This month *The Journal* presents 2 cases of rheumatoid arthritis (RA) with sustained full clinical remission up to 19 and 20 years following allogeneic hematopoietic stem cell transplantation (HSCT) for gold and penicillamine-induced severe aplastic anemia. In each case an HLA-matched sibling transplant was performed, and some degree of graft-versus-host disease (GvHD) occurred, which responded to treatment. Rheumatoid factors in both cases are now negative and in the one evaluable case, radiological changes stabilized.

Taken alone, these cases support the view held by some that only by replacing the autoaggressive immune system through allogeneic HSCT could a longterm “cure” of autoimmune disease (AD) be achieved. While this may be so for some patients, the international experience so far on around 1000 patients receiving HSCT as treatment for autoimmune disease over the past 10 years suggests a more complex paradigm.

The concept of HSCT for severe autoimmune disease evolved from supportive animal data, including autologous bone marrow transplantation, and reports of patients receiving an HSCT for conventional indications such as malignancies and in whom a coincidental AD was present and improved.

The term bone marrow transplantation has been replaced by HSCT, in which the source of stem cells is peripheral blood, bone marrow, or cord blood. When the stem cells are harvested from the bone marrow, a general anesthetic is required. For that and other reasons the majority of donors undergo peripheral blood harvesting of stem cells through leukopheresis, after driving the rare stem cells from the bone marrow into the blood. This is achieved through giving growth factors such as granulocyte colony-stimulating factor, plus or minus a bolus of cyclophosphamide. This is called mobilizing, or priming, and once collected, the graft product may be manipulated *ex vivo* either to enrich for wanted cells, especially the CD34-positive hematopoietic stem and progenitors, or to deplete unwanted cells (known as graft product manipulation or purging) and then cryopreserved.

The patient may then be admitted to hospital any time later, usually within a month, for the definitive chemotherapy-based ablative therapy (conditioning) followed by transplantation with the thawed graft product. The period of aplasia lasts usually less than 2 weeks, and the return of sufficient hematopoietic cells is called hematopoietic reconstitution. Immunological reconstitution takes longer: for CD4+ helper T cells sometimes years. Some conditioning regimens, e.g., cyclophosphamide alone, do not kill the stem cells, and the HSCT simply functions to shorten the period of aplasia. This is a great advantage, since every aplastic day is a risk. Others, for example, radiation-based or busulphan-containing (radiomimetic) are truly myeloablative, and without an HSCT the hematopoietic system would never return. In addition, antilymphocyte antibodies, for example antithymocyte globulin (ATG), are added, which achieve even more immunosuppression, referred to as *in vivo* purging.

Although both autologous and allogeneic stem cells (usually from an HLA-matched sibling) are widely used in malignancy treatment, allogeneic HSCT carries the extra risk of GvHD, with significant morbidity and mortality at between 10% and 35% depending on the clinical setting. However, only through graft versus leukemia (GvL) can a true and lasting remission of leukemia be achieved, and this has led to the concept of “graft versus autoimmunity,” a concept that mostly remains theoretical at the moment. Unfortunately, so far, the wanted GvL cannot be separated from the toxic GvHD.

Whatever the regimen used, the principle behind HSCT for autoimmune disease is that through hematopoietic stem cell support a threshold of immunosuppression can be surpassed that was previously not possible due to marrow toxicity, and that this may allow the immune system to “reset” to a tolerant state.

See 20-year remission of RA in 2 patients after allogeneic bone marrow transplant, page 812
The results so far on mostly autologous HSCT-treated patients suggest this to be so in over 30%, which is especially gratifying in systemic sclerosis (SSc) with patients followed up 10 years post-transplant. In addition, recent data in patients transplanted for multiple sclerosis (MS) suggest that despite full immune reconstitution, no clinical relapse was seen, supporting the concept of “resetting” rather than full ablation.

This is not entirely surprising, since monozygotic twins do not share the same incidence of autoimmune disease, concordance rates for RA being only 15%.8

In order to further expand these phase I/II experiences, prospective, controlled studies are under way in Europe for SSc [the Autologous Stem cell International Scleroderma (ASTIS) trial]9, MS, and Crohn’s disease; and in the US under the auspices of the National Institute of Allergies and Infectious Diseases (NIAID)/National Institutes of Health (NIH) for SSc (the SCOT trial), MS, and systemic lupus erythematosus (SLE). In the current ASTIS trial, 65 patients have been randomized and no treatment-related deaths have occurred in either arm.

Although the choice of autologous HSCT was based initially mostly on safety issues, being free from GvHD, it was recognized from the beginning that allogeneic protocols may be more effective in some patients. Case reports were conflicting; a female patient with RA received an allogeneic HSCT from her brother following gold-induced severe aplastic anemia, similar to the 2 cases discussed in this editorial. After a 2-year remission, the RA relapsed and remained active for 13 years’ further observation, despite full chimerism, i.e., all cells of hematopoietic origin were of donor type (the Y chromosome being easy to detect).10 More recent case reports of SSc/SLE overlap and RA show early positive outcomes.

Allogeneic HSCT has undergone major modifications in recent years, as it was recognized that the cellular GvL effect was more curative than the intense myeloablation, which alone can never fully eradicate every last malignant cell. The toxicity is due partly to acute organ damage, for example, melphalan pneumonitis, and partly to acute and later chronic GvHD with its attendant immunosuppression. For this reason nonmyeloablative regimens were developed to immunosuppress the host sufficiently to accept the graft, so that there would be a gradual conversion to full chimerism as the incoming hematopoietic stem cells were established in the recipient marrow.11 Such regimes may include low dose total body irradiation (TBI), fludarabine or cyclophosphamide as immunosuppressives plus ATG or CAMPATH. Often there is never a period of full aplasia, and acute organ toxicity is reduced. Although the prevention and treatment of acute GvHD has improved, chronic GvHD remains unchanged, even with these nonmyeloablative or reduced intensity regimes, which are sometimes incorrectly referred to as “mini-transplants.”

While the autologous HSCT program for autoimmune diseases is progressing, it is clear that not all patients respond, or they respond with later relapse;14 and acute organ toxicity is an issue, especially relating to TBI and cyclophosphamide in SSc.15,16 Discussions have begun to determine the appropriate circumstances for testing allogeneic HSCT in severe autoimmune disease, and an extensive consensus conference was recently published from the NIAID/NIH. In essence, protocols will be developed to complement rather than compete with existing autologous programs, but will avoid offering allogeneic HSCT to the most ill or to endstage autoimmune disease patients. Potential advantages are reduced acute organ toxicity and a graft versus autoimmunity effect.

In the end, the “holy grail” of tolerance induction without longterm immunosuppression is in our sights, a goal considered possible by some through hematopoietic stem cell transplantation. Whether this will be autologous or allogeneic and which protocol will be superior is currently not clear. Only properly designed and diligently executed controlled trials will answer these important questions, and the satisfying international collaboration already in place should guarantee this.

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REFERENCES


