# Immunoablative Therapy and Hematopoietic Cell Transplantation in the Management of Severe Rheumatic Diseases (Review)

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Rheumatic diseases can be severe and unresponsive to standard therapeutic approaches.

The use of hematopoietic stem cell transplantation for treatment of refractory rheumatic diseases is a new concept, which is based on many experimental and clinical data obtained in the past 10 years. These studies suggest that immunoablative therapy supported by stem cell transplantation may lead to long-term remissions or even cure some human rheumatic diseases. It is extremely important to develop national protocols with clear inclusion criteria on the base of international consensus. This review is an attempt to summarize some preclinical and clinical data on stem cell transplantation in the treatment of severe rheumatic diseases and define the feasibility of this new procedure. In addition to practical aspects, some future prospects are also discussed.

**Key words**: rheumatic diseases, bone marrow transplantation, immunoablative therapy

## INTRODUCTION

Rheumatic diseases (RD) comprise a variety of disorders of unknown etiology and variable clinical presentation. Autoimmune mechanisms are thought to play a crucial pathophysiological role, although exact mechanisms are still poorly understood. Glucocorticosteroids and nonspecific immunosuppressive agents are generally employed with success, nonetheless several RD, when refractory to conventional treatment, are associated with a high mortality rate (1–4). This is due to the course of the disease and to the morbidity associated with a long-term use of steroids and immunosuppressive therapy given to overcome the refractoriness.

Although the exact autoimmune mechanism of RD remains unclear, it suggests an anomalous T-lymphocyte function, which regards both the appearance of autoreactive T- cells and to anomalies in antigen presentation. The exact cell lineages responsible for the appearance of autoimmunity remain unknown, but it has been demonstrated that all the cells of the immune system are derived from hematopoietic stem cells (HSC). Therefore RD appear to be hematopoietic system-dependent, and intensive myelosuppression and immunosuppression followed by HSC tansplantation could be an alternative therapy in severe cases. Stem cell trasplantation has been traditionally reserved for the treatment of life-threatening malignant and non-malignant hematological conditions. Curative potential and economic efficacy of SCT has been well-established in these diseases. It is also well-known that RD can cause severe disability to individual patient and perceptible socioeconomic consequences to society. This form of treatment has now been cosidered also for the management of severe RD with a clear economical benefit. In this setting, HSC could be obtained from an allogeneic or autologous donor. Improved techniques of HSC collection and manipulation and general patient supportive care following hematoimmunoablation have reduced the mortality associated with allogeneic bone marrow transplantation (BMT) to 15–30% and for autologous transplantation to 3%. The use of allogeneic BMT must remain extremely limited for the treatment of RD (5), especially because of pre-existing organ damage, and can be proposed only for homozygous twins or for RD in association with an underlying hematological disorder which justifies the risk of procedure. On the other

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hand, immunoablative therapy followed by autologous bone marrow or peripheral blood HSC transplantation would appear to represent an ideal approach in patients with refractory RD whose mortality risk is clearly higher than that associated with this procedure (6–12).

## AUTOIMMUNITY MECHANISMS

Despite the heterogenous clinical expression of RD it seems clear that most autoimmunity mechanisms share the following features:

– T-lymphocytes are predominant

– a genetic component is present. This factor is mostly encoded within the major histocompatibility complex (MHC)

– disease initiation and perpetuation probably involve activation and disturbance of specific subsets of regulatory T cells

– an infectious agent may trigger RD in genetically predisposed individuals.

Presentation of self- antigens probably occurs continuously, but under normal circumstances produces apoptosis, anergy or tolerance if presented without co-stimulatory molecules. However, in particular situations, there may be upregulation of accessory molecules or increased antigen processing and MHC loading, which lead to positively stimulated T cells. Alternatively superantigen, such an infectious agent, may activate native autoreactive T cells, enabling them to travel from the lymph node and react in a target tissue. It is known that autoreactive T cells escape thymic deletion and remain in the periphery. In particular situations these lymphocytes may be activated and induce an autoimmune process. This process is probably controlled by regulatory T cell subsets, and a breakdown of this regulatory network allows the development of chronic RD (13–17). Reversal of this vicious circle and reinstitution of the normal regulatory network is one of the postulated mechanisms behind the concept of BMT in RD (18).

## PATIENT SELECTION

A critical aspect of the whole project has been patient selection. In general, a concept has developed that a possible candidate for BMT should have:

– failed conventional treatment

– severe threat to life or vital organ function enough to justify the risk of the procedure

– sufficient capacity to withstand the BMT procedure

The current guidelines for patient selection by the Consensus Meeting of the European League against Rheumatism (EULAR) and European Group for Blood and Marrow Transplantation (EBMT) were published in 1999 (11). These guidelines are summarized in Table I.

Table 1. **EULAR / EBMT guidelines for stem cell transplantation in autoimmune diseases (adopted from Tyndall and Gratwohl )**

| Potential rheumatological indications |
|---|
| Adult |
| – systemic sclerosis |
| – autoimmune pulmonary hypertension |
| – necrotizing vasculitis |
| – rheumatoid arthritis |
| – systemic lupus erythematosus |
| – antiphospholipid syndrome |
| – cryoglobulinemia |
| Pediatric |
| – systemic sclerosis with pulmonary hypertension |
| – dermatomyositis |
| – necrotizing vasculitis |

## CHOICE OF TECHNIQUES

The are no indications that BMT techniques for RD should be different in any aspect from those used in other diseases. This includes hematopoietic cell source, mobilization techniques, graft engineering, conditioning and supportive care. In the absence of experience, a consensus group decided on an initial "safety first" approach.

The initial choice of employing autologous BMT was based on the reduced risk of transplant-related mortality.

Most autologous transplants have been performed with mobilized peripheral blood progenitor cells. The choice of peripheral blood stem cells over bone marrow was based on more rapid recovery, shorter duration of hematopoiesis aplasia and fewer risk of bleeding and infectious complications.

A standard mobilization technique with granulocyte colony stimulating factor (G-CSF) – 10 mcg/kg with or without prior Cyclophosphamide has been proposed. A few cases of exacerbation of RD during mobilization have been observed (19–21).

At present, there are no data on the relative efficacy of various conditioning regimens in the treatment of human RD. The consensus group therefore proposed a choice of four regimens, all with well-defined toxicity profile: Cyclophosphamide with or without antithymocyte globulin as used in aplastic anemia, Cyclophosphamide plus total body irradiation, Cyclophosphamide plus Busulfan as used for leukemias, or BEAM (Carmustine, Etoposide, Arabinoside, Melphalan) combination chemotherapy as used for lymphomas. Selection of the regimen is thus based on toxicity aspects and as well on the experience and philosophy of the transplantation center.

## GRAFT MANIPULATION

One of the most discussional items remains to be graft manipulation. Some animal experiments suggest that autoreactive T cell clones may cause relapse of autoimmune disorder after autologous HSC transplantation.

According to consensus guidelines, for most of the recorded patients the treatment included an *ex-vivo* T-cell depletion step. The use of antithymocyte globulin in association with conditioning regimen causes a rather effective *in-vivo* T-cell depletion (11). The efficacy of this manipulation for long-term success in the treatment of RD is currently unknown, and the question of need for T-cell purging remains open (22). It is possible that the stage of the disease at the time of transplantation will be more important than the number of potential autoreactive T cells in the graft. T-cell depletion could have a negative therapeutic effect, because the graft may contain lymphocytes capable of both autoaggressive and suppressive activity. The final result depends on the balance of the two.

In addition, some of the patients who received T-cell purged transplants had persistently low CD4 (T-helper) levels 2 years after BMT and remained at high risk for nosocomial infection.

Practical aspects of HSC transplantation are summarized in Table 2.

Table 2. **Practical aspects of HSC transplantation**

| |
|---|
| Setting: Autologous peripheral blood progenitor cells |
| Stem cell mobilization: |
| G-CSF 10 mcg/kg/d or Cyclophosphamide 4 g/m$^2$ + G-SCF |
| Cell dose: > 2.0 x 10 E6/kg CD34 + HSCells |
| Graft manipulation: |
| T-cell depletion (T-cells < 1 x 10 E5/kg) |
| Conditioning regimen: |
| Cyclophosphamide 200 mg/kg ± antithymocyte globulin |
| Cyclophosphamide 120 mg/kg + total body irradiation |
| Cyclophosphamide 120 mg/kg + Busulfan 16mg/kg |
| BEAM |

## TOXICITY

There is no published data that autologous BMT in RD patients may be associated with a higher or different toxicity than in patients with malignant diseases. Autologous BMT is associated with a 2–5% mortality. It may be even higher in RD patients with a different spectrum of vital organ involvement at the moment of transplantation. Hematopoietic engraftment is rarther quick, but the majority of the patients are expected to experience neutropenic fever complicated with septicemia (23). It is possible that patients with RD may be at higher risk of posttransplant infections because of their previous immunosuppressive treatment.

Long-term risks are also important considerations. Infertility, early menopause may be an important issue in younger patients. However, the risk is dependent on the type of the conditioning regimen applied, and the sex and age of the patients. A potential long-term risk after autologous BMT is development of secondary malignancies (24). These are well-known complications of transplantation for various malignant diseases, however, they are more dependent on the type and magnitude of previous chemotherapy, which is not applied in RD, than on the conditioning regimen itself.

## PRELIMINARY RESULTS

According to the Basel European Registry, 145 autologous HSC transplantations for RD were reported (11, 18, 25). The transplant-related mortality was 8 ± 1% with a 2-year actual survival rate of 92%.

The mortality risk associated with the procedure was well below those calculated from the estimated probability of death under conventional therapy for each disease. (Table 3).

Table 3. **Death probability at 6 months and 5 years for a given pathology**

| 5 years | 6 months |
|---|---|
| Scleroderma with pulmonary or cardiac involvement | 0.13<br>0.75 |
| Myositis with pulmonary or cardiac involvement | 0.11<br>0.70 |
| Vasculitis (FFS>1) | 0.09<br>0.6 |
| Lupus with renal involvement | 0.03<br>0.25 |
| Severe rheumatoid arthritis | 0.02<br>0.20 |

## IMMUNE RECONSTITUTION AND LONG-TERM IMMUNE TOLERANCE

Whether autologous BMT is simply a form of a more profound immune suppression or offers a chance of cure through induction of peripheral immunological tolerance remains to be seen (26). The early results suggest the reason to be optimistic, and it is hoped that following autologous BMT the reconstituting immune system will be tolerant toward previously autostimulatory antigens, owing to immunological education in thymus-equivalent structures, as have been proposed to exist in the gastro-intestinal system.

It will be extremely important to observe whether such restoration of the regulatory network can occur or whether clinical effects are due to eradication of RD.

## FUTURE PERSPECTIVES

Experimental stem cell transplantation for treatment of variuos autoimmune disorders in animals formed a basis for the application of this form of treatment to human RD (27). In the future it will be important to develop new disease models resembling more their human counterpart.

At present, autologous BMT for the treatment of RD is at its infancy. Matters of patient selection, conditioning regimens, stem cells mobilization and graft engineering should be carefully assessed in future clinical trials. All patients should be registred in EULAR/EBMT Registry independently of the final outcome. It is very important to follow up carefully all the patients undergoing HSC transplantation for treatment response, immunological reconstitution, long-term effects. It is quite possible that cure or prolonged remission in autologous setting may require use of immunomodulation with, *e.g.*, Cyclosporine to induce an autologous graft-*versus*-host reaction in order to prevent early relapse after transplantation. If the concept of immune tolerance is correct, this option could be extended to patients with early poor prognosis RD, to avoid irreversible organ damage and to improve the quality of life.

Although allogeneic BMT is associated with a significant mortality and not considered suitable for treatment of human RD, this situation may change in the future. Precise graft engineering and so-called mini-transplants with less intensive non-myeloablative conditioning regimens may significantly reduce the transplant-related toxicity and mortality (28).

Despite some enthusiasm experience in stem cell transplantation in severe RD is very limited. It is evident that only international multicenter collaboration and carefully planned trials can clarify the place of BMT in the treatment of rheumatic diseases.

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**IMMUNOABLIACINĖ TERAPIJA IR KRAUJODAROS KAMIENINIŲ LĄSTELIŲ TRANSPLANTACIJA GYDANT SUNKIAS REUMATINES LIGAS**

S a n t r a u k a

Remiantis pastarojo dešimtmečio eksperimentinių ir klinikinių tyrimų duomenimis, galimybė pritaikyti imunoabliacinę terapiją ir kraujodaros kamieninių ląstelių transplantaciją reumatinių ligų gydymui gali būti vertinamas kaip naujas šiuolaikinis gydymo metodas. Straipsnyje pateikiami apibendrinti literatūros duomenys apie šio naujo metodo pasaulinę patirtį ir numatomas ateities perspektyvas reumatinių ligų terapijoje.