

Twenty-year Remission of Rheumatoid Arthritis in 2 Patients After Allogeneic Bone Marrow Transplant

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ABSTRACT. We describe 21 and 19 year followup of 2 patients with severe rheumatoid arthritis (RA) who in 1984 and 1986 underwent allogeneic bone marrow transplantation (BMT) after full myeloablative conditioning, for therapy-induced aplastic anemia. Regarding the arthritis, both patients are well, taking no medications, and free of signs or symptoms of active RA. One patient is in excellent health overall, while the other has coronary artery disease and chronic obstructive pulmonary disease attributable to smoking. We suggest that allogeneic BMT may be a curative treatment for severe RA. (*J Rheumatol* 2006;33:812–3)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
HEMOPOIETIC STEM CELLS

BONE MARROW TRANSPLANTATION
GRAFT-VERSUS-HOST DISEASE

In 1993 we reported 2 patients with severe rheumatoid arthritis (RA) who underwent allogeneic bone marrow transplants (BMT) for therapy-induced severe aplastic anemia (SAA)¹. Both achieved not only hematological remission but also remission of their arthritis, and we raised the possibility that their RA may have been cured. We have had the opportunity to study these patients 19 and 21 years after their BMT. Both remain in remission of their previously severe RA.

CASE REPORTS

Case 1. A woman now aged 49 years had an allogeneic HLA-identical, mixed lymphocyte culture (MLC) nonreactive sibling BMT for gold-induced SAA in January 1984, at the age of 27. At the time of presentation with SAA, in December 1983, her RA was in remission, although bilateral elbow nodules were present and she had damaged wrists (right worse than left) requiring splints. She had had RA for 6 years, treated by gold injections for 5 years. Transplant conditioning was with cyclophosphamide alone, 50 mg/kg/day on Days –5 to –2. Cyclosporine was given from Day –1. The posttransplant course was complicated by acute and later mild chronic graft-versus-host disease (GVHD), successfully treated with corticosteroids and methotrexate. On Day +32, she had a left internal capsule hemorrhage (confirmed on tomography scan) resulting in right hemiparesis, due to thrombocytopenia and severe hypertension. The latter was thought to be secondary to cyclosporine, which was stopped. Antihypertensive therapy was instituted. The weakness resolved, but she continued to have intermittent episodes of confusion and memory loss.

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Her arthritis remained quiescent in the years after the transplant, with no immunosuppression. When examined by a rheumatologist in 1985, there was no evidence of active RA. She continued to have minimal chronic GVHD.

Investigations in September 1985 (18 months after the BMT) showed her serum anti-DNA was 2 u/ml (normal < 10) and her Rose-Waaler (rheumatoid factor, RF) titer was 20 (normal < 32). In 1987 her antinuclear antibody (ANA) titer (on HEp-2 cells) was positive at a titer of 160 with a speckled pattern, but the RF was < 60 kIU/l (normal < 60). In 1993 the RF was “inactive,” the blood cell count normal, and the erythrocyte sedimentation rate (ESR) 18 mm.

In early 1993 she developed blistering of her hands and was diagnosed with biopsy-proven porphyria cutanea tarda (PCT) which was confirmed biochemically. As PCT has a known association with hepatitis C infection, she underwent serological testing and was found to be hepatitis C antibody-positive and to have mildly deranged liver function tests. The source of exposure to the hepatitis C virus may have been from blood products given at the time of the BMT. The PCT was treated by venesection, with good effect. Since then liver function tests have returned to normal without treatment.

In late 1993 she had deteriorating memory, headaches, urinary incontinence, and alien-hand syndrome attributed to cerebrovascular disease. The symptoms resolved except for continuing problems with short-term memory. In 1995 she had an anterior myocardial infarction. She had been a lifelong heavy smoker but gave up smoking at that time. An angiogram showed triple-vessel coronary artery disease and severe left ventricular dysfunction. However, she recovered well from this problem.

Between June 2001 and July 2005 she was admitted to hospital 6 times for treatment of chest infections. *Hemophilus influenzae* was isolated on 3 occasions. The episodes were attributed to chronic obstructive pulmonary disease from her prior smoking. The IgG level was normal at 14 g/l in 2002.

Currently she is functioning well in the community with no evidence of active RA on examination. She takes no regular analgesia. However, she has a subluxed right wrist and wears bilateral wrist splints (unchanged from 1983). There are no nodules. As she is free of arthritic symptoms, she has refused radiographs of her joints. Results of blood tests in May 2005 are given in Table 1. In summary, tests for active RA were normal or negative. The trivial abnormalities in C-reactive protein and ESR can be explained by the chest infection from which she was suffering at the time.

Case 2. A female nurse was 30 years of age when she underwent allogeneic BMT in 1986 for penicillamine-induced SAA¹. At that time she had had severe nodular RA for a total of 9 years and could barely walk 250 meters. She was particularly troubled by active swelling of the metacarpophalangeal

Table 1. Results of recent investigations of 2 patients.

Investigation	Patient 1*	Patient 2	Normal
Rheumatoid factor	4	7	< 14
C-reactive protein	24	3	< 5
ANA	40	320	≤ 40
Liver function tests	Normal	Normal	
Serum albumin, g/l	38	46	35–50
Hemoglobin, g/l	142	122	115–165
White blood cell count, × 10 ⁹ /l	9.4	6.7	4.0–11.0
Platelets, × 10 ⁹ /l	185	275	150–400
ESR, mm/h	24	< 1	< 20

* At time of a chest infection. ANA: antinuclear antibody.

(MCP) and proximal interphalangeal joints and was contemplating retirement on the grounds of incapacity. The donor was her HLA-identical, MLC-compatible brother. Transplant conditioning was with cyclophosphamide alone, 50 mg/kg/day on Days –5 to –2. Cyclosporine 12.5 mg/kg was given from Day –1 to +63, when it was stopped because of toxicity. The procedure was complicated by a series of serious infections and GVHD, but by 2 years after the BMT she was off all medication including corticosteroids. In our initial report, 6 years after the transplant, she was well, working fulltime, and playing tennis. Since then she has been seen intermittently by her rheumatologist, who has noted no evidence of active disease at any time. Now, 13 years later (19 years after the transplant), she remains well and continues to work full-time as a registered nurse. She regularly walks 3.5 km and takes no medications.

Symptomatically, she has no morning stiffness; there is no gelling. She has no joint pain, with the exception of occasional discomfort around the right trochanter if she does a lot of running.

Objective assessment showed no evidence of soft tissue swelling. There was evidence of limitation of movement from previous damage in the right elbow, both wrists, left first MCP joint, and both forefeet. There was no digital vasculitis or nodule formation. Because there has been no active arthritis, there has been no indication for any recent radiological investigation. The most recent radiographs, taken 6 years after the transplant, showed that bony deformities previously present had not progressed. In summary, clinically she had no evidence of active disease.

Because of her overall good general health, only limited blood tests have been carried out over the years. Between 1994 and 2002, her ESR was tested by her general practitioner 6 times: the results on 4 occasions were ≤ 4 mm; the other 2 tests, taken at times of intercurrent illness, gave results of 26 and 65 mm (normal < 20). In 1996 her RF was < 20 IU/ml (normal) and her ANA showed a speckled pattern at a titer of 40 (normal < 40). At the same time her anti-dsDNA antibody test was negative. The results of current investigations (2004) are shown in Table 1. In summary, all tests for active RA were normal or negative, except for mildly elevated ANA.

DISCUSSION

Based on a handful of case reports such as our original one, both allogeneic and autologous hemopoietic stem cell transplantation (HSCT) are being considered as investigational treatments for severe autoimmune disorders including RA². Although most initial reports of benefit, such as ours, were from use of allogeneic HSCT, current research activity largely involves autologous transplantation, because of its relative safety². However, most recent reports of autologous³ or non-

myeloablative allogeneic⁴ transplants for severe RA indicate that responses, although common, are generally short-lived; that is, of the order of 6–12 months. This contrasts with the prolonged response in our cases, which followed allogeneic HSCT with full myeloablative conditioning.

It needs to be pointed out that as Patient 1 was in remission of her previously severe RA at the time of the transplant, her prolonged remission cannot be said for certain to have been due to the transplant; although improbable given the usual natural history of severe RA, she may have undergone a spontaneous prolonged remission. However, Patient 2 had active RA at the time of transplant.

It is possible that the GVHD in both our patients after their transplants played a role in the apparent cure of their RA. Mild to moderate GVHD is undoubtedly beneficial in promoting cure of some types of leukemia after BMT, due to an associated graft-versus-leukemia effect⁵. In one of the few reports of longterm survival after allogeneic BMT for RA, Snowden, *et al* speculated that there may be a similar beneficial effect of GVHD on autoimmune disorders⁶.

Because most reports of HSCT as treatment for severe RA have provided only short-term followup, doubts have remained about the durability of any benefit. We can report that at least in our 2 cases the benefit has been very prolonged. Indeed, after 2 decades it seems reasonable to suggest that our patients have truly been cured of RA. There is little doubt that, regarding the arthritis, both our patients are better off having undergone allogeneic HSCT, albeit enforced, than if they had continued to receive standard antirheumatic therapy.

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