

Future Strategies in Hematopoietic Stem Cell Transplantation for Rheumatoid Arthritis

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ABSTRACT. Patients with coincidental rheumatoid arthritis (RA) treated by allogeneic hematopoietic stem cell transplantation (HSCT) for drug induced aplastic anemia have been fortuitously cured of RA. Other than these examples with allogeneic HSCT, there is no known curative therapy for RA. Despite its potential to cure, allogeneic transplantation is not being offered to patients with RA due to transplant related mortality. Advances in HSCT conditioning regimens and better prevention of graft-versus-host disease should allow consideration of allogeneic HSCT as therapy for severe RA. We propose a new, well tolerated, nonmyeloablative allogeneic stem cell transplant regimen as treatment for RA. (J Rheumatol 2001;28 Suppl 64:42–8)

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RHEUMATOID ARTHRITIS

HEMATOPOIETIC STEM CELL TRANSPLANTATION

IMMUNOLOGY OF RHEUMATOID ARTHRITIS

Patients with coincidental rheumatoid arthritis (RA) treated by allogeneic hematopoietic stem cell transplantation (HSCT) for drug induced aplastic anemia have been fortuitously cured of RA¹⁻⁴.

RA is an inflammatory disease of joints but may have extraarticular manifestations including rheumatoid nodules, interstitial pneumonitis, and vasculitis^{5,6}. The etiology of RA remains elusive. It is an immune mediated disease but whether the response is directed against an infectious agent or against an unknown self-epitope (i.e., autoimmune) or both is unknown. If there is a predominate disease mediating cell (T or B lymphocyte, macrophage or synoviocyte), its identity also remains obscure.

Like many autoimmune diseases, RA is associated with particular HLA genotypes⁷. Severe RA has been associated with MHC class II DR4. Five RA prone alleles (DRB1*0401, DRB1*0404, DRB1*0405, and DRB1*0101), whose frequencies vary for different ethnic groups, all share a similar amino acid epitope sequence (LLEQKRAA or LLEQRRAA) encoded by codons 67–74^{8,9}. While the prevalence of RA in the general population is 1 in 100 people, a heterozygote with any one of these alleles has an increased risk for RA varying from 1 in 20 to 1 in 80¹⁰. In an individual who has 2 HLA alleles associated with RA

(DRB1*0401 and DRB1*0404) the risk of developing RA is 1 in 7¹⁰.

The HLA sequence 67–74 on RA associated alleles is a HLA contact site for both peptide and T cell receptor binding. This suggests HLA presentation of a common infectious or self-antigen to T cells is involved in the pathogenesis of RA. An infection may lead to RA through molecular mimicry, bystander effects, or epitope spreading¹¹⁻¹⁵. Molecular mimicry arises from cross reactive T cell responses to peptides that have similar homology¹¹. The immune response initiated against an infectious agent may cross react with a self-peptide, leading to autoimmunity. Alternatively, inflammatory reactions against an infection may lead to bystander damage of normal tissues. Presentation of self-peptides by activated antigen presenting cells then precipitates the autoimmune disease. Once an immune process starts, T cell responsiveness can spread to other epitopes on the same or different peptides, a phenomenon termed determinant or epitope spreading¹²⁻¹⁵.

While MHC genes predispose to RA, the majority of patients with RA associated MHC genes remain disease-free. Environment and/or non-MHC genes must, therefore, contribute towards development of disease. Adjuvant arthritis (AA) and collagen induced arthritis (CIA) in rats are models for RA and are induced by injection of adjuvant or collagen and adjuvant, respectively^{16,17}. At least 14 genomic intervals or loci (Cia1 to Cia14) are associated with CIA^{18,19}. The MHC loci correlate with Cia1. Putative genes associative with non-MHC Cia regions include cytokines such as interleukin 11 and transforming growth factor and growth regulating oncogenes such as B cell leukemia/lymphoma3 (BCL3) and Bcl-2 associated X protein (BAX)^{20,21}. Mice with either AA or CIA, in which environmental stimuli are necessary to induce arthritis, may be cured by either autologous, syngeneic, or allogeneic hematopoietic stem cell transplantation²²⁻²⁵. The lowest

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relapse rate occurs in animals receiving an allogeneic transplant. Relapse after an autologous HSCT correlates inversely with intensity of the immune suppression conditioning regimen in various models of autoimmune diseases.

While RA may be an autoimmune disease, in some ways, it may be viewed as similar to a malignant lymphoproliferative disorder. Hallmarks of malignancy are loss of growth inhibition, oncogene mutations, and clonality. Fibroblast-like synoviocytes from patients with RA show autonomous *ex vivo* proliferation^{26,27}, a behavior that may contribute to *in vivo* cartilage destruction. One possible mechanism by which cells escape growth inhibition is oncogene mutation. Somatic mutations of the p53 oncogene occur *in vivo* within involved joints and *ex vivo* in RA synoviocyte cultures²⁸⁻³⁰. Skewing of B lymphocyte immunoglobulins and T cell receptors suggests clonal expansion of both B and T lymphocytes within inflamed RA synovium³¹⁻³³. Similarly to a malignancy, RA can cause severe disability and pain, and can shorten life expectancy³⁴⁻⁴⁴. In summary, the immunology of RA intersects traditional aspects of rheumatology, autoimmunity, malignancy, and possibly infectious diseases.

RESULTS OF AUTOLOGOUS HSCT TRIALS FOR RA

If RA is caused by environmental exposure, brief but dose intense immune suppression and autologous HSCT may ablate the autoreactive immune cells and allow regeneration of a new immune system. Several patients have undergone autologous transplantation for lymphoma who had coincidental RA⁴⁵⁻⁴⁷. The autografts were not purged of lymphocytes, and the transplants were not tailored as therapy for RA. Nevertheless, short term complete responses were observed for 4 months, 20 months, and at last followup greater than 19 months⁴⁵⁻⁴⁷.

Since the rationale for autologous HSCT is to use high dose chemotherapy to attempt ablation of the immune system, autologous HSCT allows maximization of immune suppression beyond otherwise marrow-limiting toxicity. Autologous stem cells are infused to reinitiate hematopoiesis and regenerate immunity. Based on testing the premise of dose intense immune suppression, several centers have reported early posttransplant outcomes when RA is the only indication for autologous transplantation (Table 1)⁴⁸⁻⁵⁴. In general, the procedure has been well tolerated without mortality. HSCT offers an almost immediate relief of symptoms. Patients become pain-free, sometimes for the first time in years. Activities required for daily living, such as buttoning a shirt or combing hair, rapidly return to normal. Morning stiffness resolves, rheumatoid nodules disappear, sedimentation rate normalizes, and rheumatoid factor may disappear.

Most of the protocols did not, however, increase immune suppression to the point of myeloablation. In the most

common regimen used (200 mg/kg cyclophosphamide with or without antithymocyte globulin), hematopoiesis would recover even without stem cell infusion. While these studies showed that relatively high dose chemotherapy was well tolerated with marked American College of Rheumatology (ACR) improvements (ACR 50 or ACR 70), a complete remission was unusual and relapse within 2 years is common. There are suggestions of a dose-response effect. A dose escalation study of cyclophosphamide at 100 mg/kg revealed transient 1–2 month responses, but at 200 mg/kg response duration increased to 18–20 months⁵⁰. The few regimens that were myeloablative (busulfan and cyclophosphamide) seem to indicate more durable remissions⁵¹.

For an intense and expensive treatment such as HSCT to be considered for RA, sustained complete remissions or 70% improvement as defined by the ACR must be achieved⁵⁵. Several modifications are being considered, including: (1) using the current easily tolerated nonablative yet highly immunosuppressive regimen with posttransplant immune modulation, e.g., a tumor necrosis factor (TNF) inhibitor, cyclosporine A, and/or methotrexate, (2) using a more intense myeloablative regimen such as busulfan and cytoxan, or (3) performing allogeneic HSCT.

One approach is to advance the current nonmyeloablative stem cell transplants (Table 2) into phase III studies, but to decrease the high relapse rate, add chronic posttransplant immune suppression. This approach assumes that the posttransplant disease is easier to control with immune suppression than prior to transplant. The risk of infections, which are one of the major causes of death for patients with RA, may increase with posttransplant immune suppression. Implicit in this philosophy is acceptance of RA as an incurable but chronic and controllable disease.

A second approach is to view RA as a disease that is potentially curable by reinduction of self-tolerance through autologous HSCT. Since nonmyeloablative regimens induced remission of refractory disease and a dose-response effect may exist, phase I/II pilot studies using more intense myeloablative regimens will be initiated in the hope of inducing more durable remissions. A proposed regimen includes fludarabine 25 mg/kg/day × 5 days plus oral busulfan (4 mg/kg/day × 3 days) or intravenous Busulfex (intravenous busulfan) (3.2 mg/kg/day × 3 days) versus a regimen of cyclophosphamide (120–200 mg/kg) and Busulfex (3.2 mg/kg/day × 3 days) (Table 3). If a high percentage of patients continue to relapse following a myeloablative regimen, an autologous transplant will probably be unlikely to cure and the regimen related toxicity of more intense conditioning regimens would probably be unacceptable.

ALLOGENEIC HSCT OF RA

Anecdotal case reports of patients transplanted for aplastic anemia who had coincidental RA suggest that an allogeneic

Table 1. Reports of autologous or syngeneic hematopoietic stem cell transplantation for RA.

Disease	Conditioning	Comment
RA ^{49,52}	CY, ATG (autograft 2-3 log lymphocyte depleted)	Marked improvement up to 18 mo, but 2 relapsed
RA ⁴⁸	CY (autograft not lymphocyte depleted)	Marked improvement 6 mo followup
RA ⁵⁰	CY (autograft not lymphocyte depleted)	*Cohort I — CY 100 mg/kg, response for 1–2 mo *Cohort II — CY 200 mg/kg — improved for 17–19 mo
RA ⁵⁴	CY, ATG (autograft not lymphocyte depleted)	Relapsed at 5 and 7 mo
RA ⁵¹	Bu, CY (autograft lymphocyte depleted)	Remission > 10 mo
RA ⁵³	CY, ATG (identical twin)	Remission > 24 mo

RA: rheumatoid arthritis; CY: cyclophosphamide; Bu: busulfan; ATG: antithymocyte globulin.

Table 2. Possible nonmyeloablative autologous stem cell transplantation.

Day -7	-6	-5	-4	-3	-2	-1	0*
Fludara	Fludara CY	Fludara CY	Fludara ATG	ATG	ATG	ATG	CD34
Day -7	-6	-5	-4	-3	-2	-1	0*
Fludara	Fludara CY	Fludara CY	Fludara C-1H	C-1H	C-1H	C-1H	CD34 or PBSC

* Some posttransplant immune modulation such as a TNF inhibitor, cyclosporine, or methotrexate will be used as maintenance.

CY: cyclophosphamide, Fludara: fludarabine, C-1H: CAMPATH.

Table 3. Possible myeloablative autologous stem cell transplantation.

Day -8	-7	-6	-5	-4	-3	-2	-1	0*
Bu	Bu	Bu	CY	CY	CY	CY		CD34

* No posttransplant maintenance therapy. Bu: Busulfex (0.8 mg/kg q 6 h), CY: cyclophosphamide (50 mg/kg/day).

transplant may induce durable remissions (Table 4)¹⁻⁴. Four were reported in the 1970s when transplant related mortality was higher than current standards¹. Three died from transplant complications¹. Four patients are in complete remission for 4–8 years after transplant despite discontinuation of all immune suppression¹⁻³. In one patient, RA relapsed⁴. Hematopoietic chimerism at a molecular level using polymerase chain reaction for VNTR (variable number of tandem repeats) revealed 100% donor chimerism⁴. This does not necessarily suggest that relapse arose from donor immune cells. Evaluation of the involved organ system (i.e., joints) was not performed to determine if infiltrating lymphocytes, macrophages, and reactive synoviocytes were

of donor or host origin. In addition, although clinically normal, the serologic status of the donor (e.g., rheumatoid factor) was not reported.

The rationale for allogeneic HSCT is to change the genetic susceptibility to disease and also provide an allogeneic graft versus autoimmunity (GVA) effect⁵⁶. Hence, replacement of genetically susceptible host stem cells with resistant donor hematopoietic cells may prevent recurrence of the disease following transplantation even if the cause of RA is still present in the host. Perhaps more important is that it is very unlikely that the “last” self-reactive lymphocytes can be eliminated by intensive chemoradiotherapy alone, whereas after allogeneic bone marrow or blood stem cell

Table 4. Results of allogeneic hematopoietic stem cell transplantation in patients with aplastic anemia (AA) and RA.

Transplant Diagnosis	Autoimmune Disease	Type of Transplant	Outcome for Autoimmune Disease
AA ¹	RA	Allogeneic	Remission, died 93 days after transplant
AA ¹	RA	Allogeneic	Remission, died 75 days after transplant
AA ¹	RA	Allogeneic	Remission, died 58 days after transplant
AA ¹	RA	Allogeneic	Remission for > 2 yrs
AA ⁴	RA	Allogeneic	Relapsed after 2 yrs
AA ²	RA	Allogeneic	Remission for > 6 yrs
AA ³	RA	Allogeneic	Remission for > 8 yrs

Table 5. Possible allogeneic transplant regimens for patients with RA.

Day -7	-6	-5	-4	-3	-2	-1	0	+1
Fludara	Fludara B/C	Fludara B/C	Fludara	Fludara			PBSC	
			CSA	→	→	→	→	→
Day -7	-6	-5	-4	-3	-2	-1	0	+1
Fludara C-1H	Fludara C-1H B/C	Fludara C-1H B/C	Fludara C-1H	Fludara			PBSC	
			CSA	→	→	→	→	→
T cell depleted (CD34 ⁺ enriched) graft								
Day -8	-7	-6	-5	-4	-3	-2	-1	0/+1
Fludara C-1H	Fludara C-1H B/C	Fludara C-1H B/C	Fludara C-1H	Fludara	Fludara			CD34 ⁺
				CSA	→	→	→	→
Day -6	-5	-4	-3	-2	-1	0		
Fludara C-1H	Fludara B/C C-1H	Fludara B/C C-1H	Fludara B/C C-1H	Fludara B/C C-1H	Fludara C-1H			CD34 ⁺
		FK506/MMF	→	→	→	→	→	→

Fludara: fludarabine, C-1H: CAMPATH, CSA: cyclosporine, FK506/MMF: tacrolimus/mycophenolate mofetil, CD34⁺: infusion of lymphocyte depleted, i.e., CD34⁺ enriched, allogeneic stem cells, B/C: use of either busulfex or cyclophosphamide, PBSC: peripheral blood stem cells.

transplant all host hematopoietic cells can be replaced with donor hematopoietic cells, resulting in elimination by displacement of all self-reactive lymphocytes. Active cell mediated GVA effects may arise from mature donor lymphocytes eliminating, regulating, or inducing apoptosis of recipient autoreactive cells. A graft versus disease effect has already been established as the mechanism of remission

for several hematologic malignancies, first discovered in 1981 and termed graft versus leukemia (GVL)^{57,58}. The feasibility of alloreactive donor lymphocytes to eliminate all hematopoietic cells of host origin, including malignant lymphocytes that are fully resistant to all available chemoradiotherapy, was documented in early 1987⁵⁹⁻⁶¹. In analogy, clinical evidence for GVA effects has recently been

reported⁵⁶. While in theory a GVA effect may be beneficial, the most significant toxicity of allogeneic HSCT is an immunologic reaction of donor cells against normal host tissues, a complication known as graft-versus-host disease (GVHD). As a consequence, compared to autologous HSCT, allogeneic transplants may be complicated by higher morbidity and mortality, predominately due to GVHD. On the other hand, it was recently documented that hazardous myeloablative conditioning can be replaced with a much safer nonmyeloablative stem cell transplant, also known as mini-allograft⁶²⁻⁶⁴. Hence, it was documented that full and rapid engraftment of donor hematopoietic cells and parallel elimination of all host hematopoiesis can be accomplished by immunosuppressive rather than myeloablative conditioning, resulting in reduced procedure related toxicity and mortality⁶²⁻⁶⁴. Unfortunately, despite major improvement of the immediate outcome following HSCT, GVHD remains a major obstacle. It remains to be seen if the potential benefit of allogeneic HSCT justifies the risk of GVHD.

Based on the above, to be qualified for an allogeneic nonmyeloablative HSCT, candidates should have failed standard therapies and be in a high risk subset. There are individuals with RA who have a 5 year mortality of 30–70%, a rate higher than for triple vessel coronary artery disease or metastatic Hodgkin's lymphoma⁶⁵. These patients may be identified by the number of involved joints or functional status as assessed by a questionnaire on activities of daily living (Health Assessment Questionnaire, HAQ). Therapies for RA include corticosteroids and disease modifying antirheumatic drugs such as hydroxychloroquine, azathioprine, gold, and methotrexate. TNF inhibitors (infliximab or etanercept) are promising new agents for RA⁶⁶⁻⁶⁸. The failure rate for TNF inhibitors is 25–40% and all patients relapse if therapy is stopped^{67,68}. TNF inhibitors have been associated with demyelinating disease, a fair amount of serious and fatal infections, and a number of cases of myelosuppression. Candidates for HSCT should probably have failed combined TNF inhibitor and methotrexate — failure being defined as patients with active high risk disease such as 4–6 swollen joints, more than 20 involved joints, and being unable to answer more than 70% of the HAQ “with no difficulty.” In summary, to justify the risk-benefit of allogeneic HSCT, candidates should be selected for refractory disease (despite TNF inhibitor and methotrexate) that are at high risk for RA related mortality (determined by number of involved joints and HAQ).

Transplant regimen related morbidity and mortality may be markedly diminished by safer conditioning of patients with nonmyeloablative regimens designed to suppress the immune system enough to allow donor engraftment. Residual host hematopoiesis is eliminated by allogeneic donor immune cells. Of about 80 patients undergoing autologous HSCT, mortality is roughly 2% (Snowden J, personal communication). Regimen related mortality from a less

intense nonmyeloablative HSCT regimen should, therefore, be under 2%. GVHD remains the major hurdle for safely performing allogeneic transplantation.

Allogeneic transplant regimens being considered include: (1) well tolerated conditioning involving the use of nonmyeloablative regimens with unmanipulated marrow cells, (2) nonmyeloablative regimens with unmanipulated peripheral blood stem cells (PBSC), or (3) nonmyeloablative regimens with CD34⁺ enriched PBSC. In an unmanipulated nonmyeloablative HSCT, the incidence of extensive chronic GVHD remains controversial, but is probably 30–50%. Newer GVHD prophylactic agents currently under investigation, such as humanized anti-CD52 (CAMPATH-1H) given during conditioning, and newer posttransplant agents such as mycophenolate mofetil or TNF inhibitors are likely to diminish the incidence and severity of GVHD. This may be particularly important in RA, which is a disease of older individuals, especially considering that the risk of GVHD increases with age.

Lymphocyte depletion (CD34⁺ enrichment) of an allograft will markedly decrease the risk of GVHD but increase the risk of graft failure. Engraftment is affected by intensity of the conditioning regimen, the number of donor stem cells infused, and the number of T cells facilitating engraftment. The risk of graft failure may be partially offset by maximizing donor stem cell numbers (target dose $\geq 10^7$ CD34⁺ cells/kg recipient weight)⁶⁹. To minimize the morbidity of allogeneic HSCT, nonmyeloablative, yet strongly immunosuppressive conditioning could be combined with CD34⁺ enrichment of donor stem cells (Table 2). The regimen of CAMPATH-1H, cyclophosphamide, and fludarabine would be intensely immune suppressive but not myeloablative. In case the allograft is rejected, autologous hematopoietic reconstitution would be anticipated within 2 weeks, with at least transient improvement or resolution of RA. Indeed, a regimen currently being used to treat autoimmune diseases employs a nonmyeloablative transplant conditioning regimen (cyclophosphamide 200 mg/kg) without stem cell infusion⁷⁰. If engraftment occurs with low level (microchimerism) or mixed chimerism, indicative of host-versus-graft tolerance, and the patient's RA returns, donor lymphocyte infusions could be given at escalating doses until full donor chimerism is accomplished or RA resolves. To minimize the risk of GVHD, donor lymphocyte infusions would have to be carefully titrated with gradual dose escalation over extended intervals to allow monitoring for GVHD onset⁷¹. Temporal separation of donor progenitor cell infusion from donor lymphocyte infusion may allow clarification of the contribution of stem cell genetics versus GVA in remission of RA.

Designing transplant protocols that minimize procedure related morbidity and mortality may offer potentially curative therapy to patients with RA. Future studies should focus on a curative procedure for patients with intractable RA.

Allogeneic stem cell transplantation should be considered for patients with a fully matched donor, focusing on adoptive allogeneic cell therapy for total elimination of self-reactive lymphocytes while using safe, reduced intensity conditioning.

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