BMT for Severe Autoimmune Diseases: An Idea Whose Time Has Come

By Richard K. Burt, MD [2]

Most patients with autoimmune diseases are thought to have a normal life expectancy, and thus are treated conservatively. However, these diseases have a diverse clinical course. A small subset of patients have "severe autoimmune diseases," or SADS, which are rapidly progressive and associated with early mortality. If patients with SADS can be identified before they develop irreversible organ damage, aggressive intervention would be indicated. Consequently, patients with SADS are now being enrolled in experimental protocols of immune ablation and hematopoietic stem-cell rescue (ie, bone marrow transplantation [BMT]) at several US institutions. For various reasons, including the high cost of BMT, it will probably be years before the benefits, if any, of this procedure are known. [ONCOLOGY 11(7):1001-1017, 1997]

ABSTRACT: Most patients with autoimmune diseases are thought to have a normal life expectancy, and thus are treated conservatively. However, these diseases have a diverse clinical course. A small subset of patients have "severe autoimmune diseases," or SADS, which are rapidly progressive and associated with early mortality. If patients with SADS can be identified before they develop irreversible organ damage, aggressive intervention would be indicated. Consequently, patients with SADS are now being enrolled in experimental protocols of immune ablation and hematopoietic stem-cell rescue (ie, bone marrow transplantation [BMT]) at several US institutions. For various reasons, including the high cost of BMT, it will probably be years before the benefits, if any, of this procedure are known. [ONCOLOGY 11(7):1001-1017, 1997]

Introduction

There are numerous autoimmune diseases that, depending on the predominant organ system involved, are treated by a variety of medical subspecialists. The common philosophy in the treatment of all these disorders is suppression or modulation of the immune system in an attempt to ameliorate pain, disability, or organ dysfunction. Many autoimmune diseases are viewed as having a good prognosis and are treated conservatively. Overall survival for most afflicted individuals is generally accepted as normal, although impairment of vocational or avocational activities may occur. Another general feature of autoimmune diseases, however, is their diverse clinical course. This may range from a single episode without residual damage, to an indolently progressive disease with significant disability to a rapidly progressive disease with early mortality (in a small subset of patients). It is this latter subset of patients with a high risk of early mortality for whom Alberto Marmont coined the term "severe autoimmune diseases" (SADS).[A. Marmont, Genova, Italy, personal communication] If patients with SADS can be identified before they develop irreversible organ damage, aggressive intervention would be indicated. For this reason, patients with SADS are now being enrolled in experimental protocols of immune ablation and hematopoietic stem-cell rescue at several institutions in the United States (Table 1).

Rationale

TABLE 1
Institutions With Protocols for Immune Ablation and Hematopoietic Stem-Cell Rescue in Patients With Severe Autoimmune Diseases (SADS)

The first successful human allogeneic bone marrow transplants were performed in children with immune deficiencies (severe combined immunodeficiency and Wiskott-Aldrich syndrome).[1] A normal immune system was generated in these children following transplantation of marrow from their unaffected siblings.

The rationale for the use of BMT in SADS is to condition the patient with a chemoradiotherapeutic regimen to ablate the immune and hematopoietic compartments and then rescue the patient from fatal aplasia by reinfusing hematopoietic progenitor cells. The infused stem cells will give rise to new differentiated cells of hematopoietic lineage, including red blood cells, platelets, neutrophils, and immune cells, such as B- and T-lymphocytes, natural killer cells, monocytes, and tissue macrophages.

The concept that BMT can cure autoimmune disease has already been demonstrated in aplastic anemia. In most cases, aplastic anemia arises from immune suppression of hematopoiesis. Depending on a patient's age and the availability of an HLA-matched sibling, initial treatment is either immunosuppression (eg, cyclosporine [Sandimmune] and antithymocyte globulin) or allogeneic BMT. Therefore, the standard of care for one human autoimmune disease, aplastic anemia, is already allogeneic BMT.

Ideally, specific immunosuppression could be targeted to regulate an autoreactive subset of lymphocytes while leaving the overall immune system intact. However, animal studies suggest that once inflammation is initiated against an immunodominant epitope, T-cell clones are recruited against other intramolecular and intermolecular subdominant or cryptic epitopes in the target tissue.[2] This phenomenon of epitope-spread would argue against any long-lasting effectiveness of specific immunotherapy and in favor of nonspecific immune ablation. Currently, corticosteroids, cyclophosphamide (Cytoxan, Neosar), and azathioprine are examples of broad-spectrum immunosuppressive agents used to treat autoimmune diseases.

Bone marrow transplantation maximizes the dose intensity of immunosuppression to the point of complete immune ablation. In addition, for more than 1 year following either autologous or allogeneic hematopoietic stem-cell reconstitution, the immune system is functionally immunosuppressed. The CD4 count is depressed, and the CD4/CD8 ratio is inverted for 12 to 18 months despite an otherwise healthy graft.[3,4]

Theoretically, BMT may induce lasting remission of an autoimmune disease by: (1) regeneration of a naive immune system, which may remain unresponsive to “self” until reexposure to the original disease-initiating agent(s); (2) generation or infusion of suppressor cells; (3) infusion of genetically distinct allogeneic stem cells, giving rise to T-cells and antigen-presenting cells with different major and/or minor histocompatibility complex surface molecules; and (4) generation of tolerance through exposure of lymphocyte precursors to self-epitopes early in development, possibly resulting in anergy and/or deletion of autoreactive repertoires.

If most autoimmune diseases were inherited as hematopoietic stem-cell defects, rescue with autologous hematopoietic stem cells would not be expected to cure the disease. However, most human autoimmune diseases do not appear to be an environmentally independent defect in hematopoietic stem cells since the majority of monozygotic twins are discordant for clinical disease. Although HLA association with certain autoimmune diseases suggests a genetic predisposition, environmental factors are probably required to initiate these diseases. Even if genetics did play a significant role in some autoimmune disorders, allogeneic stem-cell rescue from an HLA-matched but unaffected sibling might still prevent the disease.

Animal Models of Autoimmune Disease
There are two broad categories of autoimmune diseases in animals: those that arise spontaneously and those that require immunization. In general, spontaneously occurring autoimmune diseases are restricted to inbred strains and arise from genetic defects in the hematopoietic stem-cell compartment. On the other hand, diseases that arise after immunization may occur in a variety of outbred species and are due to priming (ie, activation) of normal, previously naive (ie, unresponsive) lymphocytes. The lymphocytic repertoire of animals that develop disease after immunization is obviously capable of recognizing self-antigens. What is not obvious is how these lymphocytes remain unresponsive until immunized to the self-protein.

**Spontaneously Occurring Diseases**

**TABLE 2**

Results of Bone Marrow Transplantation in Animal Models of Autoimmune Disease

Examples of spontaneously occurring autoimmune diseases include: a systemic lupus erythematosus (SLE)-like syndrome in Murphy Roth Lab lymphoproliferative (MRL/lpr mice and in the offspring between New Zealand black/New Zealand white mice (NZB/NZW F1 hybrid [B/W])[5-7]; a scleroderma-like illness in Tight-skin (Tsk) mice[8,9] and University of California Davis Line 200 (UCD) L200 chickens[10,11]; an inflammatory bowel disease in cotton top tamarin monkeys[12]; and an islet-cell inflammatory disease similar to type I diabetes mellitus in nonobese diabetic (NOD) mice[13,14] (Table 2). With the exception of the MRL/lpr mouse, the exact genetic defect(s) remain(s) enigmatic.

The MRL/lpr strain of mice develops a massive lymphoproliferative disease characterized by arthritis, glomerulonephritis, vasculitis, and anti-double-stranded (anti-ds) DNA antibody. These mice have a single gene defect that prevents high level expression of Fas, a protein that signals for apoptosis.[15,16] Normal mice express high levels of the Fas protein on CD4/CD8 double-positive thymocytes, inducing apoptosis of potentially autoreactive T-cell clones. T-cells normally upregulate Fas-surface protein when activated, which serves to control a lymphoproliferative response by inducing cell death. In MRL/lpr mice, autoimmunity results from a lack of normal lymphocyte programmed cell death. Transplantation of hematopoietic stem cells from MRL/lpr mice into an unaffected strain of mice results in the MRL/lpr phenotype and early death.

The NZB mouse develops spontaneous hemolytic anemia and a high titer of antierythrocyte antibodies.[5,6] When bred with the phenotypically normal NZW mouse, the offspring (F1 hybrid, B/W) develop a fatal immune glomerulonephritis and a high titer of anti-ds DNA antibody. Although hemolysis may occur, it is not prominent. The genetic defect in B/W mice is unknown, but transplantation of lymphocyte-depleted marrow into a normal mouse from another strain causes fatal immune glomerulonephritis.[7] Similarly, transplantation of lymphocyte-depleted marrow from Tsk[17] or NOD mice[18] into a genetically nonsusceptible strain results in a scleroderma-like illness and diabetes, respectively.

**Immunization-Induced Diseases**

Animal autoimmune diseases that arise after immunization with the appropriate self-epitope include: adjuvant-induced arthritis,[19] collagen-induced arthritis,[19,20] experimental autoimmune myasthenia gravis,[21,22] experimental autoimmune encephalomyelitis,[23,24] and experimental autoimmune myositis.[25] In all of these diseases, injection of tissue-specific protein in complete Freund's adjuvant initiates disease in susceptible species. The experimental autoimmune encephalomyelitis model will be presented as an example of an autoimmune disease that arises by immunization with target organ homogenate or immunodominant peptide(s).

Experimental autoimmune encephalomyelitis was first discovered as a disease in humans following
immunization with the Pasteur vaccine for prevention of rabies.[26] Patients developed an ascending paralysis due to contamination of the vaccine by rabbit central nervous system antigens. Subsequently, it was found that injection of spinal cord homogenate with Freund's adjuvant causes neurologic deficits in a wide variety of species, including mice, rats, rabbits, guinea pigs, and monkeys.

Disease manifestations vary by species. Lewis rats develop a monophasic ascending paralysis with a transient inflammatory spinal cord infiltrate. In the Buffalo rat, experimental autoimmune encephalomyelitis presents as an acute hemorrhagic encephalomyelitis. In the SJL/J mouse, experimental autoimmune encephalomyelitis manifests as an inflammatory, demyelinating, relapsing/remitting disease similar to relapsing/remitting multiple sclerosis (MS).

Further studies have shown that small amino acid sequences of myelin can also initiate experimental autoimmune encephalomyelitis. Several proteins are present in myelin, including proteolipid protein and myelin basic protein. Proteolipid protein is specific to the central nervous system, whereas myelin basic protein is present in both the central and peripheral nervous systems. Immunogenic myelin peptide sequences include proteolipid protein peptide sequence 139-151 or 178-191 and myelin basic protein peptide sequence 84-102. If the animal is immunized with only proteolipid protein sequence 139-151, peripheral lymphocytes during the first relapse proliferate only to proteolipid protein sequence 139-151. During subsequent relapses, epitope-spreading occurs, with lymphocytes proliferating to proteolipid protein sequences 139-151 and 178-191, as well as peptide sequences from other myelin proteins, such as myelin basic protein sequence 84-102.[1]

Use of BMT in Animal Models

Immune ablation and hematopoietic rescue has been attempted in several animal autoimmune disorders (Table 2). Diseases that arise spontaneously and are thought to be secondary to a stem-cell defect have been cured by allogeneic BMT from a strain resistant to the disease. For example, diabetes in the NOD mouse may be prevented by a hematopoietic stem-cell transplant from a nonsusceptible strain.[18] Immune glomerulonephritis, anti-ds DNA antibody, and lymphocytic infiltration of the liver and kidneys disappear in lupus-prone mice after allogeneic transplantation from a nonsusceptible strain.[27-29]

In contrast to stem cell-mediated autoimmunity, animal models of autoimmune disease induced by immunization have been arrested by either allogeneic, syngeneic, or autologous BMT (Table 2). Following autologous BMT, the inflammatory synovitis of adjuvant-induced arthritis resolves.[30,31] After syngeneic BMT in animals with experimental autoimmune myasthenia gravis, anti-acetylcholine receptor antibodies disappear and weakness reverses,[32] while in experimental auto-immune encephalomyelitis, neurologic progression is stopped.[33-36]

Syngeneic BMT from an unimmunized animal, if done before disease onset, prevents experimental autoimmune encephalomyelitis. If performed after the onset of neurologic disease, syngeneic BMT prevents clinical progression and peripheral lymphocytes no longer proliferate to myelin epitopes. Although the immunologic attack may be arrested, remyelination and/or axonal repair is necessary to reverse established neurologic damage. Therefore, depending on the animal and stage of disease, neurologic deficits may not completely resolve. The results of BMT in animal autoimmune disorders suggest that diseases arising from a stem-cell defect require an allogeneic donor from an unaffected strain to be cured. In contrast, autoimmune diseases that arise from environmental stimuli (ie, immunization) may be cured by a syngeneic or an autologous graft. The role of purging lymphocytes from an autologous graft has not yet been addressed in animal models. Finally, the results of BMT in experimental autoimmune encephalomyelitis suggest that cure of an autoimmune disease may not ultimately benefit the patient since repair of the affected target organ may not occur.

BMT in Patients With Coincidental Autoimmune Disorders

Allogeneic BMT

Several allogeneic marrow transplantations for leukemia or aplastic anemia have been performed in patients with coincidental autoimmune diseases. Most patients had rheumatoid arthritis (RA) and underwent transplantation because of aplastic anemia secondary to gold or penicillamine (Cuprimine, Depen) therapy.[37] Complete clinical remissions occurred, with disappearance of active arthritis (including rheumatoid factor [RF]) for several years after all immunosuppressive
medications were discontinued. However, one patient had a recurrence of arthritis within 2 years after BMT.[38] Interestingly, that patient's sibling donor was clinically asymptomatic but RF-positive. One patient with ulcerative colitis[39] and another with psoriasis[39] are in sustained remission following allogeneic genotypically matched BMT for leukemia. Another patient with multiple sclerosis and leukemia has a healthy allograft 1 year after BMT. Objective neurologic signs have improved while the patient is off immunosuppressive therapy.[40] These case reports suffer from publication bias, since it is unlikely that an autoimmune process that fails to improve after BMT would be reported. To overcome this bias, the International Bone Marrow Transplant Registry has included a questionnaire on autoimmune disorders for all patients enrolled in the registry.

In summary, preliminary data suggest that allogeneic BMT may cure patients with autoimmune diseases. However, the donor should be screened for asymptomatic disease (eg, serologic markers, such as RF, anti-ds DNA antibody, and others).

**Autologous BMT**

The results of autologous transplants in patients with coincidental autoimmune diseases have not been as encouraging. An autologous unpurged BMT performed in a patient with lymphoma and myasthenia gravis was complicated by early death from relapsed lymphoma.[41] However, following transplantation, anti-acetylcholine receptor antibody disappeared. Unpurged autologous transplantation has also been reported in a patient with lymphoma and systemic lupus erythematosus. Clinical disease resolved in this patient, but disease-specific anti-ds DNA antibody recurred.[42] Similarly, autologous unmanipulated stem-cell transplantation in four patients with autoimmune diseases (myasthenia gravis and Hashimoto's thyroiditis, systemic lupus erythematosus, atopic dermatitis, and RA, respectively) was followed by persistent or recurrent serologic or clinical signs of disease.[43]

An otherwise normal patient with severe CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) was treated with high-dose cyclophosphamide and autologous marrow rescue in Genoa, Italy. This therapy resulted in a complete, but transient, remission.[43] Therefore, the use of autologous marrow for hematopoietic rescue has resulted in several relapses. These results suggest that if autologous BMT is to be effective, the autograft should be purged of lymphocytes before reinfusion.

**Selection of SADS Patients for BMT**

Mortality from BMT correlates with patient age and type of graft. In general, autologous transplantation has a mortality of 1% to 5% in patients with breast cancer and 5% to 10% in those with leukemias. Allogeneic genotypically matched transplants have a 100-day mortality of approximately 20%. For both types of transplants, younger patients generally do better than older patients.

To justify any new therapy, such as BMT, the risk of dying from the disease must be higher than the risk of dying from its treatment. Therefore, patients with each disease who have a high risk of early mortality must be identified. Ideally, transplantation should be done early in the disease course before irreversible damage occurs. Otherwise, even if successful, BMT could cure the disease but not the patient.

Currently, it is standard practice to offer allogeneic or autologous BMT to patients with chronic myelogenous leukemia or indolent lymphomas who would otherwise have a median survival of 5 and 10 years, respectively. Therefore, we believe that if patients with SADS who have an anticipated survival of 5 to 10 years can be identified, an experimental procedure, such as complete immune ablation and hematopoietic stem-cell rescue, can be offered.

**Type of Transplant**

Given the higher mortality of allogeneic compared to autologous BMT, most centers are using autologous stem cells for immune reconstitution. The majority of transplant centers are also using some form of purging to remove lymphocytes from the graft prior to reinfusion to prevent transfer of potential disease-causing immune cells. Whether or not this practice is beneficial is unproven. The source of stem cells may be either the marrow or peripheral blood, although most centers are leaning toward peripheral blood cells due to their more rapid engraftment. However, peripheral
blood contains a lot more T-cells per unit volume compared to bone marrow. Therefore, most centers are using combinations of cyclophosphamide and antithymocyte globulin and/or total-body irradiation.

**Multiple Sclerosis**

Multiple sclerosis, a disease confined to the central nervous system, affects 1 in 1,000 individuals. The disease usually affects individuals between the ages of 20 and 40 and has a variable natural history; e.g., relapsing/remitting, primary progressive, and secondary progressive.[44] Most patients have relapsing/remitting disease (70%), which carries the same life expectancy as the general population. However, the majority of patients with progressive MS are wheelchair-bound, bedridden, or dead within 5 to 10 years of the onset of progressive disease. Survival correlates best with the level of disability. Fewer than 6% of patients with an unrestricted activity level are dead within 10 years, as compared with 70% of those confined to a wheelchair. The best predictor of prognosis in a patient with MS is the prior course of the disease; i.e., a history of rapidly progressive deterioration is predictive of a poor prognosis in the future. The cause of death in those with rapidly progressive disease is generally infection, pulmonary embolus, arrhythmia, or suicide. The concordance rate among monozygotic twins varies between studies but is approximately 37%.[45]

Multiple sclerosis is an immunologically mediated disease, although the initiating event(s) is(are) unclear. Epidemiologic studies from the Faroe Islands suggest that MS occurs 6 to 7 years after exposure to an unknown agent.[46] The Faroes are an isolated chain of volcanic islands in the North Atlantic originally settled by Vikings. Multiple sclerosis was unknown in the Faroese until after the islands' occupation by British soldiers during World War II. Individuals under 11 years of age at the time of exposure (British occupation) did not develop disease. In addition, MS occurred only in those parts of the island where the Faroese had prolonged contact (more than 2 years) with British troops. Therefore, one of the difficulties in identifying a putative MS agent is that the infectious agent may have been cleared by the immune system years before the onset of symptoms.

**Neurologic Disability Scales**

**TABLE 3**

Kurtzke Expanded Disability Status Scale (EDSS) for Neurologic Assessment

The clinical course of MS may be graded by neurologic disability scales, such as the Kurtzke Expanded Status Disability Scale (EDSS), the Kurtzke Functional System (FS), and the Scripps Neurology Rating Scale (NRS).[47,48] The EDSS (Table 3) is the most widely used rating scale in clinical trials. It is divided into 20 steps or half points from 0 (normal) to 10 (death). Increasing points indicate worse neurologic deficits. In the middle and higher ranges (5.0 to 8.0), the EDSS is heavily weighted by ambulatory function and is relatively insensitive to changes in the upper extremities or other neurologic changes, such as cognitive skills, that do not involve gait.

The Kurtzke FS (Table 4) allows one to rate the function of eight neurologic systems (e.g., pyramidal, visual, brainstem, and so forth) according to a scale of 0 to 5 or 6 (in which 0 represents normal function and 5 or 6, the most severe dysfunction).

In the Scripps NRS,[48] a normal neurologic system receives the full points available with
progressive loss of points for mild, moderate, or severe deficits. The maximal NRS score for a neurologically normal person is 100. Therefore, in the NRS, higher numbers indicate less severe disease, while in the EDSS the higher the number, the more severe is the deficit. The NRS gives equal weight to upper and lower extremity dysfunction and is a more sensitive indicator of clinical change than is the EDSS.

**MRI Findings**

**TABLE 4**

Kurtzke Functional System (FS) Rating Scale for Neurologic Assessment

In addition to clinical scales to score neurologic changes, MRI may be used to directly visualize CNS inflammatory plaques. In contrast to MRI, CT scans are not useful in visualizing MS lesions. Indeed, lesions detected on a CT scan suggest another etiology (eg, neoplasm, vascular lesion). Although 75% to 99% of patients with clinical MS have lesions on MRI, noncontrast MRI cannot distinguish an active from a chronic plaque. Gadolinium-diethylenetriamine penta-acetic acid IV contrast will show MRI enhancement in acute lesions. This is due to blood-brain barrier breakdown from perivenular infiltration by lymphocytes, plasma cells, and monocytes. In contrast, chronic lesions are "scarred" by repair processes, including glial cell infiltration, demyelination, and axonal loss, and do not enhance.

In general, the correlation between MRI findings and clinical disability is poor. Severe neurologic deficits may be present with minimal MRI activity. Conversely, a large number of plaques may be detected in patients with minimal clinical disability. This may be explained, in part, by the fact that lesion location determines whether clinical symptoms are appreciated. However, when compared to noncontrast MRI, the advantage of MRI with gadolinium is that it detects active subclinical disease. Gadolinium-enhancing lesions may be quantitated by number and/or total volume. Therefore, MRI with gadolinium may be used to monitor progression of clinically silent disease.[49-51] However, gadolinium enhancement fluctuates with time and treatment. Therefore, frequent scans are necessary to monitor disease. The use of frequent MRIs in the evaluation of clinical trials is more sensitive than clinical scales but also more expensive.

**Use of BMT**

Traditional therapies for MS are immune suppression (eg, corticosteroids, cyclophosphamide, azathioprine) or immunomodulation (eg, interferon-beta-1b [Betaseron], copolymer 1 [Cop I]). Although effective in decreasing relapses or slowing progression, none of these agents is curative. To be a candidate for immune ablation and hematopoietic stem-cell rescue, the MS patient needs to have rapidly progressive disease. At Rush Presbyterian Medical Center and Northwestern University
(Chicago) and the Medical College of Wisconsin (Milwaukee), rapidly progressive disease is defined as an EDSS of between 5.0 and 8.0 at the time of entry with a deterioration in the EDSS of at least 1.5 points if the EDSS was less than 6.0 in the 12 months preceding entry or a deterioration of at least 1.0 point if the EDSS was 6.0 or more in the 12 months preceding entry. In addition, gadolinium enhancement on MRI is preferred but not mandatory.

Response to immune ablation and hematopoietic stem-cell rescue will be followed with neurologic rating scores (Kurtzke EDSS, Kurtzke FS, and Scripps NRS) and by MRI. Two MRIs will be obtained within 6 months prior to transplantation; at 1, 3, and 12 months after BMT; and then yearly for 5 years.

Rheumatoid Arthritis

Rheumatoid arthritis affects 0.5% to 1% of the US population. Traditional therapy for RA consists of an incremental pyramid scheme of nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy, advancing to steroids if NSAIDs fail and then to disease-modifying antirheumatic drugs, such as methotrexate, gold, hydroxychloroquine, and penicillamine, if steroids alone are inadequate. This approach is based on the mistaken belief that, because most patients have a normal life expectancy, all patients with RA have a normal life expectancy. In fact, subsets of patients with RA can be identified who have a life expectancy of 40% to 50% at 5 years.[52-54] This survival rate is lower than that of patients with three-vessel coronary artery disease or stage IV Hodgkin's disease. Patients referred to university medical centers tend to have worse disease, characterized by a progressive chronic course, radiologic joint destruction, and extra-articular involvement.

The 1987 American College of Rheumatology criteria for RA[55] are four or more of the following: (1) more than 30 minutes of morning stiffness; (2) swelling of three or more joints for 6 or more weeks; (3) swelling of the metacarpophalangeal, proximal interphalangeal, or wrist joint; (4) symmetrical joint swelling; (5) rheumatoid nodules; (6) radiologic abnormalities of RA; and (7) RF-positivity. Rheumatoid arthritis is a chronic persistent synovitis, which may exacerbate and remit. Inflammation leads to cortical bone erosions, cartilage loss, joint space narrowing, and deformity. Rheumatoid factor, an autoantibody to the Fc region of the IgG molecule, is present in more than 70% of patients with RA.

Approximately 50% of patients with RA must stop working within 10 years of disease onset. Death does not occur from active synovitis per se, but rather, from complications of disability, immobilization, or extra-articular disease. Causes of death include cardiovascular disease, renal failure, cervical myelopathy, hip fractures, pulmonary emboli, and infections.

Prognostic Indicators

Prognostic indicators for RA are the number of joints involved and functional disability.[52-62] Patients with more than 30 abnormal joints have a 5-year survival of 40% to 50%.[52-54] Functional disability may be measured by either quantitation of musculoskeletal performance, such as the walking time test or button test, or by an activities of daily living questionnaire.[56-61] If a patient requires more than 21 seconds to walk 25 feet, 5-year survival is 60%. If the time required to unbutton and button five buttons is greater than 120 seconds, 5-year survival is 50%.[52,53] Activities of daily living can be assessed by a modified version of the Stanford Health Assessment Questionnaire (HAQ) (Table 6).[62] Twenty HAQ questions address activities of daily living in eight categories: (1) dressing and grooming, (2) arising, (3) eating, (4) walking, (5) hygiene, (6) reach, (7) grip, and (8) other. Patients are asked to indicate whether they are able to perform each activity "with ease" or "with some help," or whether they are "unable to do" that activity. Patients who state that they perform fewer than 75% of activities of daily living "with ease" on this questionnaire have a 40% 5-year survival.[54]

Use of BMT

At Northwestern University, we consider patients at high risk of early mortality from RA to be candidates for BMT. Our eligibility criteria are patients who are RF-positive, have not responded to prednisone and at least two disease-modifying agents, and have more than 30 involved joints or answered fewer than 75% of HAQ questions "with ease" or "with no difficulty" and have more than 6 swollen joints.

Systemic Lupus Erythematosus
Systemic lupus erythematosus is a multisystem, inflammatory disorder characterized by a variable presentation and clinical course. It generally affects women 20 to 40 years old. The lifetime incidence of SLE is 1 in 700 in white females; incidence is three to four times higher in black females. Patients are classified as having definitive lupus if they fulfill at least 4 of the following 11 American Rheumatism Association criteria: (1) antinuclear antibody, (2) malar rash, (3) discoid rash, (4) photosensitivity, (5) oral ulcers, (6) arthritis, (7) serositis, and a (8) renal, (9) neurologic, (10) hematologic, or (11) immunologic disorder(s).[63] Two serologic markers, anti-DNA and anti-Smith, when occurring in high titer, are specific for SLE.

Estimates of 5-year survival range from 68% to 98%.[64-67] Survival rates have increased over each successive decade due, in part, to better prevention and management of renal failure and hypertension. For patients with renal failure, survival is approximately 80% at 5 years. Within the first 5 years of disease onset, the cause of death is generally active SLE (eg, seizures, pneumonitis, vasculitis.) or infections. In disease of longer duration, the cause of death is generally infection or cardiovascular complications, probably secondary to corticosteroid use (ie, hypertension, diabetes, hyperlipidemia).

Prognostic Indicators

Autoantibody titers generally do not correlate with disease activity, although rising anti-DNA antibody may precede active glomerulonephritis. Nephritis is a strong predictor of early mortality compared to patients without nephritis. This has led to several attempts to classify and predict outcome by renal biopsy. Renal biopsy may be classified by World Health Organization (WHO)[68,69] description or National Institutes of Health (NIH) activity and chronicity indices.[70]

In the WHO classification, class I denotes a lesion that is normal by light microscopy; class II, mesangial changes; class III, focal proliferative; class IV, diffuse proliferative; class V, membranous; and class VI, prominent glomerular sclerosis. Some investigators have reported that survival correlates with WHO class. Patients with no or minimal lesions (class I and II) have the best outcomes (5-year survival, 90%). Patients with proliferative lesions (classes III, IV, and V) have 75% survival at 5 years.[71] Patients with fibrosis or glomerular sclerosis (class VI) have the worst prognosis (50% survival at 5 years).[71]

However, other investigators have reported that the WHO criteria are not a good predictor of survival, probably because these criteria do not separate lesions by activity or chronicity. To this end, the NIH developed an activity and chronicity index for renal biopsies. Histologic features of activity, in glomeruli, are: (1) cellular proliferation, (2) fibrinoid necrosis, (3) cellular crescents, (4) hyaline thrombi or wire loops, and (5) leukocyte infiltration, and, within the tubulointerstitium, (6) mononuclear cell infiltration. Features of chronicity, in the glomeruli, are: (1) sclerosis and (2) fibrous crescents and, within the tubulointerstitium, (3) interstitial fibrosis and (4) tubular atrophy. Each histologic feature is graded on a scale of 0, 1, 2, or 3 for absent, mild, moderate, or severe.

Therefore, the maximum chronicity score is 12, and the maximum activity score is 24 (fibrinoid necrosis and cellular crescents are weighted by a factor of 2). Risk of renal failure is 50% at 5 years for a chronicity score of 3 or greater or an activity score of 11 or more.[70] Even without biopsy, serum creatinine is valuable in predicting survival.

Rather than scoring disease activity in a single organ (eg, the NIH indices for nephritis), some investigators have emphasized multiorgan clinical disease activity indices, such as the Systemic Lupus Activity Measure (SLAM), Lupus Activity Index (LAI), or SLE Disease Activity Index (SLEDAI) in predicting outcome.[72-75] The SLEDAI is designed to measure the activity or extent of inflammation in nine organ systems (Table 7). It has a theoretical maximum of 105 points. However, in practice, it is unusual for a patient to have more than three to five organ systems involved. The rate of 5-year survival for patients with a SLEDAI of less than 19 is 85%, as compared with 65% for those with a SLEDAI over 19.[73]

Since creatinine and SLEDAI are predictive of survival, some people believe that the information obtained from renal biopsy is redundant. However, renal biopsy can provide information about disease reversibility (activity vs chronicity), and patients with a normal creatinine may have severe pathologic disease that is not appreciated by serum creatinine due to the large functional reserve of the kidneys.

Higher mortality in SLE is also associated with the presence of anti-phospholipid antibody.[76-79] A high antiphospholipid titer, especially greater than two to five times above titers in normal controls, is associated with venous and arterial thrombosis, leg ulcers, livedo reticularis, hemolytic anemia, thrombocytopenia, vasculitis, neuropathy, seizures, psychosis, transient ischemic attacks, transverse myelitis, pulmonary hypertension, and increased fetal loss. Therefore, antiphospholipid-associated
diseases fall within two categories: cytopenias or vascular disease (ie, thrombosis and/or proliferative occlusion). A diagnosis of antiphospholipid syndrome is made when two or more antiphospholipid related manifestations are present and the antiphospholipid titer is more than five standard deviations above the mean of normal individuals.[77]

**Use of BMT**

At Northwestern University, we consider patients with the following criteria to be candidates for immune ablation and hematopoietic stem-cell rescue: (1) lupus nephritis WHO class III, IV, or V whose serum creatinine has not returned to normal after treatment with intravenous cyclophosphamide (the NIH short course of cyclophosphamide; ie, 500 to 1,000 mg/kg monthly for 6 months); (2) a SLEDAL score greater than 19 with evidence of visceral organ involvement; or (3) immune-mediated cytopenia that fails to respond to prednisone and at least one alkylating agent, with failure defined as red blood cell transfusion dependence, a platelet count less than 40,000/mL without transfusions, or absolute neutrophil count less than 1,000/mL; or (4) antiphospholipid syndrome and pulmonary, central nervous system, or other vital organ involvement.

**Other Autoimmune Diseases**

Patients with systemic scleroderma, characterized by fibrosis and vasculopathy, have a survival duration significantly shorter than the general population. Those patients with renal, cardiac, or pulmonary involvement have the worst prognosis.[80-82] Disease may be followed by monitoring affected organ function and serology, eg, scleroderma-70 (SCL-70) titer.

Myasthenia gravis has a prevalence of 5 to 12.5 per 100,000 and a bimodal incidence with one peak at age 20 to 30 and another at age 60. It manifests as generalized weakness, fatigability, ophthalmoplegia, dysarthria, or dysphagia due to antibodies directed against the postsynaptic acetylcholine receptor.[83] These antibodies reduce the number of acetylcholine receptors by increasing endocytosis, complement-mediated damage, or blockade of the neurotransmitter binding site.

Today, most patients with myasthenia gravis have a normal life expectancy. Survival is 80% at 10 years. However, patients with respiratory or bulbar muscle involvement (Osserman group III or IV), especially if rapid in onset (ie, within 8 months of diagnosis), have high-risk features[84,85] and could be considered candidates for BMT. Disease may be followed by clinical muscle strength, antibody titer, and electromyelography.

Ulcerative colitis may be cured by resection of the colon. Crohn's disease may involve any part of the alimentary canal from the mouth to the anus. Although most patients with Crohn's disease have a normal life expectancy, survival in some patients is slightly decreased compared to the general population (10-year overall survival, 85%).[86,87] The risk of early death is increased in patients with most or all of the following: young age at onset, multiple surgical procedures, short bowel/malabsorption, chronic steroid therapy, narcotic addiction, and a history of sepsis.[87] Polymyositis is a chronic inflammatory muscle disease of unknown etiology. The incidence is 1 to 7.0 cases per year per 1 million people. Age of onset is bimodal, peaking between 5 and 14 years of age and again between 45 and 65.

Polymyositis is manifested by weakness, elevated muscle-associated enzymes, electromyelographic changes, and inflammation on muscle biopsy. Dermatomyositis with skin involvement, an erythematous rash, periorbital discoloration (heliotrope), or erythema over the metacarpophalangeal and proximal interphalangeal joints (Gottron's rash) may coexist with polymyositis. Cardiac (arrhythmias or congestive heart failure) or pulmonary (interstitial infiltrates) involvement carries an especially poor prognosis.

In polymyositis, unlike other autoimmune diseases, serologic markers are predictive of prognosis.[88] Patients with anti-signal recognition particle (anti-SRP) antibodies have early cardiac involvement and the worst prognosis. Patients with antisynthetase (amino-acyl tRNA synthetase) antibodies have a high occurrence of interstitial lung disease and a poor prognosis. Therefore, polymyositis patients with a poor prognosis may be identified early in their disease by serologic markers.

**Summary**

Immune ablation and hematopoietic stem-cell rescue for autoimmune disorders is an experimental treatment that should be reserved for patients with potentially life-threatening disease (SADS). It will
probably be years before the benefits, if any, of this procedure are known. One obstacle to this approach is the expense of BMT (approximately $150,000). Future cost analyses, including both medical expenses and loss of income from disability, will help clarify the cost-effectiveness of this approach.

References:
18. LaFace DM, Peck AB: Reciprocal allogeneic bone marrow transplantation between NOD mice and


Source URL:
http://www.diagnosticimaging.com/bmt-severe-autoimmune-diseases-idea-whose-time-has-come

Links: