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Haematopoietic Cell Transplantation and Immunotherapy for Autoimmune Diseases in Children and Adults

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1. Introduction

1.1 Autoimmune diseases

Autoimmune diseases (AD) are individually rare, but together they affect approximately 5-8 percent of the population in Western countries [1-2]. They are usually defined as a clinical syndrome caused by the activation of T cells or B cells, or both, in the absence of an ongoing infection or other discernible cause. In recent years it is well established that low level of autoreactivity is physiologic [3] and crucial to normal immune function. Autoantigen helps to form the repertoire of mature lymphocytes, and the survival of naive T cells [4] and B cells [5]. Thus, the assumption is that lymphocytes evolved not to distinguish self from foreign, but rather to respond to antigen only in certain microenvironments, generally in the presence of inflammatory cytokines [6].

There are several classifications of AD. They may appear to be either systemic (as in the case of systemic lupus erythematosus) or organ-specific (as in the case of type 1 diabetes mellitus). Another classification distinguishes between diseases in which there is a general alteration in the selection, regulation, or death of T cells or B cells and those in which an aberrant response to a particular antigen, self or foreign, causes autoimmunity.

Susceptibility to AD is multifactorial with genetic and enviromental factors being dominant together or alone in each of the syndromes. Infectious-derived antigens are also well known triggers for autoimmunity. Molecular mimicry has clearly been demonstrated in herpes keratoconjunctivitis in mice. T cells that react to the viral protein UL6 cross-react with a peptide derived from a corneal antigen [**7**]. Rheumatic fever represents an autoimmune response triggered by streptococcal infection and mediated by cross-reactivity between streptococcal and cardiac myosin [**8-10**]. In autoimmune diabetes, T-cells recognize both a peptide derived from the autoantigen glutamic acid decarboxylase and a highly analogous peptide from coxsackievirus P2-C protein [**11**], and in Guillain–Barr' syndrome antibody cross-reactivity has been demonstrated between human gangliosides and lipopolysaccharides of Campilobacter jejuni [**12**]. Drugs like Procainamide can also alter the immune repertoire. Finally, foreign substances may act as haptens and render autoantigens immunogenic.

1.2 Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) is a well established modality for the treatment of several hematological diseases; however, it can also be used for the treatment of severe forms of immunological diseases.

Conventional AD therapy is effective in most patients, but some patients are resistant to the anti-inflammatory and immunosuppressive agents used or are only capable of responding to high doses of such medicines, which are toxic. In such cases, bone marrow (BM) reconstitution is required. Thus, high doses of immunosuppressants, followed by HSCT, have become an alternative treatment for many diseases involving the immune system. These include multiple sclerosis (MS), systemic sclerosis (SS), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and systemic lupus erythematosus (SLE) [13-14].

The application of HSCT to the treatment of AD has been studied since the 1970s. The success of this approach has been widely demonstrated in animal models as well as in BM transplant patients who were shown to also have concomitant AD. For example, an allogeneic HSCT which was intended to cure aplastic anemia in 2 patients with concomitant RA, resulted in the complete remission of RA for at least 11 years [14].

The rationale of using HSCT in autoimmune diseases is to achieve the complete ablation of the aberrant immune system and to regenerate a new and antigen-naive immune system. The more widespread use of transplantation is hindered by the risks associated with cytoreductive treatments necessary to create space for the transplanted hematopoietic stem cell population and by the slow kinetics with which immune competence is restored following transplantation. Mild conditioning regimens may be insufficient to create space for donor stem cells. However, fully myeloablative approaches using irradiation and chemotherapy agents may associate with severe side-effects such as the risk of oncogenic DNA damage. Nevertheless, unlike malignancies where any visceral organ impairment is a contraindication to HSCT, disease-related organ dysfunction is often the indication for HSCT of autoimmune disorders. For this reason, the regimen must also avoid further injury to the disease-affected organ. For example, myeloablative agents such as bleomycin, BCNU (carmustine), and radiation that are complicated by pulmonary fibrosis would not be the ideal conditioning agents for a disease such as scleroderma in which a major cause of death is related to pulmonary fibrosis and pulmonary artery hypertension [**15**].

The stem cell graft may be syngeneic (from identical twin), allogeneic (from a donor with identical human leucocyte antigen – HLA – system), or autologous (from the patient). In autologous setting, the goal of regenerating a new, antigen naive immune system, from the patient's own hematopoietic stem cells requires the re-emergence of thymic educated T cells. Therefore, the goal of the conditioning regimen would focus on immune ablation rather than myeloablation [16-17]. Allogeneic grafts are associated with complications such graft versus host disease (GVHD) or graft rejection. GVHD contributes to the elimination of the host's aberrant immune system and thus theoretically, makes allotransplant a better option in the treatment of autoimmune diseases [18]. However, the HSCT treatment related mortality in hematological diseases is higher following allogeneic grafting (15–35%) than following autotransplant (3–10%). Because of these high mortality rates following allotransplants, the autologous method could prove to be a better alternative in autoimmune patients, too [19-20]. On the other hand, in recent years the transplant related mortality (TRM) is extremely low due to better peri-transplant care. Thus, it may shift again for the allo-transplant as the better choice for autoimmune diseases, in the coming years.

2. HSCT in specific clinical indications

2.1 Multiple sclerosis

Multiple sclerosis (MS) is an organ-specific AD mediated by T cells triggered against structural components of myelin in the central nervous system (CNS). Subsequent to inflammation in the CNS, demyelinization and loss of axons may occur, resulting in interruption of the electrical signal. Most MS patients present episodic relapse and improvement, known as relapsing-remitting MS, followed by a phase called secondary progressive MS. There is yet another form of MS known as primary progressive MS, which is generally resistant to conventional therapies [21].

Available treatments for MS are not curative. They are able to reduce inflammation in the CNS and to delay the advance of the disease, but disease control is frequently unsatisfactory. The use of stem cells in the treatment of MS is based on the immunosuppressor and immunomodulatory effects of HSCT, which may favor the immunological balance [21]. Furthermore, the multi-focal nature of MS makes the injection of stem cells into each affected site impracticable, which means that the cells need to be attracted to the pathological areas. The intravenous administration of stem cells may be an alternative in MS and other neuroinflammatory conditions, in which there is permeability of the hematoencephalic blood brain barrier in the inflammatory areas. Moreover, the discovery that stem cells are capable of reaching the CNS and of transdifferentiating or acquiring oligodendrocyte and possibly neuronal properties, suggests that they may be able to act in re-myelinization and neuron repair.

Intensive immunosuppresion followed by HSCT has been suggested as potential treatment in severe forms of MS. Since 1995, more than 400 patients have been treated with HSCT. Stabilization or improvement occurred in almost 70% of cases at least for 3 years post-transplant. Magnetic resonance revealed the capacity of autologous HSCT to suppress or markedly reduce gadolinium-enhancing lesions. The progression of brain atrophy declined after two years post-HSCT. The profound immunological changes following autologous HSCT may result in restoration of self-tolerance. Relatively young patients with active inflammatory lesions of relatively short duration and rapidly progressive disease, but still low disability scores, unresponsive to conventional therapy seem the best candidates for transplantation. Transplant-related mortality was 6% in the first European Group for Blood and Marrow Transplantation (EBMT) report and 5.3% in the second one. No deaths were reported since 2001. Very high-intensity conditioning regimen is associated with higher risk of toxicity without significant increase in efficacy. The effects of transplantation and transplantation-related morbidity are dependent on patient-selection, time of transplantation and conditioning regimens used [**22**].

2.2 Rheumatoid arthritis

Rheumatoid Arthritis (RA) is a systemic AD that, in the long term, can lead to irreversible destruction of the joints, loss of mobility, as well as a reduction in both the quality of life and life span. Cellular and humoral immune responses can contribute to the development of lesions. Rheumatoid factor, an autoantibody specific to the Fc region of human IgG, is found in 80% of patients with RA [23].

In a retrospective analysis summarizing the European experience of the first 78 registered patients, a significant improvement was demonstrated, with 67% achieving an American

College of Rheumatology 50% response (ACR-50) at some time post-transplant [23]. Most of the patients had failed a median of five (range, two to nine) conventional diseasemodifying antirheumatic drugs (DMARDs) before the transplant. Some degree of relapse was seen in 73% of patients post-transplant, but in most cases it was relatively easy to control with drugs that had proven ineffective pre-transplant [24]. A multi-center trial in Australia failed to show any advantage of CD34 selection of the graft after non myeloablative conditioning with cyclophosphamide [25].

2.3 Systemic sclerosis

Systemic sclerosis (SSc) is a multi-system autoimmune disease of yet unknown origin, with vasculopathy and progressive fibrosis that is highly variable in its clinical manifestations, but patients with diffuse cutaneous SSc and internal organ involvement have reduced life span [26-29]. Two major clinical subsets are widely accepted, the limited (lcSSc) and the diffuse cutaneous (dcSSc) forms, which can be distinguished by the extent of skin involvement, the autoantibody profile and the pattern of organ involvement. It has an incidence of $1/10^5$, and is responsible for significant morbidity with a 5-year mortality rate of at least 30% of all patients. In patients with rapidly progressive dcSSc, the 5-year mortality is estimated to be 40–50%. Although cyclophosphamide was observed to have a small beneficial effect, more effective therapies for the severe forms of SSc are required to improve outcome [30-34].

HSCT, mostly autologous but also allogeneic in some specific cases, has been employed worldwide since 1996 as a new therapeutic strategy in patients with a poor prognosis. Almost 200 HSCT procedures have been reported in the EBMT data base up to date. Several publication reported significant decrease in the degree of the scleroderma and dermal fibrosis, improved overall function and, in general, stability of internal organ function [35-36] post autologous HSCT. Two ongoing phase III trials have been designed in parallel, the ASTIS and the SCOTT trail aiming to analyze the benefits from autologous HSCT and its effects on survival, skin, and major organ function in patients with severe dcSSc. The backbone of the conditioning regimens focuses on immunoablation rather than myeloablation and uses cyclophosphamide, anti-thymocitic globulin and total body irradiation [37].

2.4 Autoimmune cytopenias

Immune thrombocytopenic purpura (ITP) is a disease in which platelets are sensitized by anti-platelet antibodies or circulating immune complexes, provoking the early removal of these cells from the circulation. This process results in thrombocytopenia and bleeding. About one third of patients with ITP do not respond well to conventional therapies. High doses of immunosuppressors may lead to remission of the disease; however, this involves risks related to myelosuppression. HSCT aims to accelerate reestablishment of the hematological parameters and concomitantly reduce the number of autoimmune cells in the organism [38]. Several sporadic case reports of HSCT for autoimmune cytopenias have been published, but only two studies have been reported with moderate numbers of patients. In the US, of 14 patients with chronic refractory ITP submitted to high dose cyclophosphamide (200 mg/kg) followed by autologous HSCT, 6 achieved durable complete responses and 2 obtained durable partial responses [39]. The study concluded that the infusion of

hematopoietic stem cells (HSCs) had accelerated the hematological reestablishment. Since clinical improvement was not associated with quantification of anti-GPIb or anti-GPIIIa antibodies, it is likely that other platelet antigens were involved in the ITP. The responses were not associated with the number of $CD3^+$ cells infused into the patients, although the deletion of T lymphocytes may have prevented the re-infusion of auto-reactive T cells [38].
In a recent study presented at the 2011 annual meeting of the EBMT [40], a summary of the updated EBMT registry on HSCT for autoimmune cytopenias was discussed. Twenty-four patients (14 males, 10 females) received 26 transplants. Patients had Evans syndrome (10), autoimmune haemolytic anemia (AIHA) (6), immune thrombocytopenia (5) and autoimmune lymphoproliferative syndrome (3). The median age at diagnosis was 4 yrs. (range 0.3-16) with a median age at transplant of 7.1 yrs (1.5-17). All patients failed multiple second and third line immunesuppressive treatments with median disease duration of 41 months (1 -180 months). Transplants were autologous for 7 and allogeneic for 19 patients. Seven patients died of treatment related mortality, 6 in the allo and 1 in the auto group with a total TRM of 26%. 13 patients had a complete response after a long follow-up (120 months) while 6 patients relapsed, 2 in the allo and 4 in the autologous group. The conclusions of the authors are that allogeneic and autologous HSCT may induce a response in half of patient with severe refractory autoimmune cytopenia. Given the rarity of disease and the low number of transplant per center (1 over 10 years) it is high unlikely that a prospective study can ever be done. At the same time HSCT may be considered for patients with Evans syndrome, AIHA and ITP refractory to 2-3 lines of treatment under the "Clinical Option" criterion. If an HLA identical sibling is available, an allogeneic HSCT may be considered. Alternative donor from a well matched unrelated donor may also be considered in Evans syndrome. In the case that no compatible donor can be identified, autologous HSCT is an option.

2.5 Diabetes mellitus

In recent years, there has been a rapid growth in the number of cases of diabetes throughout the world. This epidemic affects approximately 6-8% of the world population and the number of newly diagnosed patients increases yearly [**41**]. Of these, approximately 10% are type 1 diabetes, insulin-dependent diabetes mellitus, an AD caused by the progressive destruction of the insulin-secreting pancreatic ß-cells in the islets of Langerhans [**42-43**] which regulate blood sugar levels by secretion of insulin. Recent clinical data suggest that the disease could be cured if an adequate supply of new ß-cells were made available. Hence, one goal of pancreatic developmental biology is to understand how endogenous ß-cells are made, with the hope of producing them exogenously [**43**]. Pancreatic islet cell transplantation is an attractive treatment of type 1 diabetes [**44**]. Clinical islet transplantation trials based on cadaveric allogeneic islets have demonstrated that it is indeed possible to restore near-physiological insulin secretion capacity in type 1 diabetic patients through transplantation of insulin-producing cells [**45**].
The immunoablation with immune reconstitution supported by transplantation of autologous hematopoietic stem cells might save pancreatic beta cells from destruction by malfunctioning immune system. This when applied sufficiently early in the course of diabetes type 1 (i.e. prior to destruction of vast majority of these cells) may lead to insulin independence in transplanted patients. In a recently published study [**46**] 15 patients (age 19 - 32) with early diabetes type 1 (no more than 6 weeks from diagnosis, C-peptide positive, Anti GAD - antibodies positive)

underwent therapy. With a mean time of observation of 16 months (range 8 - 29 months). No severe complications were observed during the transplantation and in the post transplantation period. Fourteen out of 15 patients became independent of exogenous insulin after the transplantation with median time without exogenous insulin for all these patients of 14 months (range 3 – 29 months). Median day of insulin withdrawal was + 37 (range + 6 to + 103) post transplant. Eleven patients (73%) remain in remission for the median time from transplantation of 16 months. In three patients there was a relapse of requirement for exogenous insulin and the median post-relapse insulin dose for these patients was 0.08 IU/kg of body weight, significantly reduced from pre-transplant dose. The average HbA1c concentration was 11.5 % at diagnosis, 5.88% at 6 months and 5.76% at 12 months after the transplantation. The authors conclude that immunoablation following by autologous HSCT leads to significant reduction for exogenous insulin requirement in all patients and to exogenous insulin independence in early diabetes type 1 in majority of cases.

2.6 Crohn's disease

Crohn's disease (CD) is a chronic illness, immunologically mediated, of unknown etiology but probably induced by an exposure to intestinal bacteria or their component antigens leading to an excessive T helper type 1–mediated chronic inflammation of the gastrointestinal (GI) tract in patients with genetic susceptibility [**47-48**]. Some patients remain seriously ill with active disease after all therapeutic options have been exhausted [**49-51**]. Moreover, a distinct excessive mortality from CD exists in this group of patients [**52-55**]. This group of patients may suffer from one or more of the following morbidities: inability to eat, frequent nausea, vomiting, diarrhea, malnutrition, growth retardation in children, fistulas, abdominal pain, extra-intestinal symptoms, psychologic distress from an ileostomy or colostomy bag, iatrogenic addiction to narcotics, toxicities of standard therapies, and multiple surgeries that may lead to short-gut syndrome, chronic total parenteral nutrition, and liver failure.

Appreciating all of the above, it was reasonable to try and use the modality of HSCT in the setup of refractory CD. Thus, 2 main groups, Italian and United States (US), published their data regarding autologous HSCT for refractory CD patients [**56-58**] demonstrating beneficial short- as well as long-term clinical outcome after using the procedure in 4 and 24 patients, respectively, applying nonmyeloablative regimen.

The procedure was safe, without mortality, even in patients heavily pretreated with anti-tumor necrosis factor (TNF) therapy and with ongoing fistulas.

Although relapses have occurred in these series of patients after using a cyclophosphamide/anti-thymocytic globulin (ATG) nonmyeloablative regimen, there has been achievements of treatment-free remissions for as long as 5 years, and remission (CDAI < 150, CSI < 12) rates between 70% to 80% for 5 years. The authors emphasize that because approximately 40% of patients with CD develop intolerable side effects or lose response to anti-TNF [**59**], further investigation of stem cell therapy including the role of CD34 graft selection and type of conditioning regimen or other methods to maintain remission without surgery for anti-TNF refractory CD appears warranted.

3. Important issues related to allogeneic HSCT for autoimmune diseases

Treatment of life-threatening autoimmune diseases in animal models with induced or spontaneous autoimmune diseases can be accomplished by a 2-step procedure involving

elimination of self-reactive lymphocytes with an immune ablative conditioning regimen followed by infusion of autologous or allogeneic stem cells, respectively. In animal models it was shown that using such a strategy, autoimmunity could be adequately controlled. It is speculated that de-novo development of the T and B cell repertoire from uncommitted progenitor cells in the presence of the autoantigens may be the best recipe for re-induction of self-tolerance, similarly to the normal ontogeny of the immune system during the induction of self tolerance in fetal stage. Reduced intensity conditioning (RIC) is further applied in recent years aiming to diminish regimen-related toxicity by decreasing conditioning regimen intensity compared to conventional myeloablative transplants.

In the case of allogeneic transplants for malignant disease, instead of using chemoradiotherapy to achieve disease control, relapse is prevented by an immunological graft versus leukemia (GVL) or graft versus tumor (GVT) effect induced by donor lymphocytes, natural killer cells, and/or dendritic cells infused with the allogeneic graft or after HSCT by infusion of peripheral blood donor lymphocytes. For autoimmune diseases this allogeneic effect may also be applied. Unlike autologous HSCT in which the goal is to suppress and restart the immune system from autologous HSCs, the goal of allogeneic stem cells is twofold. First, to change the genetic predisposition to disease by changing the host's susceptible to the donor's resistant stem cell compartment. Second, to introduce donor's lymphocytes with the capacity to eliminate all residual self-reactive host lymphocytes through a process known as graft versus autoimmunity (GVA) effect, in analogy to GVL in leukemia and GVT in some metastatic solid tumors. It is not clear whether a full chimera, in which all HSCs are reconstituted from the donor, or mixed chimerism, with coexistence of both donor and recipient hemato- and immunopoiesis, is sufficient to control disease.

Full donor chimerism in malignancies has been complicated by a high rate of GVHD, an immune-mediated disease in which allogeneic donor lymphocytes are directed against the whole recipient body, resulting in donor T-cell mediated attack against different organs and tissues, causing significant morbidity and mortality. It is assumed that while suffering from GVHD, the patient has the advantage of GVL or GVT, which is the main goal of the transplant. This rational may holds true, at least partially, in the case of autoimmune diseases. Nevertheless, that means swiching one immunological disease by another one with a very similar mechanism. The only difference is the origin of the attacking T-cells. While in the basic autoimmune disease they are autologous T-cells, in GVHD they are donor-derived T-cells.

4. Stem cell mobilization from patients with autoimmune diseases

Originally, HSCs were collected directly from the bone marrow donors by repeated aspirations performed under epidural or general anesthesia. Subsequently, to facilitate hematopoietic reconstitution and avoid the discomfort associated with multiple bone punctures, as well as the need for operating room and general anesthesia, the most common method of collecting HSCs has become mobilization from the peripheral blood. Since negligible HSCs are detectable in the peripheral blood during steady state, either a hematopoietic growth factor such as granulocyte colony-stimulating factor (G-CSF) or chemotherapy (usually cyclophosphamide) with or without G-CSF is necessary in order to mobilize HSCs from the marrow to the vasculature where it can be easily collected [60].

Hematopoietic growth factors used to mobilize stem cells also have cytokine immune-modulating effects [61] and, depending on growth factor and autoimmune disease, may

either exacerbate or ameliorate disease severity. For example, in experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis (MS), growth factors such as Flt-3 ligand, stem cell factor (SCF), and G-CSF exacerbate disease, while thrombopoietin (TPO) mobilizes stem cells without affecting disease severity. G-CSF may also cause an exacerbation of MS, sometimes with significant neurological deterioration [60, 62]. In both EAE and MS, simultaneous use of daily corticosteroids or infusion of cyclophosphamide prior to starting G-CSF prevents disease flares [62]. The same may be for RA where G-CSF may cause an increase in joint swelling, tenderness and pain that responds to corticosteroids. On the other hand, G-CSF has not been reported to exacerbate scleroderma. Based on the above, growth factors selected for mobilizing HSCs from patients with autoimmune diseases need to be considered on a disease-specific basis. Hematopoietic growth factors that stimulate production of proinflammatory cytokines or alter trafficking of neutrophils, lymphocytes or dendritic cells may exacerbate some autoimmune diseases. This effect may be prevented by either administration of corticosteroids or mobilization with combined cyclophosphamide and G-CSF. Mobilization with chemotherapy alone or in combination with G-CSF may cause neutropenic fevers and infection-related mortality if prophylactic antibacterial and antifungal antibiotics are not utilized. This can be prevented if only G-CSF will be used. Nevertheless, combined cyclophosphamide with G-CSF for mobilization will sum in higher stem cell yields, an in vivo purge effect by selectively killing lymphocytes in cell cycle, and a disease-ameliorating effect.

5. Future directions and therapeutic implications

Future and near-future directions in the area of autoimmune diseases will be influenced by the general role and directions in medicine. Thus, more and more immune biology modulators and therapies directed against specific molecular pathways will become available. This may alter the need for HSCT as the only curative modality or further subject it to those who would fail all the biological treatments.

Individualize or personalized treatment will become the main stream in therapy. This is extremely true for autoimmune diseases where variety of sub-classes and genom-based mapping will give the opportunity to treat each patient in a different, more specific way. On the other hand, it is expected that HSCT would become safer with less treatment-related morbidity and mortality, making transplants more accessible to wider range of patient populations. Thus, we will see more and more allogeneic transplants done for large-scale indications.

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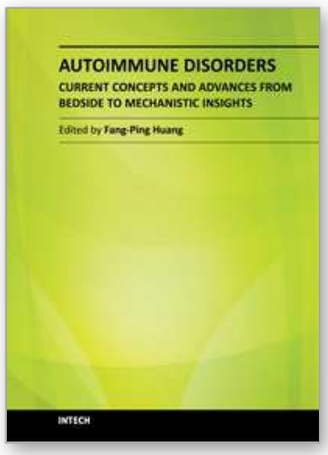

Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights

Edited by Dr. Fang-Ping Huang

ISBN 978-953-307-653-9
Hard cover, 614 pages
Publisher InTech
Published online 14, November, 2011
Published in print edition November, 2011

Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Menachem Bitan (2011). Haematopoietic Cell Transplantation and Immunotherapy for Autoimmune Diseases in Children and Adults, Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights, Dr. Fang-Ping Huang (Ed.), ISBN: 978-953-307-653-9, InTech, Available from: http://www.intechopen.com/books/autoimmune-disorders-current-concepts-and-advances-from-bedside-to-mechanistic-insights/haematopoietic-cell-transplantation-and-immunotherapy-for-autoimmune-diseases-in-children-and-adults

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