-negative HLA-matched sibling donor.

The conditioning regimen used was fludarabine (125 mg/m^2), cyclophosphamide (150 mg/kg), and CAMPATH-1H (20 mg). Selection of CD34+ enriched cells from the apheresis product was performed using the Isolex cell separator system (Baxter, Chicago, IL), with the goal of obtaining >10 million CD34+ cells/kg. After HSCT, prophylaxis against infection consisted of aerosolized pentamidine (administered monthly), daily oral vorconazole, and daily oral ganciclovir. Antibiotic prophylaxis was discontinued when the CD4 T cell count increased to >100 cells/ml.

Prior to NST, the patient had 24 swollen and 38 involved joints. Engraftment occurred on day 11. The transplant was uncomplicated, and she has not received a platelet or red blood cell transfusion since day 14. At the time of this report, 1 year post-HSCT, the patient's RA remains in remission. Her only infection was dermatomal varicella-zoster virus infection, which occurred 10 months after allogeneic HSCT and was successfully treated with oral acyclovir. Oral cyclosporin A (CSA) and oral mycophenolate mofetil (CellCept; Hoffman-La Roche, Nutley, NJ) were started 4 days before stem cell infusion as prophylaxis against both rejection (host-versus-graft) and GVHD. CSA and CellCept were discontinued 30 days and 9 months, respectively, after HSCT. There has been no evidence of either acute or chronic GVHD. Hematopoietic donor engraftment has been followed by variable-number tandem repeats of the apoprotein B locus from flow-sorted CD33+ myeloid and CD3+ T cells. Donor CD33+ engraftment was

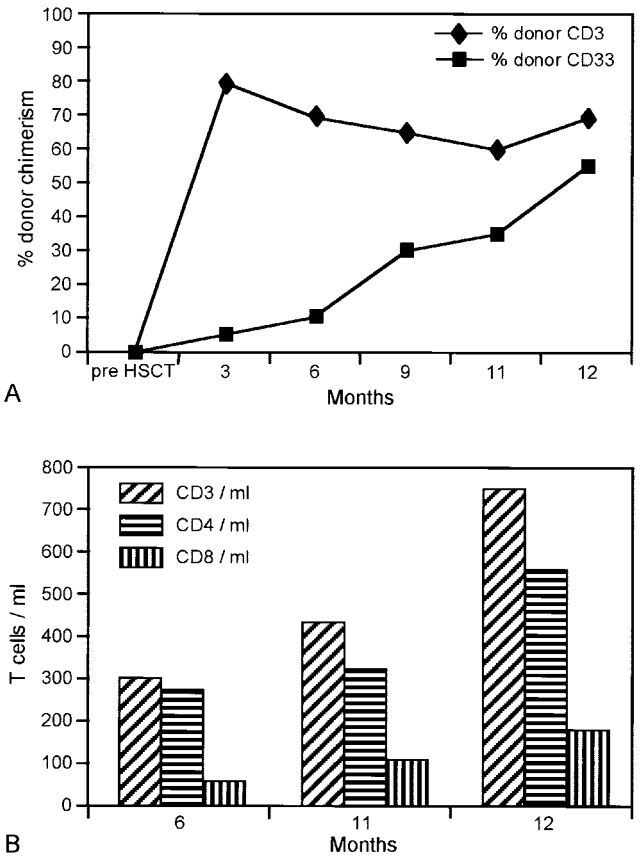

Figure 1. A, Mixed donor chimerism in T lymphocytes and granulocytes 3, 6, 9, 11, and 12 months after nonmyeloablative stem cell transplantation (NST). HSCT = hematopoietic stem cell transplantation. **B,** Total number of T cells in the patient's peripheral blood 6, 11, and 12 months after allogeneic NST.

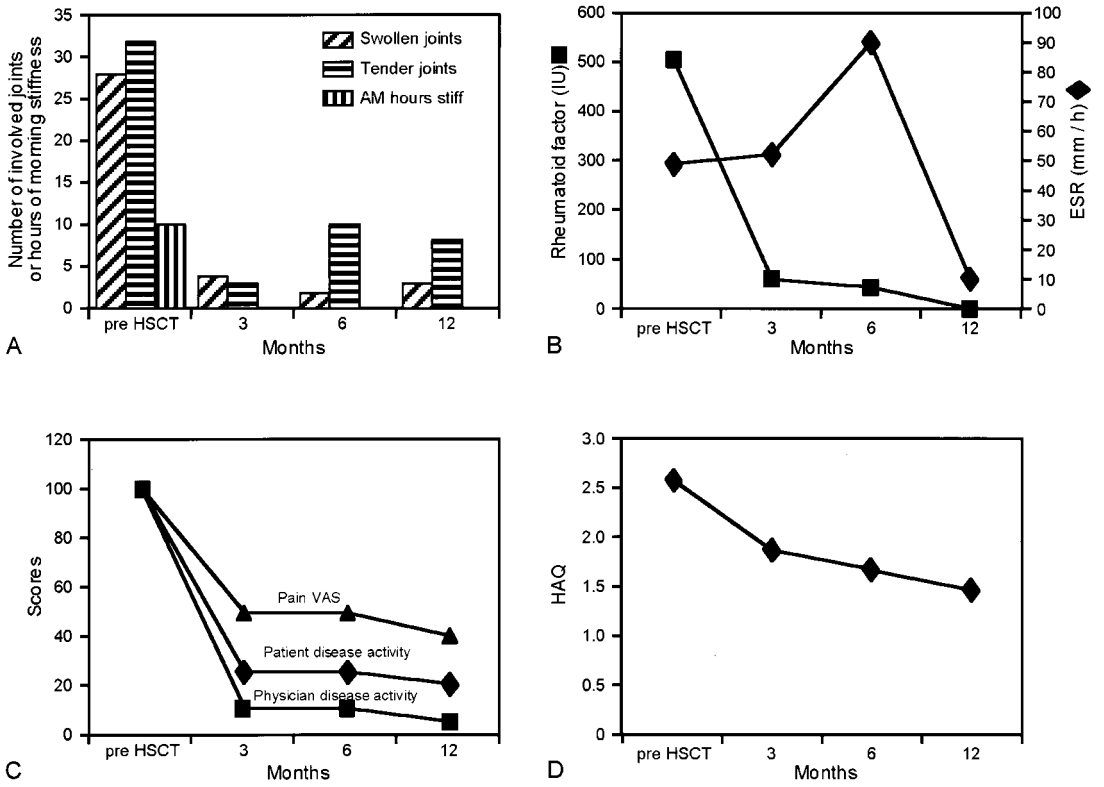

Figure 2. Clinical and laboratory course of the patient after nonmyeloablative stem cell transplantation (examined 3, 6, 9, and 12 months after transplantation). **A,** Number of swollen and tender joints, and duration of morning stiffness. **B,** Rheumatoid factor levels and erythrocyte sedimentation rate (ESR). **C,** Patient's and physician's global assessments of disease status, and patient's awareness of pain as measured on a visual analog scale (VAS). **D,** Health Assessment Questionnaire (HAQ) activities of daily living scores. HSCT = hematopoietic stem cell transplantation.

immediate and predominated early after HSCT, while donor CD3+ T cell engraftment gradually rose from 5% to 55% over 12 months after HSCT (Figure 1A). Immune reconstitution was monitored by the CD3+, CD4+, and CD8+ cell counts (Figure 1B). All antibiotics were discontinued 9 months after HSCT, when the CD4+ T cell count was $>100/\mu$l. One month later, dermatomal varicella-zoster virus infection developed but responded to treatment with oral acyclovir.

Morning stiffness, which had been present for approximately 10 hours daily prior to HSCT, completely disappeared before the patient was discharged from the hospital and has not recurred for more than 1 year after HSCT (Figure 2A). Before HSCT, the patient's swollen and tender joint counts were 28 and 32, respectively. The patient's swollen and tender joint counts markedly decreased prior to hospital discharge, and ACR 70% improvement (12) has been maintained for more than 12 months, in the absence of immunosuppressive therapy (Figures 2A and C). Golf ball–size rheumatoid nodules that were on the extensor surface of the patient's forearm pretransplantation disappeared gradually and were completely gone 9 months after HSCT (Figures 3A and B). The RF level and the erythrocyte sedimentation rate gradually normalized by 12 months after HSCT (Figure 2B). Scores for patient's assessment of pain on a visual analog scale (VAS), patient's assessment of disease activity on a VAS, and physician's global assessment of disease activity markedly improved beginning 3 months after HSCT (Figure 2C). The patient attributed her awareness of pain to permanent foot deformities due to prior erosive joint destruction that caused pain while walking. Before HSCT, the patient's score on the Health Assessment Questionnaire (HAQ) (13) was 2.6; by 12 months after HSCT, the score had improved to 1.5 (Figure 2D).

Skeletal radiographs obtained before HSCT and those obtained at the most recent evaluation (12 months after HSCT) did not differ. Radiographs of the right foot that were obtained before and after HSCT showed

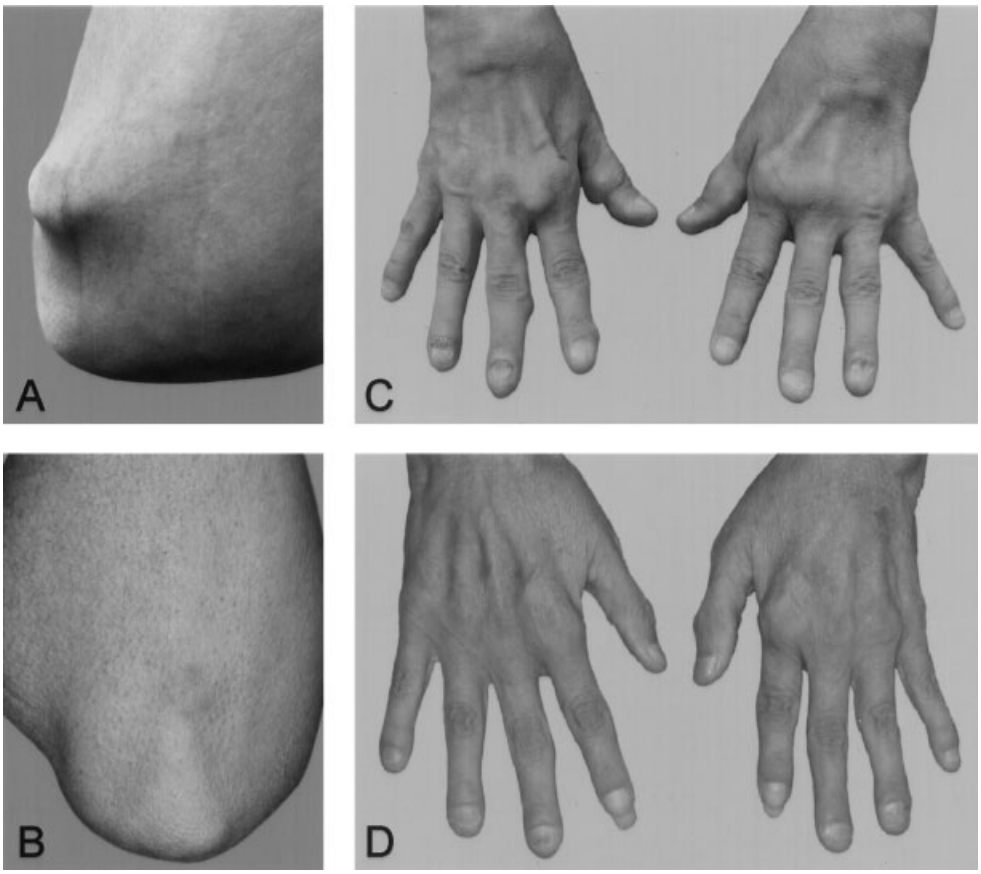

Figure 3. Photographs showing the patient's right elbow and hands before allogeneic stem cell transplantation (**A** and **C**) and 12 months after the procedure (**B** and **D**).

massive erosions of the first and fifth metatarsophalangeal joints, hammertoe deformity in digits 2–5 bilaterally, and severe hallux valgus with bunion formation. The left foot demonstrated dislocation of the second, third, and fourth metatarsophalangeal joints, hammertoe deformity of digits 2–5, and severe hallux valgus.

DISCUSSION

Mixed chimerism (i.e., both recipient and donor hematopoiesis) induces remission of diabetes and lupus-like autoimmune diseases in animal models (14,15). Due to the older age of patients with RA, an NST regimen was designed to induce mixed chimerism with minimal conditioning regimen–related toxicity or risk of GVHD. To avoid transferring occult disease with the graft, the donor must be RF negative. The disappearance of rheumatoid nodules, RF, and morning stiffness, and normalization of the erythrocyte sedimentation rate are consistent with a complete remission. In our patient, the disappearance of RF correlated with increased donor T cell engraftment. Her tender and swollen joint counts improved by 70% according to the ACR criteria but did not completely normalize. Whether this is attributable to residual RA or to tenderness and swelling secondary to permanent deformities and cartilage/bone destruction that were present before HSCT is unknown. The VAS score for residual pain and the abnormalities on the HAQ are more likely secondary to irreversible joint damage and deformity, making some tasks such as walking on deformed feet painful and difficult. This conclusion is supported by the extensive and destructive joint changes that were observed on skeletal radiographs both before and after HSCT.

After 1 year of followup, these data suggest that NST using CD34-selected hematopoietic stem cells may be performed safely, without the development of GVHD or serious infection, and results in mixed chimerism with marked resolution of the disease manifestations of RA.

Further investigation of NST in patients with RA appears to be warranted.

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