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Hematopoietic Stem Cell Transplantation: A New Therapy for Autoimmune Disease

RICHARD K. BURT, ANN E. TRAYNOR

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OVERVIEW

Allogeneic and autologous hematopoietic stem cell transplantations (HSCT) are often-used treatments for patients with lymphomas. We have proposed that autoimmune diseases may be viewed as a lymphoproliferative disorder and that subsets of patients with autoimmune disease have a high mortality despite conventional therapy. For this group of patients, we have initiated clinical trials of HSCT.

The hallmark of a lymphoma is clonality, and autoimmune diseases display skewing of the lymphocyte repertoire suggestive of oligoclonality. For example, oligoclonal bands exist within the cerebral spinal fluid of patients with multiple sclerosis (MS), suggesting B-cell oligoclonality. Patients with MS also have been reported to have skewing of the T-cell-receptor repertoire family within central nervous system (CNS) plaques, again indicating T-cell oligoclonality [1-3]. Patients with Crohn’s disease have skewing of the T-cell Vβ repertoire family within involved segments of the intestinal tract but not in uninvolved segments [4]. Systemic lupus erythematosus (SLE) is manifest by antinuclear antibodies, the production of which appears to be driven by a restricted family of T cells that recognize positively charged determinates on nucleoproteins [5]. T-cell receptor complexity within a particular Vβ family also is skewed for several autoimmune disorders when the antigen recognition site (CDR3 region) is separated at a nucleotide level by CDR3 spectratyping [6, 7]. Therefore, in terms of (oligo)clonality, a unique distinction between a malignant process (clonality) and an autoimmune disease is not always clear, although it is assumed that lymphomas proliferate independent of antigenic stimulation, while autoimmune disorders are antigen-dependent.

Autoimmune diseases are common. For example, approximately 0.5% to 1% of the U.S. population has rheumatoid arthritis (RA), while roughly 1 in 700 Americans have SLE. The severity and clinical course of these diseases vary widely. Importantly, there are subsets of patients with autoimmune diseases who have a lower life expectancy than do patients with chronic myelogenous leukemia or low-grade lymphomas, diseases which are currently considered suitable for either autologous or allogeneic transplantation. Individuals with autoimmune diseases failing conventional therapy who have organ- or life-threatening disease may be considered candidates. Patients with RA who fail current therapies and have more than 30 involved joints or significant limitations in activities of daily living have a five-year life expectancy of 30% to 40% [8-17]. As an overall group, patients with SLE have a mortality of 1% per year [18-26]. Patients who are failing corticosteroid and the NIH short-course cyclophosphamide regimen (500 to 1,000 mg/m2 monthly for at least six months) who also have visceral organ involvement could be considered candidates for HSCT, as could patients with relapsing-remitting MS and more than three relapses in one year despite treatment with interferon and progressive MS with gait involvement.

To emphasize the potential severity of these illnesses, two patients who were transplanted at Northwestern Memorial Hospital will be discussed. The first patient was a healthy Ph.D. molecular biologist until three years before referral when she was diagnosed with MS (Fig. 1A). In three years, the patient progressed from normal to being confined to a wheelchair and unable to perform serial sevens (Fig. 1B).
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She is now two years post-HSCT and has no new clinical deficits or lesions on magnetic resonance imaging. Although still confined to a wheelchair, she has reacquired cognitive ability to perform serial subtractions.

The second patient is a 15-year-old who presented with a respiratory arrest and renal failure after one week of flu-like symptoms. A lung biopsy revealed alveolar hemorrhage and vasculitis, and a renal biopsy demonstrated glomerulonephritis. The anti-double-stranded DNA was markedly elevated (1:1,280), and despite high doses of pulse and daily steroids, intravenous pulse cyclophosphamide, and daily plasmapheresis, recurrent intubation was required for alveolar hemorrhage. Upon evaluation for transplant, the patient developed recurrent pulmonary infiltrates (Fig. 2) and hemoptysis and required supplemental oxygen. After HSCT, the amount of anti-double-stranded DNA was unmeasurable, the alveolar hemorrhage had resolved, and the steroid dose tapered from 100 mg/d to 20 mg/d.

**WHAT ARE AUTOIMMUNE DISEASES?**

A disease may be immune-mediated but not be an autoimmune disease. For example, immune-mediated attack on infectious organisms may result in damage to surrounding tissue. Tuberculosis is an intracellular organism that persists within macrophages and may result in progressive inflammatory lung destruction, for which pulmonary tuberculosis has been given the nickname of “consumption.” In contrast, in an autoimmune disease, the immune-effector cells are directed against self-antigens. Criteria for autoimmunity were defined by Rose and Bona [27], who postulated that direct proof of autoimmunity is the ability to adoptively transfer disease by transferring immune cells; indirect proof exists when an animal model mimics the human disease and may be adoptively transferred by immune cells; and circumstantial disease is that which demonstrates response to immunosuppressive agents. Autoantibodies have been transferred transplacentally from mother to fetus, but T-cell-directed cytotoxicity requires recognition of self-peptide within an HLA molecule. The heterogeneity of the HLA helps determine self from non-self and limits adoptive transfer of T-cell-mediated disease to identical twin or HLA-matched donor/recipient pairs. Therefore, most evidence for human autoimmune diseases relies on indirect or circumstantial evidence.

**WHAT CAUSES AN AUTOIMMUNE DISEASE?**

The contributions of genetics versus environment in the onset and maintenance of human autoimmune disease are not clearly distinct. Genetically preordained pathways in antigen processing, presentation, and recognition (such as occur with the highly polymorphic major histocompatibility complex)
may influence predisposition to autoimmune responses. Many human autoimmune disorders occur more frequently with certain HLA combinations. Once stimulated by an antigen, the cellular immune response is regulated by a variety of genetically determined signal transduction, proliferation, and apoptotic pathways. For example, Fas is a protein involved in apoptotic signaling; MRL/lpr mice develop a spontaneous-onset lupus-like disease due to genetically deficient Fas protein expression [28, 29]. Environmentally, the response to an antigen (i.e., immunity versus tolerance) depends on the context in which it is presented. The stage of cell differentiation, local cytokine milieu, presence or absence of costimulatory molecules, antigen concentration, and duration of presentation are some of the factors that influence immune response. Some autoimmune diseases (such as relapsing-remitting MS and systemic lupus) normally fluctuate, and patients may enter prolonged clinical remissions. This suggests that the immune system is, at least in some cases, dynamic, fluctuating between immunity and tolerance. Autoregulatory cells (suppressor, veto, immune-indifferent, and idiotypic) may, therefore, modulate an immune response.

Epidemiological evidence suggests an infectious etiology for some human autoimmune diseases, such as MS [30]. The best evidence for an infectious etiology of a subsequent autoimmune disorder has been shown in animal models. Theiler’s murine encephalomyelitis virus (TMEV) is a picornavirus that induces an inflammatory demyelinating disease in susceptible mice [31]. The immune system plays a pivotal role in both preventing and causing TMEV-induced demyelinating disease. In vitro, the virus is cytopathic to neurons causing cell lysis, and the initial infection is a gray-matter disease. In resistant strains of mice, the virus is cleared from the CNS within two weeks of intracerebral inoculation, and no demyelination or chronic sequelae occur. Thymectomy of a disease-resistant mouse results in death from uncontrolled gray-matter infection. In disease-susceptible strains of mice, the virus is never cleared from the CNS [32]. Approximately 45 days after inoculation, the initial gray-matter infection evolves into a chronic demyelinating white-matter disease. This white-matter disease mimics MS histologically and clinically. With onset of white-matter disease, the immune system becomes responsive to epitopes of myelin proteins, including determinants of myelin basic protein (MBP) and proteolipid protein (PLP) [33]. Demyelination may be slowed or prevented by immunosuppressive medications [34, 35]. The mechanism(s) by which an initial viral immune-mediated reaction becomes a secondary immune-mediated reaction to myelin proteins (i.e., self-protein) is not completely clear. There is no evidence of molecular mimicry between immunogenic viral protein and MBP or PLP epitopes. One hypothesis is that immune-mediated attack on viral proteins results in bystander destruction of myelin. Within a local pro-inflammatory environment, macrophages may upregulate costimulatory molecules and, upon presentation of myelin proteins, break self-tolerance. TMEV-induced demyelinating disease indicates that progression of the autoimmune disease may be independent of the initiating infectious event.

**WHAT TYPE OF TRANSPLANT: AUTOLOGOUS OR ALLOGENEIC OR NO STEM CELL SUPPORT?**

It is generally accepted that stem cell transplants for autoimmune diseases should be initiated using autologous grafts [36-39], which are less risky and less complicated than allogeneic grafts. However, if our analogy with a low-grade lymphoma is correct, an autologous transplant may induce remission but would be complicated by a high, and probably unacceptable, relapse rate. Lymphocyte depletion has also been recommended based on a retrospective analysis of six patients with hematologic diseases and coincidental autoimmune disorders who had early relapse of their autoimmune disease after unmanipulated autologous HSCT [40]. Lymphocyte depletion is a form of purging potentially autoreactive cells from the graft. In practice, aggressive lymphocyte depletion of an allograft can prevent alloreactivity (i.e., graft-versus-host disease [GVHD]) even without immunosuppressive prophylaxis. In theory, therefore, a lymphocyte-depleted autograft may prevent recurrence of auto-reactivity. This assumes that autoimmunity is learned and is not genetically preordained.

Some investigators have argued that infusion of stem cells is not necessary [41]. This assumes that the conditioning regimen is dose-intensive, but not myeloablative. They argue that intense but nonmyeloablative immunosuppression may be sufficient. The rationale is based on remissions in patients with aplastic anemia after treatment with cyclophosphamide at doses of 200 mg/kg [42]. Aplastic anemia is, in most cases, an autoimmune-mediated suppression of hematopoiesis that may be cured by either immunosuppression or allogeneic HSCT. Whether this approach is applicable to other autoimmune disorders remains to be determined. Comparing the outcome of nonmyeloablative transplant regimens with or without infused hematopoietic progenitor cells may help delineate a role of the infused autograft in relapse and/or remission and/or prevention of infectious complications.

Ultimately, some or all patients with autoimmune diseases may require an allograft to be cured. Based on experience in leukemias and animal models, it is possible that an allograft would not only provide a new stem cell source but also confer a graft-versus-autoimmune (GVA) effect, whereby allogeneic lymphocytes induce apoptosis or
modulation of autoreactive recipient lymphocytes. Due to the high risk of GVHD, better methods for controlling or preventing GVHD will be necessary before we cross the horizon of allogeneic transplantation for autoimmune diseases.

**RESULTS OF TRANSPLANTS FOR AUTOIMMUNE DISEASES**

Only a small number of patients undergoing HSCT for an autoimmune disease have been reported [43-54] (Table 1). All were transplanted using autologous hematopoietic stem cells. These data demonstrate the feasibility of mobilizing stem cells and giving patients with these autoimmune diseases intense immunosuppressive conditioning, but it is too early to comment on durability of remission. When interpreting these results, it is important to recognize that for most autoimmune diseases, including SLE and MS, there is no established definition for a complete remission. Nevertheless, remission, improvement, and/or stabilization of disease progression ensued in a group of patients with aggressive disease that was generally heavily pretreated and failing standard therapies. Some patients, especially those with SLE and MS, have maintained remission or lack of progression beyond two years. Relapses have occurred predominantly in patients with RA and scleroderma. Numbers of patients are too small and follow-up too short to draw conclusions. However, patients with normally relapsing-remitting diseases (such as SLE and MS) appear to maintain remissions, while those with progressive diseases (such as scleroderma and RA) are having some relapses. International registries such as the International Bone Marrow Transplant Registry and Autologous Transplant Registry, European Bone Marrow Transplant Group, and European League Against Rheumatism are organizing to follow outcome on patients undergoing transplant with autoimmune diseases.

In Figures 3, 4, and 5, we list the conditioning regimens used at Northwestern University to transplant patients with MS, SLE, and RA, respectively. The best conditioning regimen has not been determined. As has been the case with transplantation of patients with leukemias, it is unlikely that any one conditioning regimen will prevail as markedly superior in preventing relapse. We chose these regimens simply to maximize immunosuppression while minimizing non-immune end-organ toxicity. The combination of total-body irradiation (TBI) at 1,200 cGy and cyclophosphamide at 120 mg/kg was used in patients with MS, because these agents are the two most immunosuppressive components of current conditioning regimens, due to our positive prior experience in using TBI in transplanting experimental autoimmune encephalomyelitis (an animal model of MS), and because of the ability of TBI to penetrate into CNS plaques without regard for the blood brain barrier. We dose-decreased TBI to 400 cGY in RA to avoid pulmonary toxicity in patients with rheumatoid interstitial lung disease. TBI was avoided in patients with SLE because we were concerned about late radiation-induced malignancies in these usually young patients (10 to 25 years old), and we felt that most patients with SLE referred for

<table>
<thead>
<tr>
<th>Journal publications</th>
<th>Disease (n patients)</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Fassas et al. [43]</td>
<td>MS (15)</td>
<td>Improvement in mean Kurtzke disability score.</td>
</tr>
<tr>
<td>Burt et al. [44]</td>
<td>MS (3)</td>
<td>No progression.</td>
</tr>
<tr>
<td>Burt et al. [48]</td>
<td>MS, SLE, RA (10)</td>
<td>All patients stabilized or improved.</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Letters to journals</th>
<th>Disease (n patients)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joske et al. [45]</td>
<td>RA (1)</td>
<td>Improved from wheelchair-bound to ambulating with ease.</td>
</tr>
<tr>
<td>Tyndall et al. [47]</td>
<td>Scleroderma (1)</td>
<td>Improved.</td>
</tr>
<tr>
<td>Burt et al. [46]</td>
<td>SLE (1)</td>
<td>Improved; no evidence of active disease after transplant.</td>
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<table>
<thead>
<tr>
<th>Abstracts</th>
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<th>Outcome</th>
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<tbody>
<tr>
<td>Brooks et al. [51]</td>
<td>RA (8)</td>
<td>At 100 mg/kg of cyclophosphamide, 4/4 relapsed at 200 mg/kg and 3/4 improved (2 at 6 months).</td>
</tr>
<tr>
<td>McSweeney et al. [49]</td>
<td>Scleroderma (5)</td>
<td>No progression; improved skin scores; one death early post-transplant.</td>
</tr>
<tr>
<td>Wolfrat et al. [50]</td>
<td>JRA (5)</td>
<td>All improved.</td>
</tr>
<tr>
<td>Hahn et al. [54]</td>
<td>ITP (4)</td>
<td>One patient steroid refractory despite transplant; one steroid independent after transplant.</td>
</tr>
<tr>
<td>Burt et al. [52]</td>
<td>SLE, RA (6)</td>
<td>All 4 SLE without evidence of active disease after transplantation; 1 RA relapsed; 1 RA improved beyond 1 year.</td>
</tr>
<tr>
<td>Burt et al. [53]</td>
<td>MS, SLE, RA (17)</td>
<td>1 patient with RA relapsed; all others improved or no progression.</td>
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</tbody>
</table>

Abbreviations: JRA = juvenile rheumatoid arthritis; MS = multiple sclerosis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.
transplant would have active disease with multiorgan failure and would not tolerate a more intense regimen. It is notable that of these regimens, the MS regimen is myeloablative, the RA may be myeloablative, while the SLE regimen is dose-intensive but nonmyeloablative.

**WHAT IS THE MECHANISM OF ACTION?**

The mechanism of remission after autologous HSCT is unknown. The immune system may be fundamentally unaltered, and an autologous transplant may be nothing more than dose-intensive immunosuppression. At the other extreme, the disease-mediating effector cells may be entirely destroyed, although this is unlikely since flow cytometric analysis of the post-transplant immune system suggests that memory cells (CD45RO+) survive and that only after three to six months do naive (CD45RA+) lymphocytes appear [48]. Alternatively, an autologous transplant may shift the scales of balance between immunity and tolerance through as yet undefined mechanisms. Theoretically, this may include clonal exhaustion, veto cells, suppressor cells, other autoregulatory cells, immune indifference, idiotypic T- or B-cell networks, cytokine alterations, infectious agents, changes in T- or B-cell (oligo)clonality, or changes in immunodominant autoantigens.

Allogeneic transplantation would change the stem cell compartment, possibly affecting signal transduction and apoptotic or proliferation pathways, HLA associations, or minor histocompatibility antigen presentation, or it may generate an immunologic donor-mediated GVA effect in which donor cells modulate recipient autoreactive lymphocytes.

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**Conditioning Regimen for SLE**

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<th>Therapy</th>
<th>Day</th>
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<th>–5</th>
<th>–4</th>
<th>–3</th>
<th>–2</th>
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<td>50 mg/kg</td>
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<td>50 mg/kg</td>
<td>50 mg/kg</td>
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</tr>
<tr>
<td>ATG</td>
<td>30 mg/kg</td>
<td>30 mg/kg</td>
<td>30 mg/kg</td>
<td>30 mg/kg</td>
<td>30 mg/kg</td>
<td>30 mg/kg</td>
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<tr>
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<td>1 g</td>
<td>1 g</td>
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**Conditioning Regimen for MS**

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<th>–5</th>
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<tbody>
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<td>Cyclophosphamide</td>
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<tr>
<td>TBI</td>
<td>150 cGy • 2</td>
<td>150 cGy • 2</td>
<td>150 cGy • 2</td>
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<td>150 cGy • 2</td>
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<tr>
<td>Methylprednisolone</td>
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**Conditioning Regimen for RA**

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<tbody>
<tr>
<td>TBI</td>
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<td>Cyclophosphamide</td>
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<tr>
<td>ATG</td>
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<td>Steroids</td>
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**Figure 3. Northwestern University conditioning regimen for multiple sclerosis.**

**Figure 4. Northwestern University conditioning regimen for systemic lupus erythematosus.**

**Figure 5. Northwestern University conditioning regimen for rheumatoid arthritis.**
CONCLUSION

The current explosive expansion of this therapy is proof of what President John Kennedy once said: “Success has many fathers. Failure is an orphan.” Nevertheless, there remains a long road ahead with many unanswered questions. Relapses and early deaths may yet deter what is an optimistic early start. This approach should, for now, remain in a few centers with carefully designed trials monitored by outside committees such as, in our case, the U.S. FDA. These trials should not just collect data on toxicity and outcome, but also analyze the pre- and post-transplant immune system. HSCT of autoimmune diseases may provide a powerful clinical tool for unraveling the mysteries of tolerance and immunity.

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