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EDITORIAL

Plasticity of Hematopoietic Stem Cells: Enough to Induce Tolerance and Repair Tissue?

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Clinical tolerance is a state in which a tissue or antigen is not rejected even in the absence of immunosuppressive therapy, and responsiveness to third-party antigens is normal. After a transplant, the recipient of a kidney, liver, heart, or other solid organ must receive immunosuppressive therapy for life in order to avoid graft rejection. In contrast, a cellular transplant of bone marrow or peripheral blood hematopoietic stem cells, whether from a sibling or an unrelated person, will, over time, be tolerated by the recipient. This state of tolerance allows withdrawal of all immunosuppressive medications without rejection of the transplanted marrow or peripheral blood.

In an attempt to induce tolerance of solid organs, transplantation of solid organs has been combined with transplantation of hematopoietic stem cells from the same donor. Although current human experience is limited, in animal models, transplantation of fetal, neonatal, or adult hematopoietic stem cells is capable of inducing donor-specific tolerance (1–5). Transplantation of allogeneic donor hematopoietic stem cells results in donor-specific tolerance to solid organ grafts with retention of immunity to third-party grafts or tissues. Because hematopoietic stem cell transplantation (HSCT) can induce tolerance to both recipient- and donor-specific tissue, it seems plausible that, under appropriate conditions, HSCT could reintroduce tolerance in an autoimmune disease (6).

Experiments in the use of HSCT to induce tolerance in autoimmune diseases first began in animal models. Animal autoimmune diseases may be classified as either induced or spontaneously occurring. The stem cells required to cure an induced versus a spontaneously occurring animal autoimmune disease come from different sources. Hematopoietic stem cells are usually obtained by flushing marrow cells from the femurs of euthanized animals. Using this approach, performing autologous animal HSCT is not possible. Therefore, rather than using autologous HSCT, either syngeneic transplantation (from a healthy, genetically identical donor), pseudo-autologous transplantation (from a syngeneic donor in the same stage of disease), or allogeneic transplantation from a non–disease-prone strain is performed.

Environmentally induced animal autoimmune diseases such as adjuvant-induced arthritis, collagen-induced arthritis, experimental autoimmune myasthenia gravis, and experimental autoimmune encephalomyelitis may be cured by syngeneic or pseudo-autologous HSCT (7–10). On the other hand, spontaneously occurring autoimmune diseases such as murine models of lupus or diabetes presumably arise from a host stem cell defect, and cure requires an allogeneic HSCT from a non–disease-prone strain (11,12).

Caution must be used in applying results of HSCT in highly inbred strains of mice to a highly outbred and polymorphic human population. Nevertheless, animal data suggest that if the autoimmune disease is genetically predetermined, then an allogeneic source of stem cells is necessary for cure. If an autoimmune disease is predominantly environmentally induced (in a genetically susceptible host), then an autologous HSCT may result in a durable remission.

The roles of nature (genes) versus nurture (environment) in most human autoimmune disorders remain intertwined and are currently inseparable. In identical twins with autoimmune disorders such as diabetes, multiple sclerosis, systemic lupus erythematosus, or rheumatoid arthritis (RA), the concordance rate is 33–50% (13). Although this incidence is much higher than that in the general population, this finding also means that the majority of twins, despite being genetically identical, are

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discordant for disease. Therefore, if autologous HSCT is performed correctly, it may possibly reintroduce tolerance in human autoimmune diseases, although a relapse rate of 33–50% may be expected. On the other hand, it is anticipated that the relapse rate following allogeneic HSCT would be very low.

Anecdotal case reports indicate that RA may be cured by allogeneic HSCT. RA patients with aplastic anemia arising as a complication of gold or D-penicillamine therapy have undergone allogeneic HSCT for the treatment of aplastic anemia. Most patients receiving this treatment were subsequently cured of both their aplastic anemia and RA. Long-term followup has demonstrated resolution of rheumatoid factor activity, rheumatoid nodules, swollen and tender joints, and morning stiffness for >8 years after cessation of immunosuppressive therapy (14).

The first indication that high-dose immunosuppressive therapy and reconstitution from autologous HSCT may cure an autoimmune disorder occurred in the 1970s when Slavin used azathioprine and high-dose cyclophosphamide to treat a patient with mixed cryoglobulinemia (monoclonal IgM) and renal failure (15). Treatment was complicated by cytopenias, including neutropenia and sepsis, but following recovery the patient was disease-free and has remained so for 25 years. In 1998, Brodsky et al reported the use of lymphopenia-inducing doses of cyclophosphamide without stem cell support in patients with a variety of autoimmune diseases. Disease remissions were common, although relapses occurred (16). Simultaneously, more intense immunosuppressive regimens with HSCT support in patients with autoimmune diseases were undertaken worldwide. The regimen design, supportive care, patient selection, source of stem cells, and conditioning (immunosuppressive regimen) need to be individualized according to disease in order to diminish toxicity and optimize outcome.

The first reported autologous HSCT in RA was in Australia in 1997 (17), and the first American HSCT was described in 1999 (18). The conditioning regimens used, although intensive by rheumatologists' standards, were not myeloablative, and although stem cell support shortened the period of neutropenia, it was not necessary for reconstitution of endogenous hematopoiesis. The results of these early studies indicated a conditioning regimen dose–response effect. Cyclophosphamide at a dose of 100 mg/kg induced remission for 2 months, and an increase to 200 mg/kg induced remissions for 12–24 months (19). This suggests that use of a more intensive but safe regimen (e.g., busulfex and cyclophosphamide) may result in remissions that are even more durable. Protocols using these regimens for RA are currently active or are being developed (20).

The first autologous HSCTs in juvenile idiopathic arthritis (JIA) were performed by Wulffraat and associates using a regimen of low-dose irradiation and high-dose cyclophosphamide, resulting in remission of refractory disease (21). Subsequently, autologous HSCT has been used in several centers to treat JIA. Remissions are the rule, although some relapses have occurred.

Can autologous HSCT cure an autoimmune disease? In this issue of *Arthritis & Rheumatism* (22), Brinkman et al describe 2 patients, both of whom have been followed up for >3 years. One has relapsed, and the other patient remains in remission. It may be that some autoimmune diseases or subset of patients can be cured with intensive immunosuppressive therapy and autologous HSCT support. After all, some autoimmune diseases, such as relapsing remitting multiple sclerosis, systemic lupus erythematosus, and even some cases of scleroderma, may remit following therapy or immune suppression.

Regardless of whether an intensive but safe conditioning regimen and autologous HSCT can cure RA or JIA, this approach induces remissions in otherwise refractory disease and offers an opportunity to study tolerance in a manner that is not possible in cross-sectional studies. In diseases such as RA or JIA, tissue biopsy samples can be easily obtained from the involved organ system (joints). In the study by Brinkman et al (22), biopsy specimens were obtained before and 6 months after autologous HSCT. Clinical improvement correlated with a reduction in the level of intraarticular proinflammatory cytokines. In both RA and JIA, the exact contribution of different cells—macrophages, T cells, and synoviocytes—to disease is unknown.

The approach taken by Brinkman et al should be expanded in future trials of HSCT to determine cellular phenotype and characteristics within the diseased organ. The infused stem cells, whether autologous or allogeneic, could be retrovirally transduced with a marker gene before infusion (23). The use of marked stem cells could help clarify whether relapse arises from cells that survived the conditioning regimen or from the stem cell compartment. Such an approach could also help determine whether hematopoietic stem cells give rise to nonhematopoietic cells such as articular synoviocytes. Understanding the cellular origin of different cells and cytokines and their contribution to disease or tissue repair could lead to future studies in which infused stem cells are genetically altered to produce an antiinflamma-

tory cytokine such as tumor necrosis factor inhibitor locally within the inflammatory tissue.

Biopsy of involved tissue can document whether tissue repair is occurring and can be used to characterize the cells involved in the reorganization and regeneration of damaged tissues. It had been dogma that adult stem cell compartments are tissue restricted (e.g., hematopoietic stem cells give rise only to blood cells; periventricular neural stem cells give rise to either neurons or glial cells; liver stem cells [ovalocytes] differentiate only into bile duct cells or hepatocytes; and muscle stem cells [satellite cells] differentiate only into muscle). This dogma is, however, changing.

In murine models, it now appears that adult stem cells can change lineage. Under appropriate conditions, murine blood stem cells can be converted into neurons, cardiac myocytes, or hepatocytes (24–27). It remains unclear whether human hematopoietic stem cells have the plasticity needed to switch tissue lineage commitment. Recently, human livers of female recipients of bone marrow transplants from male donors were analyzed, and Y chromosome–specific DNA was detected in a small percentage of hepatocytes (28). This finding implies that the male hepatocytes originated from the donor hematopoietic stem cells.

Does damaged tissue undergo repair, and does repair involve differentiation of blood stem cells? Combining HSCT with joint biopsy, especially using genetically marked autologous stem cells or HLA-matched but sex-mismatched allogeneic cells, will help answer this question. If blood stem cells can differentiate into other organs or tissues, the ethical questions and immunologic barriers surrounding embryonic stem cells become moot, because hundreds of millions of blood stem cells can be easily, safely, and repeatedly harvested from virtually any patient.

Stem cell therapy—specifically hematopoietic stem cell therapy to reintroduce tolerance or conceivably repair damaged tissue—is an important new weapon in the therapeutic armamentarium against autoimmune diseases. Stem cells, specifically hematopoietic stem cells, may be the supermen of the 21st century: able to induce tolerance, repair damaged tissues, and leap barriers of futility and toxicity that encumber our current therapies.

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