

Autoimmune Disease Treatment with Stem Cell Transplantation

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Abstract

Autoimmune Diseases (ADs) are diseases in which the immune system mistakenly attacks and destroys self-molecules due to a disruption of immunologic tolerance to auto-reactive immune cells. The goals of treatments for ADs are to 1) reduce symptoms, 2) control the autoimmune process and 3) maintain the body's ability to fight disease. Allogeneic Hematopoietic Stem Cell (HSC) transplantation has been shown to be a relatively successful treatment for experimental ADs. Intra Bone Marrow-Bone Marrow Transplantation (IBM-BMT) has been proven to be a powerful strategy for allogeneic BMT due to the rapid hemopoietic recovery and the complete restoration of T cell functions even in donor-recipient combinations across MHC barriers. In this review, we summarize the ADs treatable with IBM-BMT.

Keywords: Autoimmune disease; Stem cell transplantation; Intra-bone marrow-bone marrow transplantation; Mesenchymal stem cell

Introduction

Autoimmune Diseases (ADs) represent a heterogeneous group of disorders with genetic, environmental and individual etiological factors [1]. The etiopathogenesis of systemic ADs has previously been attributed to T cell deficiencies, polyclonal B cell activation, macrophage dysfunction and environmental factors [2]. ADs affect organs and tissues such as blood vessels, connective tissues, thyroid, pancreas, joints, muscles, and skin. Allogeneic Hematopoietic Stem Cell (HSC) transplantation has been shown to be a relatively successful treatment for experimental ADs, and there are a number of reports of Bone Marrow Transplantation (BMT) being used to treat ADs in various mice [3-10]. For example, the following were all resolved after BMT: Insulin-Dependent Diabetes Mellitus (IDDM), in which beta cells are destroyed by the immune system; Rheumatoid arthritis (RA), which primarily attacks the synovial joints; Systemic Lupus Erythematosus (SLE), which is a chronic auto-inflammatory disease of unknown etiology; Multiple Sclerosis (MS), which affects the brain and the central nervous system, and Autoimmune Pancreatitis (AIP), which produces pancreatic masses and ductal strictures [11,12]. ADs show abnormal autoimmune responses by auto-antibodies and T- cell responses to self-molecules in pathological conditions [13]. Abnormal immune regulatory processes are represented as they are characterized by activation and expansion of immune cell subsets in response to non-pathogenic stimuli. Autologous BMT can treat ADs because it can ablate an abnormal self-reactive immune system resulting from chemotherapy and regenerate a self-tolerant immune system from HSCs [11].

ADs: Criteria and Classification

The criteria for ADs include 1) direct evidence from transfer of pathogenic antibodies or pathogenic T cells; 2) indirect evidence based on reproduction of the autoimmune disease in experimental animals; 3) and circumstantial evidence from clinical clues [14]. ADs can be broadly divided into systemic and organ-specific autoimmune disorders, depending on the principal clinico-pathologic features of each disease. Systemic autoimmune disorders often affect joints although they may also affect the skin, kidneys, heart, lungs and red blood cells. They include SLE, Sjögren's syndrome, scleroderma, rheumatoid arthritis, and dermatomyositis. As the name suggests, organ-specific diseases primarily target one specific organ, and include

Insulin-Dependent Diabetes Mellitus (IDDM), Hashimoto's thyroiditis and Graves' disease [15]. Our previous report indicated that both systemic and organ-specific ADs could be prevented by BMT [16].

SLE Treated with BMT

SLE is a chronic systemic AD that affects a variety of organs and is predominantly seen in females, even though it is unclear how sex hormones could promote lupus [17]. These loci which designated *Sle 1*, *Sle 2*, and *Sle 3*, contain genes that mediate the loss of immunologic tolerance to nuclear autoantigens. B-cell hyperactivity and T-cell dysregulation have been identified to promote lupus in mice [18]. The W/BF1 mouse is known to be an animal model of SLE that produces not only anti-DNA antibodies but also anti-platelet antibodies, resulting in decreased platelet counts. These mice show a high level of proteinuria, increased white blood cell counts, hypertension, and myocardial infarction due to the high levels of anti-cardiolipin antibodies [8]. They have also been shown to develop lupus nephritis with myocardial infarction [19]. The transplantation of bone marrow cells from normal mice to W/BF1 mice was found to prevent and cure the lupus nephritis, thrombocytopenia and anti-phospholipid Ab syndrome [8]. Moreover, the platelet counts were normalized and circulating anti-platelet Ab levels as well as anti-phospholipid levels were reduced [20].

In MRL mice, the mostly recessive *lpr* mutation results in both the accumulation of CD4-, CD8- CD3+ T cells in lymphoid tissue and many features of generalized AD. A mutation of the Fas gene that induces apoptosis is -- the *lpr* mutation -- has been detected in MRL/*lpr* mice, and these mice show severe ADs such as RA and SLE [21,22]. Since MRL/*lpr* mice possess radio-resistant abnormal HSCs, they suffer a relapse 5 months after conventional BMT, and we have found that there is an MHC restriction between HSCs and stroma cells. BMT plus

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bone graft prevented the recurrence of ADs in MRL/lpr mice, which survived more than 48 weeks after this treatment. These results suggest that stroma cells play a crucial role in the prevention of graft failure in ABMT [7].

The thymus plays a crucial role in the elimination of the autoreactive clones involved in the development of ADs [23]. The combination of BMT plus Thymus Transplantation (TT) can treat the ADs in the MRL/Lpr mouse, because the allogenic T cells newly developed by TT are naïve T cells, which show less Fas expression and more resistance to apoptosis than the activated memory T cells with their high Fas expression [24]. BMT plus TT may induce early and continuous supplementation of donor-naïve T cells. In addition, although FasL-mediated apoptosis is less effective, other cytotoxic molecules such as perforin, granzyme, TNF α or TRAIL may be involved in the mechanisms to overcome chimeric resistance [25].

MS Treated with Stem Cells

MS is an inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms [26]. Genetic variations have been shown to increase the risk [27]. Specific genes that have been linked with MS include differences in the Human Leukocyte Antigen (HLA) system - a group of genes on chromosome 6 that serves as the Major Histocompatibility Complex (MHC) [26]. That changes in the HLA region are related to the susceptibility to MS has been known for over thirty years. Moreover, alleles of IL2- and IL7-receptor α genes and those in the HLA locus are identified as heritable risk factors for MS [28].

Stem cell therapy is the therapeutic plasticity by which neural precursors can replace damaged oligodendrocytes and myelin, and also effectively attenuate the autoimmune process in a local, nonsystemic manner to protect brain cells from further injury, as well as facilitate the intrinsic capacity of the brain for recovery. MSCs inhibit various components of the immune system that contribute to tissue damage, and MSCs can access the Central Nervous System (CNS) to provide protection against tissue damage [29]. MSCs and the relatively easy expansion of autologous cells have opened the way to their experimental application in MS. Phase I clinical trials are in progress to explore the use of MSC therapy for the treatment of MS [30].

IDDM Treated with BMT

The Type 1 Diabetes Genetics Consortium dataset provides a unique resource for genetic analysis because of the large sample size, the high-resolution HLA typing, and the quality control procedures for the genotype typing. A large number of studies have demonstrated that specific alleles at the DRB1, DQA1, and DQB1 loci are strongly associated with IDDM [31-34]. However, allelic variation at these loci cannot account fully for the pattern of HLA haplotype sharing among affected sib-pairs.

The Non-Obese Diabetic (NOD) mouse is a spontaneous mouse model of IDDM and has many of the same autoantigens targeted by human T cells [35,36]. There are at least fourteen different loci linked to disease development in the NOD mouse. The first Idd locus recognized, Idd1, is linked to the Major Histocompatibility Complex (MHC), and its inheritance and expression are a paradigm for the other non-MHC Idd genes [37]. Our previous report stated that when IDDM was transferred from NOD mice to normal mice (C3H/HeN), the chimeric mice developed both insulinitis and overt diabetes more than 40 weeks after BMT. These mice exhibited elevated glucose levels and

abnormal glucose tolerance, and beta cells were selectively destroyed by the infiltration of T cells [16]. NOD mice that received transplanted BALB/c nu/nu bone marrow cells displayed normal T- and B-cell functions, and newly developed T cells in the allogenic bone marrow recipients were tolerant to cells with both donor- and host-type major histocompatibility complex determinants. These results suggest that ABMT might contribute to the prevention of islet destruction, and to the restoration of self-tolerance [5]. One report has demonstrated that BMT promotes beta cell regeneration after acute injury through bone marrow mobilization [38]. Another report has described how, in rats, the transplantation of pancreatic islets from two MHC-disparate donors was achieved in combination with IBM-BMT, resulting in improved blood glucose levels and the amelioration of streptozotocin-induced diabetes mellitus [39]. Bone marrow could potentially serve as an autologous source for cells, thus minimizing rejection problems beyond the inherent autoimmune characteristics of IDDM [40]. One report has suggested that bone marrow stem cell-derived endothelial progenitor cells and beta cells regenerate in response to pancreatic injury [41]. Furthermore, MSCs significantly suppressed beta cell-specific T cell proliferation in the pancreas [42].

ADs Treated with IBM-BMT

IBM-BMT has been proven to be more effective than IV-BMT, since it can replace not only the HSCs and MSCs to be recruited, thereby preventing the risk of graft rejection, but also allows the use of a mild conditioning regimen [43]. IBM-BMT thus seems to be the best strategy for ABMT, since 1) no GVHD develops even if whole bone marrow cells are injected; 2) no graft failure occurs even if the radiation dose is reduced; 3) hemopoietic recovery is rapid and 4) the restoration of T cell functions is complete even in donor-recipient combinations across MHC barriers [44].

MSCs are used in the treatment or amelioration of inflammatory diseases and ADs [45]. MSCs from healthy donors and AD patients reduced the proliferation of autologous and allogenic Peripheral Blood Mononuclear Cells (PBMCs) by up to 90% in a cell dose-dependent fashion. The immune-suppression was independent of the proliferation of the MSCs and was also effective on already proliferating cells. Moreover, it was independent of the clinical activity of the AD. The MSC dose-dependent pattern of suppression of proliferation was observed also with transformed B-cell lines, similar to that observed with proliferating PBMCs [46]. MSCs are responsible for the normal turnover and maintenance of adult mesenchymal tissues, and have been shown to have immune-modulatory properties and immunosuppressive capacities, acting on different immune cells both *in vitro* and *in vivo*. Among animal models of AD, mouse Experimental Autoimmune Encephalomyelitis (EAE) has been successfully treated with mouse *in vitro*-expanded MSCs, whereas in a mouse model of collagen-induced arthritis (CIA), the disease was exacerbated following MSC infusion [47-49]. Autologous bone marrow-derived MSCs have been shown to be potently antiproliferative to stimulated T cells from normal participants and autoimmune patients [46].

The MRL/Lpr mouse is a suitable model for establishing a safe new strategy for ABMT because the MRL/Lpr mouse itself is radiosensitive, whereas the abnormal HSCs of the MRL/Lpr mouse are radioresistant [7]. IBM-BMT can be used to treat intractable ADs under reduced radiation doses without any immunosuppressants. This seems to be attributable to the enhanced engraftment of donor-derived cells in the early stage after this treatment. IBM-BMT rapidly accelerates the proliferation of donor-derived progenitor cells and simultaneously

maintains hemopoietic progenitor cells, resulting in the recovery of hemopoiesis [43]. The abnormal HSCs of the MRL/Lpr mouse are radioresistant, so it is also a suitable model for establishing a safe new strategy for ABMT [43].

RA Treatment with IBM-BMT

The SKG/Jcl mouse develops a chronic T cell-mediated AD that mimics RA. One report has demonstrated that serum IL-10, TGF β -1, and IL-2 concentrations were significantly increased compared to the control group when treated with N-acetyl-D: -glucosamine (GlcNAc), indicating that this has suppressive effects on experimental RA in this mouse model [50]. Bone marrow cells of C57BL/6 mice were transplanted into the tibia of SKG/Jcl mice by IBM-BMT. There was no evidence of arthritis 12 months after the IBM-BMT and the hematolymphoid cells in the recipient mice were reconstituted by donor-derived cells. Moreover, the percentages of Treg (Foxp3+/CD4+) cells, the percentage of receptor activator of NF- κ B ligand+ cells on the CD4+ T cells and the serum levels of TNF α , IL-1 and IL-6 were all normalized. IBM-BMT is a viable method of immunological manipulation that suppresses the severe joint destruction and bone absorption in SKG/Jcl mice and lends further credence to the use of this methodology in humans with intractable RA [51].

Bone marrow-derived MSC therapy has already been implemented, the rationale being to exploit its immunomodulatory properties in a CNS-targeted manner. In Phase I/II open safety clinical trials, bone marrow derived MSCs were delivered intravenously and intrathecally into patients with chronic MS who had not responded to conventional treatments, and to patients with amyotrophic lateral sclerosis [52]. Th17 cells are a subset of T helper cells that play an important role in host defense and the pathogenesis of various human autoimmune and inflammatory diseases [53]. Elevated IL-17 levels are found in the serum and tissues of patients with various ADs, including RA, MS and systemic lupus sclerosis [54-56]. IL-17-deficient ABMT prevents the induction of collagen-induced arthritis in DBA/1J mice [57].

AIP Treated with IBM-BMT

AIP is a chronic pancreatitis with raised levels of serum IgG4, responsiveness to immunosuppressive therapy, and no apparent underlying cause such as chronic alcoholic pancreatitis. AIP has been reported to show chronic pancreatitis with pancreatic duct stenosis [58,59]. Pancreas-specific autoantigens and significant reactivity to lactoferrin, carbonic anhydrase, pancreas secretory trypsin inhibitor, amylase-alpha, heat-shock protein and plasminogen-binding protein have been detected in the sera of patients with AIP, even though these are not specific for AIP [60-66]. Patients with ADs in the liver, intestine and blood vessels often show AIP [67].

The male wistar Bonn/Kobori (WBN/Kob) rat is known to be a unique animal model for chronic pancreatitis with widely distributed fibrosis and degeneration of parenchyma because of infiltration of lymphocytes. These findings have been shown to be related to sex hormone, genetic factor and immune disturbances [68-70]. Our previous report demonstrated that WBN/Kob rats develop duxyoadenitis, sialoadenitis, thyroiditis, sclerotic cholangitis and tubulointerstitial nephritis, and is a useful animal model for AIP and Sjögren-like syndrome in humans. IBM-BMT has been shown to prevent these ADs in this animal model [12]. However, IBM-BMT has a long way to go before an effective standard regimen of AD therapy for patients has been developed. There are several important ethical problems, as well as concerns regarding graft-versus-host diseases and graft rejection, and improvements in life span. Ethical problems center

on finding appropriate donors, the transplantation phase, and short- and long-term follow-up care during the BMT procedure.

In conclusion, most intractable diseases are not only HSC disorders but also MSC disorders. ADs show aberrant reactions of adaptive or innate immune systems. Stem cell transplantation has been shown to improve the functions of immune systems and to be a valuable strategy of the treatment various ADs.

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