

# Hematopoietic Cell Transplantation for Autoimmune Disease: Updates from Europe and the United States

Keith M. Sullivan,<sup>1</sup> Paolo Muraro,<sup>2</sup> Alan Tyndall<sup>3</sup>

Considerable advances have been made in our understanding of the immunobiology of autoimmune disease and its treatment with hematopoietic cell transplantation (HCT). In autoimmune disorders, the reconstituted immune system following lymphoablation and autologous HCT yields qualitative changes in immune defects and modifications in adaptive immune responses. Seminal experiments in animals demonstrated that allogeneic or autologous HCT could prevent progression or reverse organ damage from inherited (genetic) or acquired (antigen induced) autoimmune diseases. Convincing animal and clinical data now show that after HCT, the immune system is normalized and “reset”. Following autologous transplantation, this resetting occurs via repertoire replacement. It is currently being studied whether and to what extent suppression of inflammation after HCT is due to reregulation of function or due to the eradication of disease associated T and/or B cell populations. There are now a number of published clinical reports with sufficient follow-up for determinations of safety and efficacy of HCT for autoimmune diseases. On behalf of colleagues in the European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT), we review the experience with more than 1000 transplants for autoimmune disease in Europe along with the three major multinational randomized trials in for systemic sclerosis (SSc, the ASTIS study), multiple sclerosis (MS, the ASTIMS study), and Crohn’s disease (CD, the ASTIC study). Completed phase II studies in the USA of transplantation for severe SSc, SLE and MS yield promising results. For individuals with SSc, there is dramatic improvement/resolution of dermal fibrosis and stabilization/improvement of pulmonary dysfunction reported up to 8 years after lymphoablative conditioning and autologous HCT. Currently, randomized phase III studies are recruiting subjects in the USA with SSc, MS and CD. In addition, 9 other phase I and II trials in the USA are recruiting patients with autoimmune diseases for nonmyeloablative transplants from allogeneic stem cell donors. Research opportunities abound, but recruitment challenges restrict study entry due to organ impairment from advanced autoimmune disease or insurance denial of coverage for HCT. However, within several NIH sponsored trials there are ongoing immunologic, genomic and mechanistic studies to further understand the molecular mechanisms of autoimmunity, immune regulation and response to treatment. These clinical trials will provide basic scientists with insight into immunoregulatory pathways and clinicians with a context to weigh the progress and evidence in this evolving treatment for autoimmune diseases.

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## INTRODUCTION

For decades, the application of allogeneic blood and marrow transplantation has been a curative treatment for inherited nonmalignant disease such as thalassemia, sickle cell disease (SCD), immunode-

ficiency diseases, and storage disorders, and for acquired hematopoietic disorders such as aplastic anemia (AA). The premise that lymphoablative conditioning and allogeneic or autologous transplant could prevent progression or reverse organ damage from inherited or acquired autoimmune disease

From the <sup>1</sup>Division of Cellular Therapy, Duke University Medical Center, Durham, North Carolina; <sup>2</sup>Division of Neuroscience and Mental Health, Imperial College London, London, United Kingdom; and <sup>3</sup>Department of Rheumatology, University of Basel, Switzerland, on behalf of the European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT).

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Correspondence and reprint requests: Keith M. Sullivan, MD, Division of Cellular Therapy, Duke University Medical Center, Durham, NC 27708 (e-mail: [sulli025@mc.duke.edu](mailto:sulli025@mc.duke.edu)).

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derives from the pioneering animal experiments of Ikehara, van Bekkum and their colleagues [1,2]. Still, a decade elapsed between the preclinical studies and human trials. Appreciation of the potential for cure of autoimmune disease was bolstered by illustrative experiments in nature wherein patients with coincident autoimmune disease and hematologic malignancy or AA remained in long-term remission of both diseases after allogeneic transplantation [3]. As predicted by Thomas, a variety of problems and opportunities encompassed these first clinical translations [4]. Now, with initial trials in several autoimmune diseases published with sufficient follow-up for determinations of safety and efficacy, it is opportune to review the biology and results to date and glimpse from both sides of the Atlantic into the future of transplantation for autoimmune diseases.

### **RESETTING THE IMMUNE SYSTEM TO CONTROL AUTOIMMUNE DISEASE: PRECLINICAL AND CLINICAL TRANSPLANT EXPERIENCE**

Current concepts on the pathogenesis of autoimmune disorders attribute a crucial role to T and B cells inappropriately recognizing self antigens and initiating a cell-mediated or humoral reaction, or both, resulting in inflammatory tissue and vascular damage [5]. Treating autoimmune disease with antigen-specific tolerization has been an ambitious, but largely elusive, goal and both pharmaceutical and academic-driven drug development efforts have targeted shared effector or regulatory pathways with immunosuppressive/modulatory compounds.

Autologous hematopoietic cell transplantation (HCT) is being evaluated as treatment for severe forms of immune-mediated disorders including multiple sclerosis (MS), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and rheumatoid arthritis (RA) or juvenile idiopathic arthritis (JIA). The goal of this therapy is to induce medication-free remission from disease activity by correcting the immune aberrations that promote the attack against self tissue ("immune repair").

#### **Animal Models**

Collagen-induced arthritis (CIA) and experimental autoimmune encephalomyelitis (EAE) are examples of antigen-induced autoimmune diseases, and serve as models for human RA and MS, respectively. Data in both disease models suggest that tolerance induced by autologous HCT can prevent autoimmunity even after antigenic reencounter. In van Bekkum's studies of bone marrow transplantation (BMT) in experimental models, amelioration of autoimmune disease was observed not only after syngeneic but also after autol-

ogous or pseudoautologous BMT (reviewed in [6]). Remarkably, arthritic rats treated with syngeneic BMT did not relapse with CIA even after being reimmunized with the antigen [2]. Syngeneic transplantation also conferred protection from disease relapse in EAE [7]. To explain these observations we must postulate the induction of protective changes of the immune system not linked to a correction of an underlying stem cell defect. We have recently observed that BMT applied to mice in the late phase of EAE development resulted in different clinical outcomes. Numbers of activated macrophage/microglial cells were significantly greater in mice that progressed, and tracking of green fluorescent protein-transduced BM cells showed the endogenous origin of the activated microglia [8]. Therefore, tissue-specific factors such as the persistence of local inflammatory cell types may influence the clinical outcome independent of the effects of BMT on the peripheral adaptive immune system (T and B lymphocytes).

#### **Not Just Immune Suppression**

Early studies on immune reconstitution following autologous transplant for both autoimmune diseases and cancer showed a profound lymphopenia in the first year after transplantation. The cytopenia was observed to affect the lymphocyte subsets differently, the kinetics of reconstitution likely depending on different timing of recovery for each cell type. Whereas B cells, natural killer (NK) cells, and CD8<sup>+</sup> T cells display a rapid and complete reconstitution to pretransplantation levels, the recovery of CD4<sup>+</sup> T cells has consistently been observed to be delayed, and often incomplete. By extending longitudinal follow-up of patients, recent studies have shown a recovery of the number of CD4<sup>+</sup> T cells after a 2-year follow-up in young adults treated for MS [9] and RA [10], and after 12 months in children with JIA [11]. The observation that quantitative recovery of lymphocytes was not correlated to inflammatory activity or disease relapse revealed that numeric immune deficit is an insufficient explanation for a prolonged absence of autoimmune disease activity after autologous HCT.

#### **Immune Resetting via Repertoire Replacement**

The rationale for using autologous HCT in autoimmune disease is to purge the existing immune system and regenerate a new and healthy repertoire of immune cells. However, the notion of an immune "resetting" remained conjectural until Muraro et al. [9] demonstrated the regeneration of a new, naïve T cell repertoire emerging from the thymus of patients with MS who had been treated with myeloablative (MA) conditioning and autologous HCT. In this study, a detailed analysis of T cell receptor repertoire showed the regeneration of a different and more

diverse TCR repertoire posttransplant. Thymic reactivation, expansion of naïve T cells following auto-grafting, and improved repertoire diversity were subsequently also demonstrated in individuals with SLE [12]. Important lessons also come from studies on antibody responses to foreign antigens such as after vaccination or revaccination preceding or following autologous transplant. In a recent study, immunoablative conditioning and autologous HCT eliminated immunologic memory for a neoantigen given after the graft harvest, and diminished, although did not completely eliminate, the immunologic memory for a recall antigen boosted before harvest following nonrigorous T cell depletion of the autograft [13]. Serologic evidence of attenuation of immunologic memory suggests that the B cell compartment, until now less extensively investigated, may also undergo a renewal through autologous HCT.

### Immune Resetting via Restoration of Immune Regulation

Potentially pathogenic autoimmune responses are generated not infrequently and failure of tolerance toward self may also require the failure of protective immunoregulatory mechanisms. Autoimmune disease can therefore be regarded as the final outcome of a series of events that likely include not only a genetic susceptibility, but also the failure of the checkpoints available to prevent autoimmunity following exposure to environmental challenges, such as infections (Figure 1). It is reasonable to postulate that the normalization of immune regulatory mechanisms could play a role in the suppression of autoimmunity following autologous HCT. The CD4<sup>+</sup> CD25<sup>+</sup> expressing the forkhead transcription factor 3 (FoxP3) cells are potent

suppressors of immune responses, which are generated in the thymus both in rodents [14] and in humans [15]. CD25<sup>high</sup> FoxP3<sup>+</sup> CD4<sup>+</sup> T cells were reported to be more resistant to irradiation than effector cells and mediated the amelioration of experimental graft-versus-host disease (GVHD) [16]. In EAE rats, there was an increase of CD4<sup>+</sup> CD25<sup>+</sup> T cells after syngeneic BMT and this was seen in connection with attenuation of active disease and protection from induction of relapses [17]. Longitudinal enumeration of CD4<sup>+</sup> CD25<sup>high</sup> T cells in children with JIA, studied following autologous HCT, showed recovery of the pretreatment frequency at 6 months posttransplant and a continued increase for the remaining 12-month follow-up. Their frequency correlated directly with clinical remission. Therefore, reinstallation of immune regulation could be involved in long-term tolerance posttransplant.

### AUTOLOGOUS HCT FOR SEVERE AUTOIMMUNE DISEASE: THE EXPERIENCE IN EUROPE

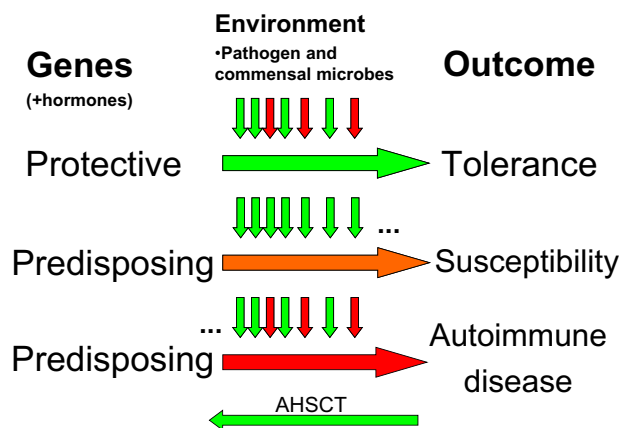
#### The Hypothesis

As detailed before, autoimmune diseases result from failure of an organism to recognize its own parts as “self,” thereby producing an autoaggressive response. The components of this response are as pleomorphic as the immune system itself, ranging from cells and molecules of the innate immune system such as dendritic cells (DCs) and NK cells to the tightly regulated members of the adaptive immune system. Targeting these individual components with chemical or biological agents has been extremely effective in controlling symptoms in many patients, but still some patients do not respond sufficiently and may lose life or vital organ function or suffer severe toxicity from treatment. Also, no therapy to date has induced long-term drug-free remission in any autoimmune disorder.

Based on animal models and anecdotal experience of HCT patients with coincidental autoimmune diseases mentioned earlier, it was proposed that by eradicating the whole immune system, tolerance could be reestablished during the immune reconstitution that follows lymphoablation. As in other HCT protocols, it was hoped that the early increased transplant-related toxicity, compared with standard of care, would be offset by a later increased disease-free survival (DFS).

#### The Plan

Colleagues from hematology, rheumatology, immunology, neurology, and gastroenterology sat together 14 years ago in Basel [18] and Seattle [19] to work out a structured research agenda that had as its mission statement 2 main objectives: (1) to show



**Figure 1.** Both genetic and environmental factors play a role in the development of autoimmune disease. Development of autoimmune disease in adulthood suggests that multiple immunizing events are required to break immune tolerance. It is proposed that autologous HCT, by “resetting” the immunological memory, may return the individual’s immune system to a premorbid state, resulting in a prolonged clinical remission.

through prospective, randomized controlled trials (RCTs) whether autologous HCT offered a durable and significant improved quality of life for patients suffering from severe autoimmune disease; and (2) to study immune reconstitution in such patients to understand better the cellular and molecular mechanisms involved.

Autologous HCT was initially chosen because of its lesser toxicity compared with allogeneic HCT. A limited number of protocols were proposed to allow comparison of more aggressive MA and reduced intensity conditioning (RIC) regimens. At the time, it was not known whether complete eradication of all autoreactive immune competent cells was required, or rather simply an autoimmune “debulking” to allow natural immune regulation to be reestablished. A gratifying international scientific collaboration became established, which remains today.

### The Early Results

From the first case report of a 45-year-old female with untreatable pulmonary hypertension and SSc [20], through the small case series and then phase I/II studies, there was a strong impression that autologous HCT influenced the natural history of several autoimmune disorders, including SSc, MS, RA, JIA, SLE, and Crohn's Disease (CD). In addition, impressive positive results were also seen for less common disorders, such as chronic inflammatory demyelinating polyneuropathy (CIDP) and various vasculitides.

A first mega analysis on 473 patients from the EBMT in 2005 showed that 11% has died, either from treatment-related toxicity (TRM) (7%) or disease progression (5%), adjusted to an average 3 year follow-up [21]. Of the patients evaluable for response ( $n = 299$ ), 81% responded and this was sustained in 71%. Not reported then, but subsequently demonstrated, were many of these responders with apparent long-term, drug-free remission demonstrating tissue remodeling. Conditioning regimens were classified as low, intermediate, or high intensity, and although responses were better in the high-intensity regimes, the associated increased toxicity with these initial trials was considered unacceptably high. Subsequent protocol designs for the prospective RCTs in Europe were based on the intermediate intensity regimens, mostly consisting of mobilization with cyclophosphamide (Cy) and granulocyte-colony stimulating factor (G-CSF) followed by Cy (or BEAM) and antithymocyte globulin (ATG) plus or minus CD34<sup>+</sup> cell selection. Randomized trials have been designed for SSc, MS, CD, RA, and CIDP.

### Events Along the Way

In December 1993, a landmark article was published showing a dramatic and hitherto unseen response in

20 RA patients over 8 weeks to the tumor necrosis factor (TNF)- $\alpha$  blocking agent, the chimeric monoclonal antibody (mAb), infliximab [22]. Toxicity was modest and this experience opened an era of biopharmaceuticals, first revolutionizing the treatment of RA, then rapidly spreading to CD, MS, and now becoming established or investigational therapy in most autoimmune diseases.

Although none of these offer a “cure,” the toxicity is rather low and the trials are supported by the pharmaceutical industry. This had an impact on the recruitment of patients with autoimmune disease onto transplant trials, because whereas best results with HCT are seen in early, reversible autoimmune disease, such patients are also suitable for less toxic biopharmaceuticals. Of note, so far an effective disease modifying agent for SSc is not available for this highly morbid and mortal disorder.

In 2001, the European Parliament enacted the European Union's Clinical Trials Directive 2001/20/EC, which has had a profound effect on clinical trials in Europe. This is a lengthy document specifying all aspects of the clinical trials process, and has proved complicated for investigator-initiated trials such as studies of HCT for autoimmune disease, which are often university based and extend across national borders. This regulatory burden has hindered the clinical trialist, especially as it relates to professional indemnity.

### Randomized Clinical Trials

Table 1 presents the current status of RCTs in Europe as of August 2009. The Autologous Stem cell Transplantation International Scleroderma Trial (ASTIS) has almost completed enrollment, and although deaths have occurred in both arms, the independent safety committee has adjudicated that no unexpected toxicity occurred. The Autologous Stem cell Transplantation International Rheumatoid Arthritis trial (ASTIRA) never started because of a plethora of biopharmaceutical agents for RA including anti TNF- $\alpha$ , interleukin (IL)-1, IL-6, and costimulation blockade.

### Impact of HCT on Autoimmune Disease

#### SSC

Some patients have achieved complete remission (CR) including unexpected and dramatic clinical and biopsy regression of dermal fibrosis as well as normalization of the microvasculature [23].

#### SLE

In a small series of patients, clinical CRs as well as loss of autoantibody (antinuclear antibody) have been described, suggesting a true resetting of autoimmunity. This has been attributed to eradication of long lived plasma cells.

**Table 1. Randomized Trials in Europe for Autoimmune Disease**

Disease	Acronym and Web site	Design	Status: No. Patients Randomized	Endpoint Comment	Principle Investigator
Systemic sclerosis	ASTIS <a href="http://www.astis-trial.com">http://www.astis-trial.com</a>	HCT (CY+ ATG; CD34 selected) Control: Monthly Cy	150	Survival without organ failure at 2 years. No unexpected toxicity.	J van Laar, D Farge, A Tyndall
Multiple sclerosis	ASTIMS <a href="http://www.astims.org">http://www.astims.org</a>	HCT (BEAM + ATG; unselected graft) Control: mitoxantrone	21	MRI lesional load (surrogate end point). No TRM	G Mancardi
Crohn's disease	ASTIC <a href="http://www.nottingham.ac.uk/icr/astic/">http://www.nottingham.ac.uk/icr/astic/</a>	All mobilized. Randomized to immediate versus late (1 year) HCT (CY + ATG; unselected graft)	14	Sustained remission at 1 year. No TRM	C Hawkey

TRM indicates treatment-related mortality; HCT, hematopoietic cell transplant.

## MS

Both clinical improvement and loss of active MRI lesions have been described [24]. These improvements persist despite return of a normal immune repertoire.

## The Future

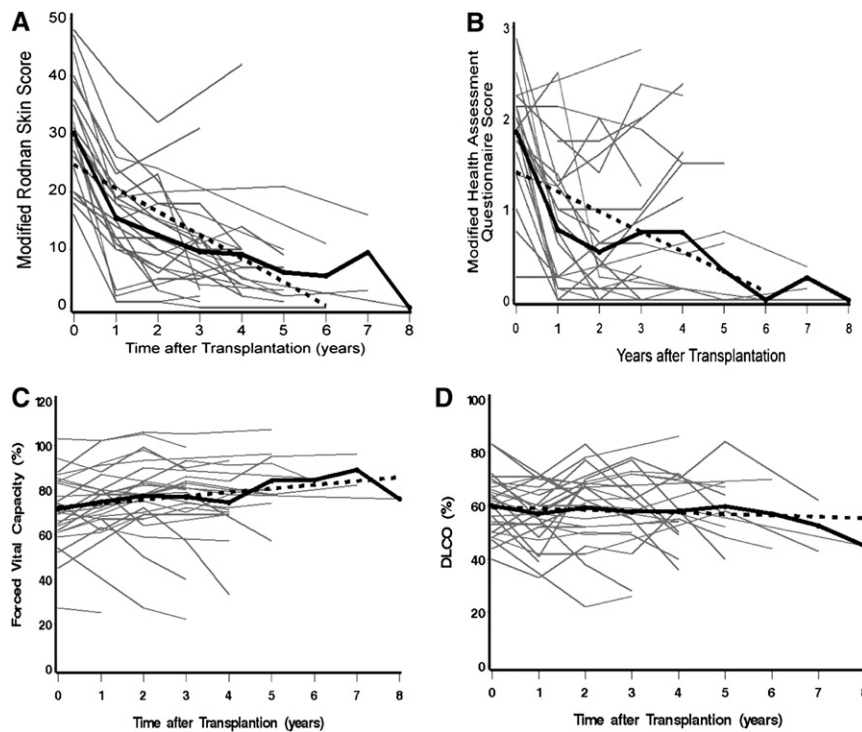
Since the 2005 analysis, additional patients have been registered in the EBMT/EULAR database (status update March 2009, courtesy of D Farge): total  $n = 1031$  consisting of MS  $n = 379$ , SSc  $n = 207$ , SLE  $n = 92$ , RA  $n = 88$ , JIA  $n = 70$ , ITP  $n = 23$ , CD  $n = 23$ . A recent analysis of the EBMT/EULAR database (D. Farge, personal communication) suggests a reduction in TRM attributable to more precise patient selection. However, some long-term follow-up data are missing, and one must assume that HCT will always be associated with some degree of TRM. The EBMT, EULAR, and the other learned societies are committed to completing these prospective RCTs and, if positive, developing more focused future protocols including mechanistic side studies to exploit the effectiveness and reduce the toxicity of HCT in autoimmune disorders. In the meantime, members of the Autoimmune Disease Working Party of the EBMT "consider it noncontributory to transplant patients with autoimmune disease outside the context of an approved, prospective RCT."

## AUTOGRAFTS AND ALLOGRAFTS FOR AUTOIMMUNE DISEASE: CHALLENGES AND OPPORTUNITIES IN CROSSDISCIPLINARY RESEARCH IN THE UNITED STATES

### Transplant Activity in the United States

Initial published experience focused on autologous HCT for 3 autoimmune disorders: severe diffuse scleroderma with internal organ involvement (SSc), SLE, and MS. Among 34 patients with life-threatening SSc followed up to 8 years after autologous transplant, stabilization/improvement of pulmonary disease and significant improvement in dermal sclerosis and functioning were observed [25]. Figure 2 depicts these transplant outcomes. This experience formed the basis of a phase III randomized comparison of intensive immunosuppression with 12 monthly pulses of i.v. Cy (750 mg/m<sup>2</sup>) versus immunoablation followed by CD34<sup>+</sup> selected autologous HCT in the SCOT (Scleroderma: Cyclophosphamide Or Transplantation) protocol (<http://www.sclerodermatrial.org>).

Encouraging results have also been reported in 50 patients with SLE followed to 7.5 years after autografting [26]. A subsequent phase III LIST (Lupus Immunosuppressive/immunomodulatory therapy or Stem cell Transplant) trial will be discussed below. In addition, 2 phase II U.S. trials in MS with 4-year follow-up



**Figure 2.** Improvements in serial Rodnan skin score (A), Health Assessment Questionnaire (B), Forced Vital Capacity, FVC (C) and Diffusion Capacity, DLCO (D) following immunoablation and autologous HCT. Gray solid lines depict individual patient parameters. Solid black lines are mean values and dashed lines represent the generalized estimating equation (GEE) for repeated measures. Mean Rodnan scores (0 is normal, 51 is maximal skin hardening throughout the body) decreased over time ( $P < .001$ ). Improvements in mean Health Assessment Scores (0 is normal) were also significant ( $P < .001$ ). The mean FVC values improved over time ( $P = .01$ ), whereas the mean DLCO did not change significantly ( $P = .5$ ). This research was originally published in Nash RA, McSweeney PA, Crofford LJ, et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study. *Blood*, 2007;110:1386-1396. Copyright the American Society of Hematology.

have been reported with apparent reduction in MS episodes [27,28].

Table 2 lists currently open HCT trials for adults with autoimmune disorders as registered with *ClinicalTrials.gov*. Six major diseases each with 2 to 6 accruing studies are presented. Of these 26 trials, 15 are autologous and 11 allogeneic transplant studies. Only 5 of the 26 are randomized trials and only 4 are NIH supported.

**Cross Disciplinary Considerations**

For patients with severe SSc, comorbid organ impairment is common; for those with MS, timing of HCT is an issue; and for individuals with SLE, a host of conventional treatments are competing options. With experience gained in autologous HCT for autoimmune disease, and with considerable allograft experience with RIC regimens for hematologic malignancies, allogeneic transplant regimens are being investigated for autoimmune disorders [29]. Collaboration across disciplines promotes recruitment of patients onto HCT trials despite restricted funding by insurers that remains a significant issue, as predicted at the beginning of this clinical research [19]. What was less clear a decade ago was the relentless growth in regulatory steps in protocol development. For example, for 16 trials of the East-

ern Cooperative Oncology Group, some 481 distinct processes were required to activate a protocol consuming a median of 808 days effort from study concept to enrollment [30]. This delay is not unique to oncology. The LIST study was an NIH supported randomized transplant trial in SLE [31]. It was never activated because of delays in protocol development.

**Physician Barriers to Protocol Recruitment**

Despite formation of cooperative and community research groups, annual enrollment onto oncology trials in the United States remains stuck at 3% of all newly diagnosed adults with cancer [32]. Factors cited by physicians as road blocks to patient recruitment include extra uncompensated time required to enroll subjects, regulatory paperwork, and insurance overload. It has recently been estimated that \$31 billion represents the collective cost to U.S. physician practices for time spent on interactions with insurers for approval of nonprotocol tests and treatments [33]. As the authors of the study note, this cost to interact with health plans is equal to 6.9% of all U.S. expenditures for physician and clinical services. Health insurers may further restrict protocol recruitment by denial or delay of coverage for treatment on a study. Because of uncertainty about insurer reimbursement for clinical

**Table 2. Recruiting Clinical Trials of HCT for Adults with Autoimmune Disease (Listed on ClinicalTrials.gov as of 8/30/09)**

Study	Autologous	Allogeneic	Phase	Randomized	Location	# Patients Needed	NIH Sponsored	Start Date
Scleroderma (systemic sclerosis)								
1	+		II	+	USA	60		Sep 2005
2		MSD/MUD	II		USA	20		Aug 2006
3		MSD/CBD	II		USA	10	NCI	May 2005
4	+		III	+	USA	113	NIAID	Jun 2005
5		MSC	II		China	20		Aug 2009
6		MSD	I		USA	12		Aug 2007
Systemic lupus erythematosus								
1		MSD	I		USA	15	NHLBI	Jun 2004
2		MSD	I		USA	10		Jul 2004
3		MSD	I		USA	12		Aug 2007
4		MSD	II		USA	20		Jan 2003
5		MSC	I/II		China	20		Mar 2007
6	+		I		Germany	30		Aug 2008
Multiple sclerosis								
1	+		II		USA	30	NIAID	Jul 2006
2		MSD	II		USA	20		Jan 2003
3	+		III	+	USA, Canada, Brazil	110		Jan 2006
Rheumatoid arthritis								
1	+		I		USA	10		Jun 1997
2		MSD	I		USA	20		Sep 2002
Inflammatory bowel disease								
1	+		II	+	USA	110		Apr 2005
2	+		II		USA	25		Apr 2001
3	+		III	+	EBMT	48		Jun 2006
Type I diabetes mellitus								
1	+		I/II		Brazil	24		Dec 2003
2	+		I		UK	18		Nov 2008
3	+		I/II		China	200		Mar 2006
4	+		I/II		China	30		Jan 2008
5	+		I/II		Philippines	30		Nov 2007
6	+		II		China	30		Feb 2008

CBD indicates cord blood donor; EBMT, European Bone Marrow Transplant Group; HCT, hematopoietic cell transplant; MSC, mesenchymal stem cells; MSD, HLA matched sibling donor; MUD, matched unrelated donor; NCI, National Cancer Institute; NHLBI, National Heart, Lung Blood Institute; NIAID, National Institute of Allergy and Infectious Diseases; NIH, National Institutes of Health.

trials, 26 states have enacted legislation requiring all third-party payers to cover participation in cancer clinical trials (21 states) or in trials for life-threatening diseases (5 states). Laws require that trials be approved by the NIH, NIH Cooperative Group or Center, FDA, or the Departments of Defense or Veterans Affairs (<http://www.cancer.gov/clinicaltrials/ctlaws-home>). Unfortunately, only 5 of the 50 states mandate insurers to support clinical trials for life-threatening, nonmalignant diseases.

### Patient Barriers to Protocol Recruitment

Although adults in America are either very willing (32% of those surveyed) or inclined (38%) to participate in a clinical trial, most do not [34]. Fewer than 1% of the U.S. population enrolls each year in approximately 80,000 open clinical trials. When surveyed, major barriers to enrollment were not patient attitude; rather, the unavailability of an appropriate trial, disqualification because of comorbidities, and concerns about transportation or insurance coverage were the major impediments [34].

### Insurance Barriers to Protocol Recruitment

Unique among the wealthy nations, the United States has tens of millions of citizens without any

health care coverage from private insurer or third-party agency. The national debate on health care for the uninsured continues, but it remains true that HCT treatment trials are not available for the uninsured. Less obviously, clinical trials in HCT may also be unavailable for the insured. Health insurers make determinations for coverage that vary widely across and within plans. In a study by Peters and Rogers [35], 533 women with stages II-IV breast cancer were tracked for decisions on treatment coverage for high-dose chemotherapy and autologous HCT. Requests for coverage were denied in 121 (23%) of the women. In an accompanying editorial in 1994, a call was made to bring fairness, rationality, and public accountability to this reimbursement process [36].

Fifteen years on, problems not only persist but, arguably, are worse. Data from the first 95 patients with severe SSc submitted for health insurance coverage for the SCOT trial found that 51 (54%) subjects were initially denied coverage even though both treatments had been published in top-tier, peer-reviewed journals and found to have promising results [25,37]. Nevertheless, insurers judged the trial as “experimental or investigation” and denied coverage. Coverage decisions varied widely both across and within plans and funding

decisions within the same company were inconsistent or persistent in denial despite repeated prior reversals of denial on outside independent review. As stated in a recent Technology Assessment report prepared for the Agency for Healthcare Research and Quality (AHRQ), although published data are near nonexistent to quantify the magnitude of the effect of third party insurance denials on recruitment into clinical trials, insurance policies do restrict recruitment onto NIH supported clinical studies, and thus impede clinical research and the evidence needed to advance health care of the nation [38].

### Research Opportunities

The irony is that as protocol development and recruitment become more difficult and more laden with processes, the opportunity for mechanistic and genomic studies generated within clinical trials flourishes. For allogeneic HCT, studies of non-HLA encoded genes and their influence on outcomes is just beginning. Genes controlling drug metabolism and immune response are being discovered and will predict greater individualization of treatment as biobanks of relevant materials are being established worldwide [39]. Among subjects funded by insurance and randomized on the SCOT trial, over 4000 samples to date have been stored at baseline and 10 time points after randomization. Stored materials include serum, plasma, cells, DNA, and RNA. Requests for proposal for scientific studies using repository specimens were recently sent to over 5100 rheumatologists and 180 medical school directors of HCT programs and basic science departments in North America. In addition to the biobank, the NIH has funded 9 additional mechanistic research studies from materials from consenting subjects enrolled in SCOT to determine the molecular mechanisms of SSc, immune regulation, and responses to treatment.

### CONCLUSIONS

Considerable advances have been gained in our understanding of the immunobiology of autoimmune disease and HCT. Transient numeric depletion of immune cells does not explain the prolonged remissions observed after autologous HCT in patients with autoimmune disorders. The sustained clinical effects are better explained by qualitative change in the reconstituted immune repertoire. Autologous HCT induces substantial posttransplant modifications in the adaptive immune system. It remains to be determined whether and to what extent the suppression of inflammation observed posttherapy depends on the eradication of disease-associated T and/or B cell populations or on their regulation of function.

Pilot clinical trials of HCT for autoimmune diseases have paved the way for controlled RCTs that are underway in Europe and the United States. These studies illustrate the challenges of conducting clinical treatment trials in an intense regulatory environment found on both continents. Although impediments from the U.S. health insurance system can restrict clinical trial entry, there is vibrant opportunity and NIH support of basic science investigations within pivotal clinical trials.

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