EMERGING THERAPIES OF MULTIPLE SCLEROSIS

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LEARNING OBJECTIVES

1. The attendee will be able to list novel therapies on the horizon for treatment of relapsing forms of MS.
2. The attendee will be able to elaborate immunologic strategies for the treatment of MS.
3. The attendee will be able to discuss the novel concept of chronic cerebrospinal venous insufficiency in MS.

CME QUESTIONS

1. Novel targets for immunomodulatory therapy in MS include all of the following except:
   a. B lymphocytes
   b. Pyrimidine synthesis
   c. Natural killer cells
   d. Astrocytes

2. Chronic cerebrospinal venous insufficiency is associated with:
   a. Elevated intracranial pressure
   b. Venous sinus thrombosis
   c. Extracranial venous sinus stenosis
   d. Pulmonary hypertension

3. A unique complication associated with alemtuzumab therapy is:
   a. antibody-mediated autoimmunity
   b. macular edema
   c. cardiac conduction block
   d. malignancy

KEYWORDS

1. Multiple Sclerosis
2. Immunotherapy
3. Stem Cells
4. Venous Insufficiency
5. Monoclonal Antibody

Multiple sclerosis (MS) is a complex immunopathologic disorder of the central nervous system (CNS). For the past several years, there have been six agents approved by regulatory agencies to treat relapsing forms of multiple sclerosis (MS): interferon beta-1b, intramuscular interferon beta-1a, subcutaneous interferon beta-1a, glatiramer acetate, natalizumab, and mitoxantrone. Phase III registration trials and post marketing experience have delineated the efficacy, tolerability, and relative safety of these agents. The recent approval of oral fingolimod to the MS therapeutic roster has added a novel agent to our current therapeutic options, but many additional compounds, antibodies, cell therapies, and treatment interventions remain on the horizon.

As a result of animal research, clinical translational studies, and past therapeutic successes, emerging MS therapies are primarily focused on limiting CNS inflammation. Mechanistic approaches include immunomodulation, inhibition of immune cell migration, immunodepletion, and immune cell transplantation. Recently, an alternative theory of MS pathophysiology has been raised: chronic cerebrospinal venous insufficiency (CCVSI). The result has prompted a several studies designed to examine the role of transluminal angioplasty and venous sinus stenting in MS therapy. In this review, we will examine the current list of emerging MS therapies in later phase development and inventory the ongoing clinical trials designed to evaluate their efficacy.

IMMUNOMODULATION

Four immunomodulatory MS therapies in late phase clinical development are teriflunomide, laquinomod, dimethyl fumarate, and daclizumab. While the overall design of these therapies is to modify immune system function in the absence of cell depletion, the modes of action, clinical and MRI data are quite distinct.

Teriflunomide

Teriflunomide is an oral, redox silent coenzyme Q, antagonist of dihydroorotate dehydrogenase that blocks de novo pyrimidine synthesis. Teriflunomide is an active metabolite of leflunomide (Arava), an immunomodulatory and anti-inflammatory prodrug used worldwide for the treatment of rheumatoid arthritis. Teriflunomide reduces T cell and B cell proliferation and may inhibit tyrosine kinase activation and calcium mobilization.
In an initial Phase II clinical trial,\(^3\) the effects of teriflunomide (7 mg/day or 14 mg/day) on MRI and disease activity were compared to placebo in 179 relapsing-remitting (RRMS) and secondary progressive (SPMS) multiple sclerosis patients. The number of combined unique active lesions, T1 Gad+ lesions, new or enlarging T2 lesions, T2 lesion burden, and proportion of subjects with increased disability were monitored over a 36-week treatment period. Both doses of teriflunomide showed a significant reduction in the median number of combined unique active lesions (0.5 placebo vs. 0.2 teriflunomide 7 mg/day [\(p < 0.03\) vs. placebo] vs. 0.3 teriflunomide 14 mg/day [\(p < 0.01\) vs. placebo]). Teriflunomide-treated subjects had reduced mean T1 Gad+ lesions and reduced mean new or enlarging T2 lesions. Subjects receiving the higher dosage demonstrated reduced median change T2 lesion burden and a reduced proportion of subjects with disability increase. The results of a recently completed Phase III study (TEMSO) were presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting (O’Connor, 2010, October 15). A placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis: clinical efficacy and safety outcomes. Platform session conducted at the ECTRIMS conference. Abstract retrieved from [http://www.congres.ch/ectrims2010.html](http://www.congres.ch/ectrims2010.html). Teriflunomide (7 mg or 14 mg/day) was compared to placebo in 1088 RRMS subjects over a 108-week duration. Both doses of teriflunomide showed a significant reduction in the primary outcome measure: annualized relapse rate (Placebo: 0.539 vs. teriflunomide 7 mg: 0.370 [– 31.2%, \(p=0.0002\)] vs. teriflunomide 14 mg: 0.369 [– 31.5%, \(p=0.0005\)]. The risk for disability progression (sustained for 12 weeks) was significantly reduced only in subjects receiving 14 mg/day of teriflunomide (29.8% \([p=0.0279]\) but not 7 mg/day (23.7% \([p=0.0835]\)). However, the number of T1 Gad+ lesions (7 mg: 0.570 [– 57.2%, \(p<0.001\]); 14 mg: 0.261 [– 80.4%, \(p<0.001\]), the mean reduction in T2 burden of disease (7 mg: 39.4% \([p=0.0317]\); 14 mg: 67.4% \([p=0.0003]\)), and the proportion of subjects free of T1 Gad+ lesions (7 mg: 51.4% \([p<0.001]\); 14 mg: 64.1% \([p<0.001]\)) were significantly reduced in both treatment arms.

Teriflunomide was well tolerated in the Phase II and III trials. There was no difference in the frequency of adverse events (AEs) and severe adverse events (SAEs) in teriflunomide-treated and placebo subjects.\(^3\) The most common reported AEs in teriflunomide-treated subjects were nasopharyngitis, alopecia, nausea, alanine aminotransferase increase, paresthesia, back pain, limb pain, diarrhea, and arthralgias. In the Phase II trial 19 subjects (placebo, \(n=7\); teriflunomide 7 mg/day, \(n=5\); teriflunomide 14 mg/day, \(n=7\)) suffered SAEs that included elevated liver enzymes, hepatic dysfunction, neutropenia, rhabdomyolysis, and trigeminal neuralgia. In the TEMSO trial, no difference was observed in the incidence of serious transaminase elevations in treated and untreated subjects. There were no serious infections reported. Eleven pregnancies were reported in the TEMSO trial. There were 4 spontaneous abortions (1 - placebo, 3 - 14 mg/day), 6 induced abortions (5 – 7 mg/day, 1 – 14 mg/day), and 1 healthy baby was delivered in the 14 mg/day treatment group.

A Phase III trial investigating the efficacy of teriflunomide in subjects with high-risk clinically isolated syndromes (CIS) is currently under way. This double blind placebo-controlled trial will enroll 1200 subjects for a 24-month duration. Trial endpoints include relapse rate, expanded disability status scale (EDSS), MRI (T1/T2/black holes, brain volume), and multiple sclerosis functional composite (MSFC).

### Laquinomod

Laquinomod is an orally administered quinoline-3-carboxamide derivate that is structurally related to roquimixem (linomide). Although the direct mechanism of action has yet to be illuminated, possibilities include modulation of Th1/Th2 cytokine axis; increased production of interleukin-4 (IL-4), IL-10 and transforming growth factor b (TGF-β); reduction of MHC-class II gene transcription factors; stimulation of neurotrophin-3 (NT-3), neurotrophin-4 (NT-4) and brain derived neurotrophic factor (BDNF) secretion, promotion of CD8+ T cell and B cell apoptosis; and suppression of the metabolic activity of CD14+ monocyte and natural killer (NK) cells.

In an initial phase IIb clinical trials (LAQ5062),\(^4\) two doses of laquinomod (0.3 mg/day and 0.6 mg/day) were compared to placebo in 283 RMS subjects over a 36-week duration. Only the 0.6 mg/day dosage was effective in meeting the primary outcome measure and demonstrated a 40% reduction (\(p = 0.0048\)) in the cumulative number of T1 Gad+ lesions. The same dosage showed a 33% reduction in annualized relapse rate (\(p = 0.09\)). In a 36-week extension of the original phase IIb trial (LAQ5063), subjects were either continued on their original laquinomod dosage or switch from placebo to 0.3 mg or 0.6 mg of laquinomod. Subjects maintained on 0.6 mg/day of laquinomod continued to have a significant reduction in the mean number of T1 Gad+ lesions, and subjects switched from placebo to laquinomod showed a significant reduction in T1 Gad+ lesions. Due to the results of the Phase II trials, only the 0.6 mg/day dosage of laquinomod was brought forward into Phase III testing.

There were no differences in the frequency of AEs and SAEs in laquinomod- and placebo-treated subjects in the LAQ5062 and LAQ5063 trials.\(^4\) No opportunistic illnesses were reported in laquinomod-treated subjects, and there were no instances of AEs that characterized linomide: myocardial ischemia, infarction, pleuritis, or pericarditis. SAEs reported in laquinomod-treated subjects included Budd-Chiari syndrome in a Factor V Leiden positive subject, menometrorrhagia associated with myofibroma, liver transaminase elevation, and exacerbation of glaucoma.
Two Phase III trials investigating the efficacy of laquinomod for the treatment of subjects with RRMS are currently underway. The ALLEGRO trial will enroll 1000 subjects for a 24-month placebo-controlled, double masked trial to evaluate oral laquinomod 0.6 mg/day in the treatment of relapsing MS. Trial endpoints include relapse rate, MRI (T1/T2/black holes, brain volume), and MSFC. The BRAVO trial is a 24-month, three-armed trial that includes both placebo and active comparator (β-interferon 1a 30 μg IM). 1200 subjects will be enrolled in a 1:1:1 ratio, and the trial endpoints are identical to the ALLEGRO study.

**Dimethyl Fumarate**

Dimethyl fumarate (BG00012) is an oral fumaric acid ester with a long history of use in treatment of psoriasis. BG00012 is administered 2-3 days daily. The primary metabolite is monomethyl fumarate which has multiple immunomodulatory effects through the activation of nuclear factor E2–related factor-2 transcriptional pathway. BG00012 induces apoptosis of activated T cells and stimulates a Th1 to Th2 cytokine shift. In the murine model of neuroinflammation, experimental autoimmune encephalomyelitis (EAE), dimethyl fumarate demonstrated both anti-inflammatory and neuroprotective properties, elevating IL-10 and producing antioxidant effects.

A Phase II clinical trial compared several dosages of BG00012 to placebo in RRMS subjects. The trial enrolled 257 subjects for a 24-week treatment phase and a 24-week extension. The primary outcome was the total number of T1 Gad+ lesions at 12, 16, 20, and 24 weeks. Secondary outcomes included new or enlarging T2 lesions, T1 black holes at 12, 16, 20, and 24 weeks. The primary outcome was the total number of T1 Gad+ lesions. A significant reduction was also observed in new or enlarging T2 lesions (68%, [p = .007]); however, there was no significant effect on the volume of T1 black hole or T2 lesions nor the annualized relapse rate. The MRI activity returned to baseline quickly during washout period. Interestingly, consistent with one of the presumed mechanisms of action, CD56br NK cells were 8-9x higher in daclizumab-treated subjects.

In the Phase II trial, BG00012 was well tolerated. The incidence of infection was not significantly different in BG00012-treated subjects when compared to placebo. The most common AEs were gastrointestinal problems (10% diarrhea; 11% abdominal pain; 14% nausea), flushing, headache, fatigue. The frequency of AEs decreased significantly following the first month of treatment. SAEs were similar between BG00012-treated and placebo subjects and most were MS relapse-related.

Two Phase III trials investigating the efficacy of BG00012 in RRMS are currently underway. The DEFINE trial will enroll 1011 subjects for a 24-month placebo-controlled, double masked trial to evaluate oral BG00012 (240 mg BID or TID) in the treatment of relapsing MS. The primary endpoint of the trial will be the proportion of relapsing patients. The CONFIRM trial is a 24-month, three-armed trial that includes an active comparator (glatiramer acetate 20 mg SQ daily). Subjects will be enrolled in a 1:1:1 ratio, and the primary endpoint will be annualized relapse rate.

**Daclizumab**

Daclizumab is a humanized IgG1 monoclonal antibody (mAb) against the interleukin-2 (IL-2) receptor (IL-2R) α chain (CD25). The antibody is currently delivered subcutaneously SQ every other week; however, initial successful single center pilot trials on RRMS and SPMS subjects delivered the medication intravenously. The mAb blocks binding of IL-2 to the high-affinity IL-2R inhibiting IL-2R-mediated T cell and B cell activation and down-modulating IL-2R on activated T cells. Daclizumab expands a subpopulation of CD56 bright (CD56br) NK cells that can lyse activated autologous T cells and augment NK cell function. The expansion of CD56br NK cells is inversely proportional to T1 Gad+ lesion load in daclizumab-treated subjects suggesting that this mechanism plays an important role in the immunomodulatory action of the mAb.

A recent placebo-controlled Phase II trial, daclizumab (1 mg/kg SQ every 2 weeks alternating with placebo or 2 mg/kg SQ q 2 weeks) was evaluated in 230 RRMS subjects failing β-interferon. Enrolled subjects required either stable β-interferon therapy for 6 months with 1 clinical relapse or stable β-interferon therapy for 1 year with one or more T1 Gad+ lesions. The treatment phase lasted 24 weeks and was followed by a 48-week washout phase. The 2 mg/kg dose of daclizumab demonstrated a 72% reduction (p < 0.004) in the primary outcome measure: mean number of T1 Gad+ lesions. A significant reduction was also observed on new or enlarging T2 lesions (68%, [p = .007]); however, there was no significant effect on the volume of T1 black hole or T2 lesions nor the annualized relapse rate. The MRI activity returned to baseline quickly during washout period. Interestingly, consistent with one of the presumed mechanisms of action, CD56br NK cells were 8-9x higher in daclizumab-treated subjects.

There was no difference in frequency of AEs and SAEs between daclizumab-treated and placebo subjects. The most common AEs were gastrointestinal disorders, fatigue, cutaneous reactions, and infections; no novel autoimmune disorders were observed. Two malignancies were reported: breast cancer and pseudomyxoma peritonei. SAEs were elevated in daclizumab-treated versus placebo subjects (13% versus 5%). Most were infections (5% daclizumab vs. 1% placebo).

There are two ongoing clinical trials investigating the efficacy of daclizumab in RRMS. Both trials use daclizumab high-yield process (DAC HYP), a new high concentration, liquid formulation of the mAb developed to reduce the frequency of subcutaneous delivery. The SELECT trial is a Phase IIb trial that will enroll 600 RRMS subjects for a 48-week placebo-controlled, double masked trial to evaluate the relative efficacy of two dosages of DAC HYP (150 mg or 300 mg SQ monthly). The primary endpoint of the
trials will be the reduction in the annualized relapse rate. The secondary endpoint will be the reduction in new or enlarged T1 Gad+ lesions. The DECIDE trial is a two-armed trial (96-144 week duration) that compares DAC HYF (150 mg SQ monthly) to an active comparator (β-interferon 1a 30 μg IM weekly). The primary outcome measure is relapse rate; secondary endpoints include reduction in disability progression, MRI outcomes, improvement in quality-of-life indices.

CELL MIGRATION
There are two FDA-approved medications for the treatment of relapsing MS that primarily affect immune cell migration: natalizumab and oral fingolimod. Natalizumab is a humanized anti-very late antigen 4 (VLA4) mAb that inhibits activated leukocyte migration across the blood-brain barrier.12 Oral VLA-4 inhibitors have been developed but currently there are no active Phase II or Phase II clinical trials in progress. This is likely due to significant concerns for the risk of progressive multifocal leukoencephalopathy (PML) in treated subjects. Once risk-modification strategies are developed for PML in natalizumab-treated patients, new oral inhibitors may emerge into the developmental pipeline. Oral fingolimod is a S1P receptor agonist that prevents lymphocyte egress from secondary lymphoid organs.13 There is a novel S1P receptor agonist with enhanced S1Pα selectivity (ONO-4641) that is currently in Phase II clinical testing (DreaMS). Three dosages of ONO-4641 (0.05, 0.1 or 0.15 mg daily) are being evaluated in a 26-week, placebo-controlled trial with 1:1:1:1 enrollment. The primary endpoint is the total number of T1 Gad+ lesions. Multiple pharmaceutical companies are currently developing a variety of S1P receptor agonists with varying subtype selectivities. The ultimate objective is to maintain or improve clinical efficacy while limiting significant adverse events such as first-dose bradycardia.

IMMUNODEPLETION
Immunodepleting strategies have a long history in the treatment of MS. Older non-selective agents such as cyclophosphamide and azathioprine have been used off-label under varying clinical circumstances for years, and in October 2000, mitoxantrone was approved for the treatment of patients with secondary progressive, progressive relapsing or worsening relapsing-remitting multiple sclerosis. Two novel immunodepleting strategies have reached Phase III clinical testing in MS. Both are centered on the use of mAb technology but their targets, efficacy and adverse events are distinct.

Alemtuzumab
Alemtuzumab is a humanized mAb directed against CD52 antigen. CD52 is a cell surface glycoprotein of unknown function that is present on >95% of T cells, B cells (not plasma cells), monocytes, and eosinophils. Following intravenous infusion, there is targeted depletion of CD52-expressing cells within 2 days with a rapid destruction of B cells, T cells, monocytes by complement-dependent (CDC) and antibody-dependent cell-mediated (ADCC) cytotoxicity.14,15 The result is a prolonged lymphopenia and reduced CNS inflammation. T cells recover over 16 months, whereas B cells recover over 3 to 6 months.

The clinical efficacy of alemtuzumab was originally investigated in small single center pilot trials using SPMS subjects.16,17 While there were significant reductions in relapse rate and MRI activity, there was no significant reduction in disability progression. Focus was then diverted to the treatment of earlier relapsing disease, and a Phase II clinical trial was conducted comparing two doses of intravenous alemtuzumab (12 mg/day or 24 mg/day for 5 d at month 0 and 3 d at month 12 and 24) to an active comparator β-interferon 1a 44 μg SW tiw.18 334 RRMS patients were enrolled in the 36-month protocol; however, dosing of alemtuzumab was halted during the trial when a fatality occurred in the alemtuzumab arm due to the complications of idiopathic thrombocytopenic purpura (ITP). As a result, only some subjects received alemtuzumab at 24 months. Despite the abrupt interruption in alemtuzumab administration, clinical and MRI data demonstrated strong efficacy in the alemtuzumab-treated subjects. Both doses of alemtuzumab showed 72% reduction (p < 0.001) in annualized relapse rate and 71% reduction (p < 0.001) in 6-month sustained disability progression versus high frequency β-interferon 1a. Secondary outcomes were equally impressive with a 55% reduction (p = 0.005) in mean T2 lesion load and reduced brain atrophy (change T1-weighted brain volume: -0.2 vs. 0.9 [p = 0.02]).

Several safety concerns, however, were identified in alemtuzumab-treated subjects.18 There were an increased number of infections associated with alemtuzumab treatment (66% alemtuzumab vs. 47% β-interferon 1a) and sporadic alemtuzumab-induced infusion reactions. Of particularly novel concern was the significantly increased incidence of antibody-mediated autoimmunity in alemtuzumab-treated subjects. Conditions observed included Grave’s disease (23%), ITP (2.7%), and Goodpastures Syndrome (1%). The frequency of SAEs was not different among the treatment groups. The frequency of serious infusion reactions was 1.4%.

As noted previously, there was a fatal hemorrhage secondary to ITP that halted the 24-month infusion in most subjects. Malignancies included non–EBV-associated Burkitt’s lymphoma, breast cancer, and cervical cancer in situ.

There are two ongoing Phase III clinical trials investigating the efficacy of alemtuzumab in RRMS (CARE-MS I and CARE-MS II). In CARE-MS I, alemtuzumab (2 annual cycles of 12 mg/day for 5 days) is being compared to β-interferon 1a 44 μg SQ tiw in a 24-month, double-masked trial enrolling 525 RRMS patients with 2:1 enrollment favoring alemtuzumab. The primary endpoints are reduction in the annualized relapse rate and time to sustained disability progression. In
CARE-MS II, 1200 RRMS patients, relapsing on glatiramer acetate or β-interferon 1a, are being enrolled 2:2:1 in a 24-month trial to compare two doses of alemtuzumab (12 mg/day or 24 mg/day) to β-interferon 1a 44 mg SQ tiw. The primary endpoints are reduction in the annualized relapse rate and time to sustained disability progression.

**Rituximab/Ocrelizumab**

Rituximab and ocrelizumab are mAbs against the CD20 antigen. Rituximab is a chimeric murine-human mAb; whereas, ocrelizumab is a humanized mAb. Due to their engineering, there are slight differences in the effector function of the mAbs on CD20-bearing cells. Ocrelizumab has 3-4x lower CDC activity and 2-5x greater ADCC activity than rituximab. CD20 is a surface protein on pre-B cells, naïve B cells, memory B cells than is absent on plasmablasts and mature plasma cells. The intravenous infusion of rituximab or ocrelizumab causes a rapid and targeted depletion of CD20-expressing naïve and memory B cells resulting in the loss of B cell antigen presentation, a potential reduction in B cell proinflammatory mediators, and a potential redistribution of proinflammatory and regulatory B cell populations. The mAbs are reinfused at 24-week intervals when the B cell population begins to reconstitute.

Phase II clinical trials were recently completed for rituximab and ocrelizumab. 104 RRMS subjects were evaluated in a 48-week placebo controlled trial using a single treatment with rituximab at study onset (1000 mg IV on days 1 and 15). In the rituximab-treated population, there was a 91% reduction (p < 0.001) in total T1 Gad+ lesions at weeks 12, 16, 20, and 24 and a 50% reduction (p = 0.04) in the proportion of relapsing patients. The results of a Phase II ocrelizumab trial were recently presented at the 2010 ECTRIMS meeting (Kappos. [2010, October 15]. Efficacy and safety of ocrelizumab in patients with relapsing–remitting multiple sclerosis: results of a phase II randomized placebo-controlled multicentre trial. Platform session conducted at the ECTRIMS conference. Abstract retrieved from [http://www.congrex.ch/ectrims2010.html](http://www.congrex.ch/ectrims2010.html). The Phase II study enrolled 220 RRMS subjects for a 24-week placebo controlled study investigating two doses of ocrelizumab (600 or 2000 mg IV on days 1 and 15) and an active comparator (β- interferon 1a 30 mg IM weekly). Both doses of ocrelizumab showed significant effects on the total number of T1 Gad+ lesions at weeks 12, 16, 20 and 24 versus placebo: 600 mg (90% reduction [p < 0.001]) and 2000 mg (96% reduction [p < 0.001]). Similarly, both doses significantly reduced the annualized relapse rate versus placebo: 600 mg (80% reduction [p < 0.001]) and 2000 mg (73% reduction [p < 0.001]). Both ocrelizumab groups were superior to β-interferon 1a for the primary endpoint. There was no clear dose separation on the efficacy endpoints. Future Phase III investigations with anti-CD20 therapy will be limited to ocrelizumab.

There was no significant difference in the frequency of SAEs between rituximab- or ocrelizumab-treated, placebo, and β-interferon 1a subjects in the respective Phase II trials. Infusion-related adverse events were significantly higher in the first 24 hours following anti-CD20 treatment: rituximab (78.3% versus 40% placebo) and ocrelizumab placebo (34.5% and 43.6% for 600 mg and 2000 mg doses versus 9.3% placebo). Infusion reactions were predominantly mild to moderate and decreased to rates comparable to placebo with the second infusion. There were an equal frequency of infections in the treatment groups, and no opportunistic infections were observed. There was a single death in an ocrelizumab-treated subject due to acute onset thrombotic microangiopathy. The death occurred following a bee sting and may have been secondary to systemic inflammatory response syndrome.

**CELL THERAPIES**

Advancement in our understanding of adult stem cell biology has led to significant progress in the field of cell therapy in MS. Autologous hematopoietic stem cell transplantation (AH SCT) and mesenchymal stem cell transplantation (MSC T) offer two alternative approaches to cell-based immunotherapy in MS. The use of AH SCT has already been shown to be a powerful, high-risk therapy for some forms of MS, while the study of MSC T in MS is just initiating a Phase I investigation.

**Autologous Hematopoietic Stem Cell Transplantation (AH SCT)**

AH SCT is a common treatment strategy proposed for severe autoimmune disorders. The therapeutic mechanism centers on intense immunosuppression with destruction of autoreactive cells followed by immune reconstitution resulting in qualitative changes in the reconstituted immune repertoire. Although the renewed immune repertoire is established with naive CD4+ T cells of recent thymic origin, self-reactive T cells may persist after transplantation.

The AH SCT procedure is accomplished through several distinct steps. First, peripheral blood stem cells (PBSCs) are mobilized from marrow stores. Following mobilization, PBSCs are collected by leukopheresis and cryopreserved. Prior to grafting, the collected PBSCs are conditioned for subsequent transplantation through positive (CD34+ stem cells) and negative (T cell) selection. Before receiving the graft, the recipient is conditioned through a high, medium or low intensity protocol. High intensity protocols include total body irradiation or busulphan-containing chemotherapy. Medium intensity protocols include BEAM chemotherapy (BCNU, Carmustine, etoposide, Cytosine-arabinoside, melphalan), Carmustine, or cyclophosphamide. Low intensity protocols generally involve cyclophosphamide or fludarabine treatment. The conditioned PBSCs are subsequently reinfused with antithymocyte globulin (ATG) and re-engraftment occurs.
Initial Phase I/II studies of AHSCT in MS showed limited therapeutic success. This was likely due to the enrollment of multiple disease forms and the use of diverse treatment protocols. Overall, the progression-free survival favored the AHSCT treatment groups with 60-70% of the treated subjects remaining stable at 3 years and 50-60% at 6-8 years. Subsequent studies have focused on early, aggressive forms of disease. AHSCT was examined in 50 subjects with either early RRMS (EDSS 1.5) or late SPMS (EDSS 8.0) disease. EDSS improved at least 0.5 points in 62% of patients, particularly in those who were treated early in their disease course. Overall, progression-free survival was 72% at 6 years. The Canadian MS BMT Study Group evaluated 17 aggressive MS patients with AHSCT using a high-intensity conditioning regimen. Of the subjects, 75% showed progression-free survival at 3 years, and there were no relapses or new MRI lesions nearly 5 years following treatment. A Phase I/II Low Intensity AHSCT Trial was recently completed. 21 RRMS patients with mild disability and short disease duration were subjected to a low-intensity conditioning regimen of cyclophosphamide 200 mg/kg followed by alemtuzumab or ATG. Of the subjects, 81% showed a 1-point EDSS improvement at years and 62% of the subjects were disease free at 3 years. AHSCT has also proven to be successful in individual case studies of MS subjects with rapidly evolving, “malignant” disease. In these cases, AHSCT was able to halt disease progression and reverse disability in individuals that were refractory to conventional treatments.

One of the major drawbacks of AHSCT is the high rate of mortality, approximately 3-6% across trials. Most of the mortality was secondary to myelotoxic or infectious sequelae of the procedure. AHSCT with low intensity conditioning may significantly lower the frequency of these issues but may not sufficiently clear autoreactive clones from the repertoire.

There are two ongoing studies of AHSCT in MS. The Halt-MS study is a multicenter US trial involving BEAM conditioning, ATG and CD34+ cell selection in RRMS or relapsing-progressive MS subjects. A second study involves the use of stem cell therapy for patients with MS failing interferon. The Phase II ASTIMS (Autologous Stem cell Transplantation International Multiple Sclerosis) study comparing AHSCT and mitoxantrone was recently stopped for the insufficient accrual of patients.

Mesenchymal Stem Cell Transplantation
MSCT involves the transfer of autologous multipotent stromal precursors (MSCs) isolated from bone marrow. Similar cells with the phenotype of MSCs may be present in the perivascular region. Recent studies have demonstrated that MSCs have regulatory effects of the innate and adaptive immune systems and may have the ability to differentiate into unrelated germ lineages including neural cells. The immunomodulatory effects of MSCs include the inhibition of T cell proliferation in vitro, the inhibition of B cell proliferation and differentiation in vitro, the production of immunosuppressive factors such as indoleamine 2,3 dioxygenase and nitric oxide, and the impairment of dendritic cell maturation. Injection of MSCs has been shown to ameliorate murine EAE. An international, multicenter Phase I trial is currently underway.

CIRCULATORY THERAPY
A recent publication has reported a significant incidence of chronic cerebrospinal venous insufficiency (CCSVI) in individuals with MS. CCVS1 is defined as chronic impaired venous drainage from the central nervous system and is operationally diagnosed by the observation of at least 2 of 5 patterns of anomalous CNS venous drainage by ultrasound: (1) reflux in the internal jugular (IJV) and vertebral veins (VV); (2) reflux in the deep cerebral veins; (3) high-resolution B-mode evidence of IJV stenosis; (4) flow not detectable by Doppler in the IJV and/or the VV; or (5) reverted postural control of the main cerebral venous outflow pathways. In the initial study of 65 MS patients and 235 controls, there was 100% sensitivity, 100% specificity, 100% positive predictive value, and 100% negative predictive value. CCVS1 was not observed in neurologic disease controls including Parkinson’s, amyotrophic lateral sclerosis, cerebrovascular disease, myasthenia gravis, and multifocal motor neuropathy. Selective catheterization demonstrated stenosis of the azygous veins (AV) in 86% of patients and the IJV in 91% of patients. It is hypothesized that CCSVI causes venous reflux leading to iron buildup in the brain and subsequent CNS injury.

As a result of these clinical observations, an 18-month observational single center trial was performed on 65 MS subjects using transluminal angioplasty study. During the trial, subjects remained on their disease-modifying therapy. 35 of 65 treated subjects improved in some clinical outcomes. 47% of the treated subjects had restenosis. The study design, however, was flawed by the small sample size, lack of controls, lack of standard MRI protocols, and unblinded neurologic evaluations. Nevertheless, the favorable results have prompted several centers to provide off-label treatment of MS subjects at significant cost.

Is there truly a strong association between CCSVI and MS? And, if so, is the association due to correlation or causation? Ultrasound is a rather poor modality for the reliable assessment of deep venous structures. In a recent study using phase-contrast MRI, contrast-enhanced MRA and ultrasound, only 3 of 21 RRMS subjects had IJV stenosis, and no differences were observed between IJV outflow, aqueductal CSF flow, and IJV reflux between RRMS cases and 20 controls. To further address this issue of diagnostic accuracy, multiple investigations were recently funded by the National Multiple Sclerosis Society to provide a more definitive assessment of the frequency of CCSVI among MS patients and the specificity of the finding for disease. Since iron deposition is observed in
other neurodegenerative disorders, an association between CCSVI and MS will need to address several key questions to establish a causal link. Examples include:

- How does mechanism explain female bias towards disease in MS?
- How does mechanism explain HLA-DR bias? Other genetic links?
- What is the link with geography, vitamin D, EBV?
- Why is MS pathology not observed after radical neck procedures or venous sinus thrombosis or stenosis?

**SUMMARY**

The future of MS therapeutics remains bright. Endeavors are being made along multiple fronts to address inflammatory injury, and new theories are being proposed to challenge current paradigms. Over the next decade, MS patients and their caregivers will have a large number of therapies to choose from for the treatment of relapsing disease. Anticipated benefits include multiple routes of administration (subcutaneous, intravenous, oral), improved tolerability, and greater efficacy. The use of new therapies, however, will be accompanied by long-term safety concerns and the possibility of unanticipated short-term safety issues such as those observed with natalizumab. The balance of efficacy, safety, and tolerability data will ultimately determine the adoption of new medications into the MS treatment algorithm.

**CME ANSWERS**

1. D  
2. C  
3. A

**REFERENCES**


