Clinical Policy Bulletin: Multiple Sclerosis

Number: 0264

Policy

I. Intravenous Steroid Treatment

A. Aetna considers intravenous steroid therapy medically necessary for either of the following indications:

1. Treatment of acute exacerbations of multiple sclerosis (MS) when the acute relapse is characterized by functionally disabling symptoms with documented evidence of neurological impairment (persons who have previously responded in a relapse phase are more likely to do so in the future).
2. Use of intermittent pulse dose corticosteroids as a maintenance treatment for MS to delay disease progression. In many cases, members can be treated in the outpatient setting.

B. Aetna considers hospital admission for intravenous steroid therapy medically necessary for the treatment of an acute exacerbation of MS that results in any of the following severe neurological deficits:

1. Acute cerebral symptoms with severe loss of intellectual capacity; or
2. Acute epileptic seizure(s); or
3. Acute fulminant MS characterized by headache, vomiting, convulsions and eventually coma, with severe compromise of functioning of the central nervous system; or
4. Acute pseudobulbar palsy; or
5. Acute quadriplegia; or
6. Acute transverse myelitis (or Brown-Sequard syndrome) with loss of function below the level of a suspected lesion in the spinal cord; or
7. Acute visual loss.

An inpatient stay may also be considered medically necessary for persons who have had previous complications from high dose intravenous steroids that justify an inpatient admission.

II. Outpatient Treatment
A. Clinically isolated syndrome (CIS) suggestive of MS. Aetna considers Copaxone and interferon beta (see CPB 404 - Interferons for selection criteria) medically necessary for treatment of persons who have experienced a first clinical episode and have magnetic resonance imaging (MRI) features consistent with MS.

B. Relapsing, remitting MS. Aetna considers monotherapy with any of the following medications medically necessary for treatment of relapsing, remitting MS (but not for treatment of chronic progressive MS):

1. Alemtuzumab (Lemtrada) for HIV negative persons who have failed an adequate trial of interferon beta and Copaxone.
2. Avonex (interferon beta-1a) for persons with a contraindication, allergy, intolerance, or failure of an adequate trial of Rebif (see CPB 0404 - Interferons for selection criteria) plus a contraindication, allergy, intolerance, or failure of an adequate trial of Copaxone.
3. Betaseron (interferon beta-1b) for persons with a contraindication, allergy, intolerance, or failure of an adequate trial of Rebif (see CPB 0404 - Interferons for selection criteria) plus a contraindication, allergy, intolerance, or failure of an adequate trial of Copaxone.
4. Cladribine (Leustatin, 2-CDA)
5. Cyclophosphamide (Cytoxan)
6. Extavia (interferon beta-1b) for persons with a contraindication, allergy, intolerance, or failure of an adequate trial of Rebif (see CPB 0404 - Interferons for selection criteria) plus a contraindication, allergy, intolerance or failure of an adequate trial of Copaxone
7. Glatiramer acetate, copolymer-1 (Copaxone, Glatopa)
8. Imuran (azathioprine)
9. Intravenous immune globulin (IVIG) when standard approaches (i.e., interferons, glatiramer acetate) have failed, become intolerable, or are contraindicated (see CPB 0206 - Parenteral Immunoglobulins)
10. Novantrone (mitoxantrone)
11. Plegridy (peginterferon beta-1a) for persons with a contraindication, allergy, intolerance or failure of an adequate trial of Rebif (see CPB 0404 - Interferons for selection criteria) plus a contraindication, allergy, intolerance or failure of an adequate trial of Copaxone.
12. Rebif (interferon beta-1a) (see CPB 0404 - Interferons for selection criteria)
13. Tysabri (natalizumab), for persons who meet criteria in CPB 0751 - Natalizumab (Tysabri).
14. For fingolimod (Gilenya) capsules, teriflunomide (Aubagio) tablets, dimethyl fumarate delayed release (Tecfidera) capsules, and dalfampridine (Ampyra) tablets, see Commercial Pharmacy CPB on Multiple Sclerosis for selection criteria.

Aetna considers experimental and investigational combination use of alemtuzumab (Lemtrada), fingolimod (Gilenya), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), interferon beta, glatiramer acetate (Copaxone, Glatopa) and/or natalizumab (Tysabri) because there is inadequate evidence that use of two or more these drugs in combination results in better clinical outcomes than use of a single drug.

Note: For policy on H.P. Acthar Gel, see CPB 0762 - Repository Corticotropin Injection (H.P. Acthar Gel).

C. Chronic progressive MS. Aetna considers Novantrone (mitoxantrone)* medically necessary for clinically deteriorating persons with either relapsing remitting or chronic progressive forms of MS.
D. Plasma exchange/plasmapheresis is considered medically necessary for individuals with acute, severe neurological deficits caused by MS who have a poor response to treatment with high-dose glucocorticoids.

*Note: Because of the potential for functional cardiac changes, the product labeling for Novantrone states that persons receiving Novantrone should have their left ventricular ejection fraction (LVEF) evaluated by echocardiogram or MUGA prior to every dose.

**Note: Interferon beta and glatiramir acetate (Copaxone, Glatopa) are first-line treatments for multiple sclerosis. There are several brands of interferon beta on the market. There is a lack of reliable evidence that any one brand of interferon beta is superior to other brands for relapsing-remitting multiple sclerosis. Rebif (interferon beta-1a) brand of interferon beta ("least cost brand of interferon beta") is less costly to Aetna. Consequently, because other brands (Avonex (interferon beta-1a), Betaseron (interferon beta-1b), Extavia (interferon beta-1b), and Plegridy (peginterferon beta-1a)) are more costly than the least cost brand of interferon beta, and the least cost brand of interferon beta is at least as likely to produce equivalent therapeutic results, no other brands of interferon beta will be considered medically necessary unless the member has a contraindication, allergy, intolerance or failure of an adequate trial of the least cost brand of interferon beta plus a trial of Copaxone.

For purpose of this policy, failure of an adequate trial of therapy for multiple sclerosis is defined as follows:

- The member has increasing relapses (defined as two or more relapses in a year, or one severe relapse associated with either poor recovery or MRI lesion progression); or
- The member has lesion progression by MRI (increased number or volume of gadolinium-enhancing lesions, T2 hyperintense lesions or T1 hypointense lesions); or
- The member has worsening disability (sustained worsening of Expanded Disability Status Scale (EDSS) score or neurological examination findings).

Intolerance is defined as intolerable side effects despite optimized management strategies.

***Note: Policy requirements for a trial of an injectable drug therapy may be waived for persons who meet diagnostic criteria for needle phobia (see appendix for DSM 5 criteria), if there is documentation of preexisting excessive fear (outside of the particular request being considered) of injections and blood draws with documented attempts at management and psychological counseling, especially if there are associated symptoms (vasovagal syncope, panic attack).

III. Experimental and Investigational Interventions:

Aetna considers the following interventions experimental and investigational for MS:

- Alpha-interferon
- Anti-T-cell monoclonal antibodies other than natalizumab (Tysabri, Antegren)
- Anti-lymphocyte globulin
- APOE genotyping
- Balloon angioplasty/venous angioplasty with or without stent placement
- Brainstem auditory evoked response for diagnosing MS
- Cerebrospinal fluid levels of neurofilament as a biomarker of MS,
- Cooling garment
- Cosyntropin (Cortrosyn)
- Cyclosporine (Sandimmune)
Daclizumab (Zenapax)
Dietary interventions (e.g., gluten-free diets, low fat diets, linoleate supplementation to diet, and dietary regimens with polyunsaturated fatty acids)
Electronystagmography (in the absence of vertigo or balance disorder)
Erythropoiesis stimulating agents (unless criteria are met in CPB 0195 - Erythropoiesis Stimulating Agents)
Ferritin/iron status (blood or CSF) for the diagnosis of MS
Gamma-interferon
gMS®DX and gMS®Pro EDSS tests for the diagnosis of MS
Hyperbaric oxygen
IL-2-toxin
Interleukin-1 gene polymorphisms testing
IVIG for progressive MS (see CPB 0206 - Parenteral Immunoglobulins)
Methotrexate
MTHFR testing for MS
Myxovirus resistance protein A (MxA) as a biomarker for MS relapse/treatment response
Naltrexone
Optical coherence tomography for screening of member receiving fingolimod (Gilenya) for macular edema (see CPB 344 - Optic Nerve and Retinal Imaging Methods)
Oral myelin (Myloral)
Otoacoustic emissions (in the absence of signs of hearing loss)
Photopheresis (see CPB 0241 - Extracorporeal Photochemotherapy (Photopheresis))
Plasmapheresis for chronic or secondary progressive MS (maintenance therapy)
Procarin (transdermal histamine)
Prolactin
Pulsed magnetic field therapy
PUVA (psoralen ultraviolet light)
Retinal nerve scanning for screening/monitoring persons on fingolimod (Gilenya)
Ribavirin
Rituximab for the treatment of RRMS (see CPB 314 - Rituximab (Rituxan))
Sildenafil
Statins
Stem cell transplantation (seeCPB 0606 - Stem Cell Transplant for Autoimmune Diseases and Miscellaneous Indications)
T-cell receptor therapy
T-cell vaccination
Total lymphoid irradiation
Transcranial brain sonography for predicting disease progression in MS
Transforming growth factor (TGF)-beta
Tumor necrosis factor antagonists
Tympanometry (in the absence of hearing loss).

IV. Neutralizing Antibodies Against Interferon Beta

Aetna considers assays of neutralizing antibodies (NABs) against interferon beta (Betaseron) to be experimental and investigational because its clinical value has not been established.

Background
Multiple sclerosis (MS) is an acquired inflammatory disease characterized by the destruction of myelin sheaths with preservation of axons occurring in multiple anatomic sites in the brain and spinal cord. Its clinical course is variable and unpredictable and exact etiology is unknown, although data suggests that it is an autoimmune disease triggered by a viral infection in genetically susceptible individuals.

The clinical course of MS can be classified as exacerbating-remitting, acute progressive, or chronic progressive. Classical exacerbating-remitting usually begins with the acute or subacute onset of focal neurologic signs and symptoms, typically evolving over 1 to 3 days, stabilizing for a few days, and then improve spontaneously, followed by an onset of new focal symptoms months or years later. On rare occasions, MS has a relatively acute onset with a rapidly progressive course involving multiple areas of the nervous system simultaneously and leading to severe impairment and death within a few weeks or months. In chronic progressive MS, the course is insidious and progressive from the onset, usually occurs in patients greater than 35 years of age, and presents as a chronic myelopathy with slowly or intermittent, progressive symptoms. Neuromyelitis optica (Devic’s syndrome) is a clinical syndrome consisting of both optic neuritis and transverse myelitis, occurring simultaneously or separately by only a brief interval in a patient without prior evidence of MS.

Patients with MS initially present with sensory disturbances in 1 or more limbs, disturbances of balance and gait with ataxia, optic nerve dysfunction with visual loss in 1 eye, diplopia, nystagmus, dysarthria, upper motor neuron spastic weakness, intention tremors, autonomic dysfunction, bladder dysfunction, spastic paraparesis, and retrobulbar neuritis, in various combinations. About 50 % of patients with isolated optic neuritis will develop MS.

The diagnosis of MS remains clinical at present, with demonstration of signs and symptoms spread out in time and space being required. Most patients have initial symptoms which totally resolve only to relapse with progressive residual disability after each exacerbation and significant neurologic dysfunction developing over a period of several years. Less than 1/3 of MS patients have a very benign course with minimal or no disability, and about 10 % have a very malignant course with severe disability within months to a few years.

At onset, about 65 % of patients have a relapsing-remitting form of the disease. These patients have exacerbations with symptoms attributable to central nervous system (CNS) lesions or plaques. The flare-ups usually develop subacutely and resolve over weeks to months. About 15 % of patients have exacerbations similar to the relapsing-remitting disease but less complete recovery that leaves the patients with significant residual disability. This form is referred to as the relapsing-progressive form. Finally, there is the chronic progressive form dominated by spinal cord and cerebellar dysfunction. In about 20 % of patients, the initial symptoms start with this chronic progressive form, whereas, more often, it develops out of the relapsing-remitting disorder over time.

The inflammatory response in the CNS consists predominantly of activated T lymphocytes and macrophages accompanied by a local immune reaction with the secretion of cytokines and the synthesis of oligoclonal immunoglobulin within the CNS. Multiple sclerosis is thought to either be a cell-mediated autoimmune attack against myelin antigens or the presence of a persistent virus or infectious process within the CNS against which the inflammatory response is directed.

Many scattered, discrete areas of demyelination, termed plaques, are the pathologic hallmark of multiple sclerosis. Only limited regeneration of myelin occurs once the myelin sheath is destroyed (shadow plaques). Conduction of nerve impulses along axons denuded of their myelin is slowed or blocked. This loss of conduction is analogous to a segment of electrical wire being stripped of its insulating cover, allowing escape of current and diminishment of its force down the rest of the wire.
The essentials of diagnosis are: episodic symptoms that may include sensory abnormalities, blurred vision, sphincter disturbances, and weakness with or without spasticity; patient is usually under 55 years of age at onset; single pathologic lesion cannot explain clinical findings; and multiple foci best demonstrated by magnetic resonance imaging (MRI).

An accurate diagnosis is extremely important because this disorder mimics many diseases of the central nervous system. The clinical history, including a history of at least 2 episodes of neurologic deficit, and physical examination showing objective clinical signs of lesions at more than one site within the CNS, remain of paramount importance in establishing a correct diagnosis. However, the sine qua non of the initial diagnosis is the MRI demonstration that different regions of the white matter of the CNS have been affected by lesions at different times by demonstrating multiple white matter lesions (plaques) which represent a clearly defined patch of demyelination of sheaths of neurons in the CNS signifying areas of slowed or loss conduction leading to symptoms. Diagnosis is confirmed with the aid of a number of procedures. Cerebrospinal fluid (CSF) examination show elevated immunoglobulin G (IgG) and oligoclonal banding (electrophoretic bands which represents fractionations of IgG). Evoked potential testing demonstrates conduction disturbances. The diagnosis of MS rests as much as ever on the considered opinion of the neurologist, based heavily on the clinical features of the patient's illness.

Intravenous steroids are safe and effective in treating acute exacerbations of MS. Its use is directed at the early halting or diminishing of the destructive inflammatory process in the central nervous system, so that neurologic disability doesn’t accumulate. For an acute relapse, a course of intravenous corticosteroids is typically given (500 mg to 1 gram of methylprednisolone (Solu-Medrol) over 30 to 60 mins for 3 days). This course can be extended up to 5 days (or to even 10 days) if the attack continues to progress or is slow in improving. Intravenous methylprednisolone is also the usual primary treatment for optic neuritis. The somewhat rapid effect of steroid treatment is based partly by reduction of white matter edema, and somewhat by an alteration of immunological factors. It is unusual in practice to give more than 2 or 3 courses of steroids for the treatment of relapses.

The treatment of MS must be individualized to the patient. Patients with stable disease, mild acute attacks, consisting of minor paresthesias, slight weakness, or incoordination that do not significantly interfere with normal activities require no treatment, as these attacks subside in 1 to 2 weeks without treatment. Symptomatic treatment for spasticity, paresthesias, fatigue, and bowel and bladder difficulties may be required. Patients with progressive MS are treated with immunomodulating therapy, however, unfortunately no therapy has had a significant beneficial effect on the course of progressive MS. Because the clinical examination is a relatively crude indicator to assess the efficacy of treatment, recent studies are using MRI to assess therapeutic benefit.

Early in the disease course, many patient exhibit little neurologic dysfunction and require minimal therapy. Many times their attacks are self-limiting and the main therapy offered is counsel and advise. When intervention is required, therapy is directed toward altering the clinical course with the use of immunosuppressives, or alleviating symptoms (spasticity, fatigue, depression, pain, bladder dysfunction, and cerebellar dysfunction).

An acute relapse of MS may require no treatment if it is mild or does not produce functional decline. However, relapses that cause significant disability are usually treated with a course of intravenous corticosteroids. Studies have shown that corticosteroids or ACTH decrease the length of a clinical relapse of MS, and some studies have shown that corticosteroids are superior to and have fewer side effects than ACTH. It is not unusual to see the onset of a major depressive episode coincident with the first relapse episode, in spite of appropriate patient education as to the nature of the illness and in spite of mild severity of symptoms. The response to steroids is often exhilarating (hypomanic, or even psychotic) followed by the return of severe
depressive symptoms once the steroids are discontinued. It is not unusual, therefore, that these patients may require a psychological assessment early on if depressive symptoms persist.

Adrenocorticotropic hormone (ACTH) is secreted by the anterior pituitary and stimulates the adrenal cortex to secrete cortisol, aldosterone, and androgenic hormones. The anti-inflammatory, and possibly the inhibition of antibody production, appear to the effects most relevant to MS. The growth of the use of synthetic glucocorticoids arose from efforts to minimize the many undesirable side effects related to aldosterone and androgen stimulation. Therefore, the use of oral glucocorticoids and the intravenous use of high-dose methylprednisolone has largely supplanted ACTH treatment.

Beta interferon (Betaseron) has been demonstrated in controlled trials to reduce the frequency and severity of acute attacks. It has been shown to decrease the number of acute attacks of MS by about 1/3 and to decrease the average severity of attacks so that attacks classified as moderate to severe were reduced by more than 50 %, as well as causing a dramatic reduction in the appearance of new lesions on MRI.

As a result of the current thoughts on the immunological pathogenesis of the disease, immunosuppressive and immunomodulating drugs remain the mainstay of treatment for progressive MS. These drugs are used to prevent relapses and progression, to provide symptomatic treatment of MS, and occasionally for acute flare-ups. There are no large controlled trials of the efficacy of this therapy on acute exacerbations. The immunosuppressive agents currently used are all controversial, with data published supporting and disproving their efficacy. These therapies for acute flare-ups should be reserved for debilitating exacerbations, as patients appear to become resistant to therapy and there is no evidence that the ultimate degree of recovery is altered. A Cochrane review (La Mantia et al, 2007) concluded that the overall effect of cyclophosphamide (administered as intensive schedule) in the treatment of progressive MS does not support its use in clinical practice.

Cladribine (Leustatin) provides immunomodulation through selective targeting of lymphocyte subtypes that is being investigated in the treatment of patients with relapsing remitting MS. Giovannoni et al (2009) presented the results of the CLARITY study, a phase III, randomized, double-blind study to evaluate the safety and efficacy of oral cladribine in relapsing–remitting MS. Relapsing–remitting MS patients were randomized to one of two cladribine regimens or to placebo. Cladribine tablets were administered for 5 days per 28-day treatment course for 2 or 4 consecutive courses during the first 48 weeks and for 2 consecutive courses at the beginning of the second 48 weeks to achieve a total dosage of 3.5 or 5.25 mg/kg. Of the intention-to-treat population (n = 1326) randomized to 5.25 mg/kg (n = 456), 3.5 mg/kg (n = 433), or placebo (n = 437) groups, 89 %, 92 %, and 87 % completed the study, respectively. Cladribine 5.25 and 3.5 mg/kg versus placebo resulted in significantly lower annualized relapse rates (the primary study endpoint) (0.15 and 0.14 versus 0.33; relative reduction in annualized relapse rate 54.5 % and 57.6 % respectively; both p < 0.001). Of subjects receiving cladribine, 78.9 % and 79.7 % of the 5.25 and 3.5 mg/kg groups were relapse free versus 60.9 % of placebo patients (odds ratios: 2.43 and 2.53, respectively; both p < 0.001). Cladribine groups had an approximately 30 % relative reduction in risk of disability progression (hazard ratio; 95 % confidence interval [CI]: 0.69 [0.49 to 0.96] and 0.67 [0.48 to 0.93]; p = 0.026 and p = 0.018; 5.25 mg/kg and 3.5 mg/kg groups versus placebo, respectively). The investigators reported that highly significant reductions in brain lesion activity were seen in all 3 MRI measures: T1-Gd+, active T2, and new combined lesions. The investigators stated that, overall, frequencies of adverse events in the cladribine groups were low and comparable with placebo. The investigators noted that events related to cladribine’s mechanism of action, such as lymphopenia, were reported more frequently with cladribine treatment. The investigators concluded that cladribine treatment resulted in significant improvements in clinical and MRI outcomes and was accompanied by a favorable safety and tolerability profile, suggesting that annual short-course treatment with cladribine may provide an important new option in multiple sclerosis therapy.

Glatiramer acetate injection (Copaxone, Teva Pharmaceutical Industries Ltd., Jerusalem, Israel) has been approved by the U.S. Food and Drug Administration (FDA) for the reduction of the frequency of relapses in
relapsing remitting MS, including patients who have experienced a first clinical episode and have MRI features consistent with MS. The FDA approved an expanded indication for glatiramer acetate injection to include the treatment of patients who have experienced a first clinical episode and have MRI features consistent with MS.

Up to 85% of MS patients initially experience a single neurological event suggestive of MS, known as clinically isolated syndrome (CIS), and it has been demonstrated that early treatment initiation delays conversion from CIS to clinically definite MS (CDMS). The FDA granted approval of Copaxone after reviewing the results of the PreClSe study, which indicated time to development of a second exacerbation was significantly delayed in patients treated with glatiramer acetate injection compared to placebo (hazard ratio = 0.55; 95% CI: 0.40 to 0.77; p = 0.0005). The cumulative probability of developing the second attack during the 3-year study period was significantly lower in the glatiramer acetate injection group versus the placebo group (24.7% versus 42.9%). The PreClSe study was a multinational, multi-center, prospective, double-blind, randomized, Phase III study that included 481 patients presenting with a single clinical episode and MRI scans suggestive of MS. Patients included were those who had a unifocal disease manifestation (i.e., clinical evidence of a single lesion). Patients received either glatiramer acetate 20mg/day or placebo as a subcutaneous injection and continued treatment for up to 3 years, unless a second exacerbation was experienced. Patients who experienced a second exacerbation continued the trial on active treatment for an additional 2 years. The primary efficacy outcome was time to development of second exacerbation. A pre-planned interim analysis was performed on data accumulated from 81% of the 3-year placebo-controlled study exposure. The investigators reported that the 25th percentile of number of days to second exacerbation with glatiramer acetate injection increased from 336 days to 722 days compared with placebo (hazard ratio = 0.55; 95% CI: 0.40 to 0.77). In addition, the investigators reported that there was a significant reduction in the number of new T2 lesions and in the number of T1-enhancing lesions in the glatiramer acetate injection arm compared to the placebo arm, both at year-1 and year-2 MRI scans.

In April 2015, Glatopa (glatiramer acetate, Momenta Pharmaceuticals and Sandoz) became the first FDA-approved generic version of Copaxone. Like Copaxone, Glatopa is indicated to treat individuals with relapsing forms of multiple sclerosis.

Novantrone (mitoxantrone for injection) acts in MS by suppressing the activity of T cells, B cells, and macrophages that are thought to lead the attack on the myelin sheath. Novantrone has been approved by the FDA for treatment of both the relapsing-remitting and chronic progressive forms of MS. Because of the potential for functional cardiac changes, the product labeling for Novantrone states that persons receiving Novantrone should have cardiac monitoring. The FDA recommends that the left ventricular ejection fraction (LVEF) should be evaluated by echocardiogram or MUGA prior to every dose administered to patients with MS. Additional doses of Novantrone should not be administered to MS patients who have experienced either a drop in LVEF to below 50% or a clinically significant reduction in LVEF during Novantrone therapy. The labeling states that patients with MS should not receive a cumulative dose greater than 140 mg/m2.

The use of multiple sclerosis drugs in combination is an active area of research. The primary rationale for polytherapy in multiple sclerosis is that the involved treatments target different mechanisms of the disease and therefore their use is not necessarily exclusive. Synergies, in which one drug potentiates the effect of another are also possible, but there can also be important drawbacks such as antagonizing mechanisms of action or potentiation of deleterious secondary effects. There have been several clinical trials of combined therapy, yet none has shown positive enough effects to merit the consideration as a viable treatment for multiple sclerosis (Milo & Panitch, 2011).

It is not known whether statins are effective therapy for MS. Birnbaum et al (2008) explored whether high-dose atorvastatin can be administered safely to persons with relapsing-remitting MS taking thrice-weekly, 44 microg dose subcutaneous interferon (IFN) beta-1a. Subjects were randomized in a double-blind fashion to receive either placebo or atorvastatin at dosages of 40 or 80 mg/day for 6 months. Blinded neurological examinations and brain MRI readings were obtained at months 0, 3, 6, and 9. Laboratory blood testing was performed.
monthly. Main outcome measures were the determination of drug toxicity using blood tests and ECG and determination of MS-related disease activity, either clinical relapses or new or contrast-enhancing lesions on MRI. A total of 26 subjects received at least one dose of study drug. Ten of 17 subjects on either 80 mg or 40 mg of atorvastatin per day had either new or enhancing T2 lesions on MRI or clinical relapses. One of the 9 subjects on placebo had a relapse with active lesions on MRI. Subjects receiving atorvastatin were at greater risk for either clinical or MRI disease activity compared to placebo (p = 0.019). Significant changes in blood tests were noted only for lower cholesterol levels in subjects receiving atorvastatin. The authors concluded that the combination of 40 or 80 mg atorvastatin with thrice-weekly, 44 microg IFN beta-1a in persons with MS resulted in increased MRI and clinical disease activity; caution is suggested in administering this combination.

In an editorial that accompanied the afore-mentioned article, Goldman and Cohen (2008) stated that “there are several ongoing larger studies of statins in MS, both as monotherapy and combined with other medications. Hopefully these studies will clarify whether statins are useful as MS therapy”.

Alleviation of the symptoms of MS becomes necessary, since effective curative therapy is not yet available. Symptomatic treatment provides the means of improving the quality of life of individuals with MS. Oral baclofen commonly is used to treat spasticity, however, a major side effect is increased weakness of the limb with possible negative effects on ambulation. Oral tizanidine can also be used to treat spasticity, where loss of strength appears to be less of a problem. Intrathecal baclofen via an implantable pump has been shown to be very effective in treating severe, intractable spasticity; however, careful selection of patients is mandatory as this is an invasive procedure with a number of potentially dangerous complications (hypotension, respiratory insufficiency, and meningitis). When all forms of medical treatment are insufficient to prevent spasticity-related complications, injection of phenol can be used to perform neurolysis. Tenotomies of fixed contractures can also be useful in extremely disabled patients to allow adequate nursing. Oral clonazepam, hydroxyzine and beta-blockers can be used to treat tremors. Irritative or obstructive bladder symptoms, as a result of spinal lesions causing detrusor hyperreflexia and incomplete bladder emptying, can be treated with oral anticholinergic medication (e.g., oxybutynin) and intermittent self-catheterization. Carbamazepine can be used to treat trigeminal neuralgia, the most common neurologic symptom in multiple sclerosis patients, and bouts of itching, burning sensations, twitching of the face, and a current of electricity flowing the length of their spine.

Hyperbaric oxygen (HBO) therapy has not been shown to be effective in the treatment of MS. Hyperbaric oxygen therapy, the intermittent inhalation of 100 % oxygen under a pressure greater than 1 atmospheres pressure (atm), is one of many unconventional treatments tried as a possible treatment for MS. It can be administered in either a mono-place or multi-place chamber. The latter accommodates 2 to 14 people and can achieve pressures up to 6 atm. Patients breath 100 % oxygen through a face mask, head hood, or endotracheal tube and can be cared for by medical personnel directly within the chamber. Monoplace chambers treat a single patient in an environment maintained at 100 % oxygen, thus, no mask is required. Possible complications of HBO therapy include barotrauma (ear or sinus trauma, tympanic membrane rupture, pneumothorax, air embolism), oxygen toxicity (central nervous system or pulmonary), fire, reversible visual changes and claustrophobia. Although early uncontrolled clinical trials and anecdotal reports suggested that HBO may be beneficial in the management of MS, more recent controlled studies with larger sample sizes indicate that this modality is not effective in the treatment of this central nervous system disease.

Ehrenreich et al (2007) performed an investigator-driven, exploratory open label study (phase I/IIa) in patients with chronic progressive MS. Main study objectives were (i) evaluating safety of long-term high-dose intravenous recombinant human erythropoietin (rhEPO) treatment in MS, and (ii) collecting first evidence of potential efficacy on clinical outcome parameters. A total of 8 MS patients: 5 randomly assigned to high-dose (48,000 IU), 3 to low-dose (8,000 IU) rhEPO treatment, and, as disease controls, 2 drug-naïve Parkinson patients (receiving 48,000 IU) were followed over up to 48 weeks: a 6-week lead-in phase, a 12-week treatment phase with weekly EPO, another 12-week treatment phase with bi-weekly EPO, and a 24-week post-treatment phase. Clinical and electrophysiological improvement of motor function, reflected by a reduction in
expanded disability status scale, and of cognitive performance was found upon high-dose EPO treatment in MS patients, persisting for 3 to 6 months after cessation of EPO application. In contrast, low-dose EPO MS patients and drug-naïve Parkinson patients did not improve in any of the parameters tested. There were no adverse events, no safety concerns and a surprisingly low need of blood-lettings. The authors concluded that this first pilot study demonstrated the necessity and feasibility of controlled trials using high-dose rhEPO in chronic progressive MS.

In a phase II, double-blind, 48-week clinical trial involving 104 patients with relapsing–remitting MS, Hauser et al (2008) assigned 69 patients to receive 1,000 mg of intravenous rituximab and 35 patients to receive placebo on days 1 and 15. The primary end point was the total count of gadolinium-enhancing lesions detected on MRI scans of the brain at weeks 12, 16, 20, and 24. Clinical outcomes included safety, the proportion of patients who had relapses, and the annualized rate of relapse. As compared with patients who received placebo, patients who received rituximab had reduced counts of total gadolinium-enhancing lesions at weeks 12, 16, 20, and 24 (p < 0.001) and of total new gadolinium-enhancing lesions over the same period (p < 0.001); and these results were sustained for 48 weeks (p < 0.001). As compared with patients in the placebo group, the proportion of patients in the rituximab group with relapses was significantly reduced at week 24 (14.5 % versus 34.3 %, p = 0.02) and week 48 (20.3 % versus 40.0 %, p = 0.04). More patients in the rituximab group than in the placebo group had adverse events within 24 hours after the first infusion, most of which were mild-to-moderate events; after the second infusion, the numbers of events were similar in the 2 groups. The authors concluded that a single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks. However, the authors noted that this phase II study was not designed to evaluate long-term safety or to detect uncommon adverse events. They stated that the safety and effectiveness of rituximab for the treatment of MS need to be validated by larger and longer-term controlled studies. MacFarland (2008) noted that a phase II clinical trial leaves many questions unanswered including the duration of the treatment effect, the effect of progression of disability, and most importantly the types of adverse events that may occur at low frequency. Issues of long-term safety of rituximab must still be addressed, given reports to the FDA of progressive multi-focal leukoencephalopathy in patients with lupus who were treated with rituximab.

In a cross-sectional study (n = 15), Sheffler and colleagues (2008) examined if an ankle foot orthosis (AFO) would improve gait velocity and tasks of functional ambulation in patients with MS. Subjects experienced dorsiflexion and eversion weakness, and had used a physician-prescribed AFO for more than 3 months. Ambulation was evaluated (i) without an AFO and (ii) with an AFO. Outcome measures were the Timed 25-Foot (T25-FW) Walk portion of the Multiple Sclerosis Functional Composite and the 5 trials (floor, carpet, up and go, obstacles, and stairs) of the Modified Emory Functional Ambulation Profile (mEFAP). The mean timed differences on the T25-FW and the 5 components of the mEFAP between the AFO versus no device trials were not statistically significant. The authors concluded that in MS subjects with dorsiflexion and eversion weakness, no statistically significant improvement was found performing timed tasks of functional ambulation with an AFO.

Plasma exchange has not been proven for the treatment of various stages of MS. Laboratory abnormalities are suggestive that MS is an immune-mediated disease; this is the rational basis of offering plasma exchange. Specifically, it is hypothesized that humoral factors may be involved, as evidenced by the presence of anti-myelin antibodies and non-antibody demyelinating factors in the sera of patients with MS and the presence of circulating autoantibodies. The specific identity of these humoral factors has not yet been identified. Further evidence supporting the use of PE has been its success in other autoimmune diseases. However, available clinical studies, including randomized controlled clinical trials, have not proven that plasma exchange is effective for MS. A systematic review of the literature on plasma exchange for MS (Nicholas and Chataway, 2006) concluded that there is "insufficient evidence to assess plasma exchange in people with acute relapses of multiple sclerosis."
Assays of neutralizing antibodies (NABs) against interferon beta (Betaseron) have not been proven to be useful in MS. About 1/3 of individuals develop NABs against interferon beta. A number of laboratories have developed assays for these NABs (e.g., MxA Assay (Berlex Laboratories), NabFeron (Athena Diagnostics)). However, according to the peer-reviewed medical literature, the clinical utility of these assays has not been established. Evidence-based guidelines on MS from the American Academy of Neurology (Goodin et al, 2002) state: "The rate of neutralizing antibody (NAb) production is probably less with IFN-1a treatment than with IFN-1b treatment, and the presence of NAb may be associated with a reduction in clinical effectiveness of IFN treatment. The existing data are, however, ambiguous in this regard, and the clinical utility of measuring NAb in an individual on IFN therapy is uncertain."

While the European Federation of Neurological Societies Task Force on anti-IFN-beta antibodies in multiple sclerosis (Sorensen et al, 2005) recommended that tests for the presence of NABs should be performed in all patients at 12 and 24 months of interferon beta therapy, the consensus statement from an international conference on the significance of NABs to interferon beta during treatment of MS (Hartung et al, 2005) stated that "an international standardized assay for NAb is needed; and all patients with MS who receive IFN-beta therapy should be evaluated for the presence of NAb. Moreover, guidelines on how to manage NAb-positive patients should be developed to optimize IFN-beta therapy; these treatment guidelines should be based on the results of well-controlled clinical studies. An international standardized assay will facilitate direct comparison of NAb titers amongst studies and will provide further information regarding the immunogenicity of the various types of IFN-beta products and how NAb impact clinical efficacy."

Antonelli and colleagues (2005) stated that "[t]here is a lack of substantial information on the biological/immunological phenomenon of neutralising antibodies in vivo development. Nevertheless, sufficient experimental data are available to provide a rationale for monitoring the presence of anti-IFN antibodies in patients treated with IFN beta. A standardised quantitative assay to detect antibody to IFNs must be agreed. Only when results can be compared, both in terms of the qualitative presence and quantitative measurement of antibodies, will it be possible to monitor fully the ability of antibodies to cause a relapse during treatment. Although there is increasing evidence to indicate that the development of antibodies to IFN beta may be associated with a failure of the beneficial effects of the therapy, the use of the seropositivity for neutralising antibodies to IFN beta as the only surrogate marker for clinical and therapeutic decision-making is questionable. Also, guidelines on MS from the Association of British Neurologists (2001) stated that monitoring neutralizing antibodies for beta interferon is not necessary."

Noronha (2007) noted that an effect on relapse rates and imaging parameters was noted in patients who tested positive for NAbs, but disability measures were unaffected or showed a trend toward improvement. Patients who developed NAbs during IFN-beta1a therapy tended to remain NAb+, whereas those who developed NAbs during IFN-beta1b therapy tended to revert to NAb- over time. The author stated that the prevalence of NAbs in suboptimal responders does not support a causal relationship of suboptimal responses to the development of NAbs. Thus, decisions to alter treatment should be rendered by clinicians based on the clinical state of the patient.

Natalizumab (Tysabri, Biogen-Idec, Cambridge, MA) is indicated for persons with relapsing forms of MS who have not responded adequately, or cannot tolerate, other treatments for MS. Tysabri was initially approved by the FDA in November 2004, but was withdrawn from the market in February 2005, after 3 patients in the drug’s clinical trials developed progressive multifocal leukoencephalopathy (PML). Two of the cases were fatal.

The FDA allowed a clinical trial of natalizumab to resume in February 2006, following a re-examination of the patients who had participated in the previous clinical trials, confirming that there were no additional cases of PML. To decrease the possibility of patients developing PML in the future, the manufacturer, Biogen-IDEC, submitted to the FDA a Risk Management Plan, called the TOUCH Prescribing Program, to ensure safe use of
the product. The FDA has determined that natalizumab can be made available under the TOUCH Prescribing Program with the following main features:

Natalizumab will only be administered to patients who are enrolled in the program.
Patients on natalizumab are to be evaluated at 3 and 6 months after the first infusion and every 6 months after that, and their status will be reported regularly to the product’s manufacturer.
Prior to initiating the therapy, health care professionals are to obtain the patient's MRI scan to help differentiate potential future MS symptoms from PML.
The drug will only be prescribed, distributed, and infused by prescribers, infusion centers, and pharmacies registered with the program.

To date, 7 cases of PML have been identified in users of natalizumab. The FDA has reviewed information pertaining to the most recent cases and continues to recommend that natalizumab monotherapy may confer a lower risk of PML than when natalizumab is used together with other immunomodulatory medications.

An assessment of natalizumab for MS by the American Academy of Neurology included the following recommendations.

Because of the possibility that natalizumab therapy may be responsible for the increased risk of PML [progressive multifocal leukoencephalopathy], it is recommended that natalizumab be reserved for use in selected patients with relapsing remitting disease who have failed other therapies either through continued disease activity or medication intolerance, or who have a particularly aggressive initial disease course. This recommendation is very similar to that of the FDA. Similarly, because combination therapy with IFN-beta and natalizumab may increase the risk of PML, it should not be used. There are also no data to support the use of natalizumab combined with other disease-modifying agents as compared to natalizumab alone. The use of natalizumab in combination with agents not inducing immune suppression should be reserved for properly controlled and monitored clinical trials.

Shi et al (2008) stated that while the role of apolipoprotein E (APOE) polymorphism has been well recognized in cognitive neurodegenerative disorders, its role in MS is less clear. Studies indicated that 40 % to 60 % of patients with MS have evidence of cognitive impairment. These researchers examined if there is an association between APOE epsilon 4 and cognitive deficits in MS. They performed a standardized battery of neuropsychological tests investigating the 4 cognitive domains commonly impaired in MS and assessed the association of the presence of APOE epsilon 4 with cognition in these patients. A strong association was found between the presence of APOE epsilon 4 and cognitive deficits in patients with MS, especially in the domains of learning and memory. This association was strongest in the youngest cohort (aged 31 to 40 years) of patients with MS. The authors concluded that APOE epsilon 4 is significantly associated with cognitive impairment in patients with MS. However, the modest effects do not justify APOE genotyping of patients with MS in clinical practice.

Guerrero et al (2008) evaluated if there is any correlation between APOE genotype and severity according to Multiple Sclerosis Severity Score (MSSS). This study included 82 patients with disease duration of at least 2 years. These investigators collected data concerning demographic and clinical variables including age of onset, disease duration, Expanded Disability Status Scale (EDSS) score and the total number of relapses. They determined the latency to EDSS scores of 4.0 and 6.0; calculated progression index (PI) and relapse rate (RR); and ascertained MSSS in the global MSSS table. The authors reported that 4 patients heterozygous for the E2 allele and 16 for the E4 allele. No patient was homozygous for E2 or E4. RR (p = 0.017 with 95 % CI: 0.005 to 0.57) and PI (p = 0.016 with 95 % CI: 0.004 to 0.38) were significantly lower in E4 carriers. Multiple Sclerosis Severity Score was not associated with carriership of E2 or E4. The authors concluded that these findings show no effect of the APOE genotype on the severity of MS measured by MSSS, as a recently published meta-analysis has noticed. Thus, the data do not support a role for APOE in MS severity.
The Multiple Sklerose Therapie Konsensus Gruppe (2006) stated that the monoclonal antibodies provide considerable improvement of treatment for MS, but their use in basic therapy is restricted by their side effect profile. Thus, natalizumab is only approved for monotherapy after basic treatment has failed or for rapidly progressive relapsing-remitting MS. In contrast, long-term data on recombinant beta-interferons and glatiramer acetate (Copaxone) show that even after several years no unexpected side effects occur and that a prolonged therapeutic effect can be assumed which correlates with the dose or frequency of treatment. Recently IFN-beta1b (Betaferon) was approved for prophylactic treatment after the first attack (clinically isolated syndrome, CIS). During treatment with beta-interferons, neutralizing antibodies can emerge with possible loss of effectivity. In contrast, antibodies play no role in treatment with glatiramer acetate. During or after therapy with mitoxantrone, serious side effects (cardiomyopathy, acute myeloid leukemia) appeared in 0.2 to 0.4 % of cases. Plasmapheresis is limited to individual curative attempts in escalating therapy of a severe attack. According to the revised McDonald criteria, the diagnosis of MS can be made as early as the occurrence of the first attack.

Tackenberg et al (2007) stated that the natural course of MS is probably more favorable than previously assumed years ago. Since the introduction of interferons in Germany, the establishment and further development of new diagnostic criteria (McDonald criteria), the causal and symptomatic treatment possibilities and initiation of therapy early in the course of the disease have led to a considerable change in the treatment of MS. Attacks of MS are usually treated with the intravenous administration of high-dosed steroids. When the attack symptoms do not sufficiently subside, plasmapheresis can be considered. For long-term treatment of MS, beta interferon, glatiramer acetate and natalizumab are available as basic causal therapy and natalizumab and mitoxantrone are available for escalation therapy. Frequently occurring spasticity, chronic fatigue syndrome, depression, cognitive disturbances, incontinence, pain, ataxia and sexual disorders must be treated symptomatically. Overall, the outpatient treatment of MS is complex and should be carried out with close cooperation between the family doctor, neurological practices and outpatient departments specialized in treating MS.

Oh et al (2008) noted that B-cells and humoral immunity have been implicated in the pathogenesis of MS. The most common pattern of demyelinating pathology in MS is associated with the deposition of antibodies and the activation of complement, as well as T-cells and macrophages. Plasmapheresis has been found to be an efficient therapeutic approach in patients with this type of pathological lesion.

Matsui (2008) noted that Japanese patients with relapsing-remitting MS (RRMS) consists of 2 groups. One is opticospinal form (OSMS), in which major neurological symptoms derive from optic neuritis and myelitis, and the other is conventional form (CMS) that shares similar genetical and clinical features with western type of MS. Patients with OSMS tend to experience disease relapses more frequently with the resultant severer neurological deficit than CMS ones. Both OSMS and CMS patients are treated with intravenous high-dose methylprednisolone in acute exacerbations, and plasmapheresis may be considered for those who do not respond to repeated intravenous steroids. For prevention of disease relapse, interferon-beta is effective; however, patients with long spinal cord lesion extending over 3 vertebral segments should be followed-up with caution, as this finding indicates a risk of treatment failure.

Ohji and Nomura (2008) discussed steroid pulse therapy and apheresis therapy indicated for the treatment of MS. In the basic treatment course for MS, steroid pulse therapy is a first-line treatment for RR-MS in the course of the exacerbation, and apheresis therapy is performed in refractory cases. Treatment strategies for chronic progressive MS are not to be established. Steroid pulse therapy has been established as a treatment for MS in the active phase through randomized controlled trials (RCT). Apheresis therapy includes plasmapheresis and cytapheresis, and plasmapheresis includes plasma exchange (PE) and immunoadsorption plasmapheresis (IAPP). Plasma exchange and IAPP are performed for MS treatment. The former has been established as a useful treatment for active phase MS. The efficacy of IAPP has been frequently reported, but no reports have been based on RCT.
Schroder et al (2009) stated that apheresis is a general term that describes removal of abnormal blood constituents by extracorporeal blood purification methods. To date, therapeutic PE is the most common apheresis procedure. Here, plasma is separated from corpuscular blood constituents and replaced with a substitution fluid. In contrast to immunoabsorption, PE is a non-specific treatment modality with elimination of the entire plasma. The therapeutic effect is based on the removal of circulating, pathogenic immune factors including autoantibodies. Currently, PE is used for treatment of several immune-mediated neurological disorders. While first experiences relate to acute life-threatening conditions, such as treatment of Guillain-Barré syndrome or myasthenic crisis, therapeutic success was also shown in chronic diseases where immunosuppressive therapy is often required for long-term management. Plasma exchange has been applied successfully in chronic inflammatory demyelinating polyneuropathy, paraproteinemic polyneuropathy, stiff person syndrome, and may also be tried in several diseases of paraneoplastic origin. In recent years, PE was also established as an escalation therapy for steroid-unresponsive relapses of MS, and thus has gained more widespread attention.

Olek (2009) stated that PE may be beneficial in patients with acute central nervous system (CNS) inflammatory demyelinating disease who do not respond to glucocorticoid therapy. In the only formally reported clinical trial, 22 patients with CNS demyelinating disease (12 with MS) were randomly assigned to either active PE or sham treatment, with a total of 7 treatments, given every 2 days over 14 days. Moderate or greater improvement in neurologic disability occurred during 8 of 19 (42 %) courses of active treatment compared with 1 of 17 (6 %) courses of sham treatment. Improvement occurred early in the course of treatment and was sustained on follow-up. However, 4 of the patients who responded to the active treatment experienced new attacks of demyelination during 6 months of follow-up. Given these data, the author suggested treatment with PE for patients with acute, severe neurologic deficits caused by MS who have a poor response to treatment with high-dose glucocorticoids.

An early neurodegenerative affection of subcortical gray matter has been suggested in patients with MS. Transcranial sonography (TCS) shows hyper-echogenic lesions of substantia nigra (SN) and basal ganglia, thought to reflect iron accumulation, in a number of primary neurodegenerative diseases. Walter and colleagues (2009) examined if TCS can also display deep gray matter lesions in patients with MS and whether sonographic findings relate to severity and progression of MS. These researchers prospectively studied 75 patients with different courses of MS and 55 age-matched healthy subjects clinically and with TCS. Additionally, 23 patients had 1.5-T MRI at the time of TCS. Disease progression was assessed clinically 2 years after TCS. Abnormal hyper-echogenicity of SN, lenticular nucleus (LN), caudate nucleus, and thalamus was found in 41 %, 54 %, 40 %, and 8 % of the patients with MS, with similar frequency in patients with relapsing-remitting and primary or secondary progressive MS if corrected for disease duration, but only in 13 %, 13 %, 5 % (each, p < 0.001), and none (p = 0.028) of the control subjects. Hyperechogenicity of SN and LN correlated with more pronounced MRI T2 hypointensity, thought to reflect iron deposition. Larger bilateral SN echogenic area was related to higher rate of disease progression, whereas small SN echogenic area (SN hypo-echogenicity) predicted a disease course without further progression within 2 years. The authors concluded that neurodegenerative disease-like deep gray matter lesions can be frequently detected by TCS in patients with MS. They stated that these findings suggest that TCS shows changes of brain iron metabolism which correlate with future progress of MS. These investigators also noted that future studies are needed to determine if patients with MS with or without LN hyper-echogenicity represent different pathological sub-types that may benefit from different treatment strategies.

In an editorial that accompanied the afore-mentioned article, Pirko and Zivadinov (2009) stated that there are a number of issues that raise questions regarding the universal applicability of this technique: (i) increased echogenicity of gray matter nuclei was reported only in 40 to 50 % of MS cases at baseline; (ii) the echo-genecity was evaluated by means of a 3-grade visual scale as opposed to an objective calculated numerical intensity measure; and (iii) investigator agreement -- a human factor that may introduce bias -- was needed to ascertain
if the TCS findings are really abnormal; and (iv) blinding in this study was practically impossible. The editorialists stated that to validate these TCS findings, large case-control studies are needed.

On September 22, 2010, the FDA approved fingolimod (Gilenya capsules; formerly spelled Gilenia), the first oral drug for MS. Fingolimod is indicated for reduction of relapses and delay of disability progression in patients with relapsing forms of MS.

In January 2011, the American Academy of Neurology (AAN) published a new guideline on PP in neurologic disorders (Cortese et al, 2011). It states that PP/PE can be used as second-line treatment of steroid-resistant exacerbations in relapsing forms of MS. Moreover, PP is established as ineffective and should not be offered for chronic or secondary progressive MS.

In a review on new drug therapies for MS, Mangas et al (2010) reviewed the most recent data on drug candidates for MS. In the pre-clinical phase, such drug candidates have shown a beneficial effect on the onset of experimental autoimmune encephalomyelitis (microtubule-stabilizing drugs, MS14, lithium, GEMSP...), a decrease in CNS cell infiltrates (recombinant T cell receptor ligand, lovastatin-rolipram, ribavirin, GEMSP...), prevention of demyelination (lovastatin-rolipram, calpain inhibitor, lithium...); and a reduction of axonal loss (phenytoin, lovastatin-rolipram, calpain inhibitor).

Chronic cerebrospinal venous insufficiency (CCSVI) has been suggested to be a possible cause of MS. If the presumed mechanism of venous stasis-related parenchymal iron deposition and neurodegeneration were true, then up-regulation of intra-thecal iron transport proteins may be expected. Worthington et al (2010) carried out a cross-sectional (n = 1,408) and longitudinal (n = 29) study on CSF ferritin levels in patients with MS and a range of neurological disorders. Pathologic (greater than 12 ng/ml) CSF ferritin levels were observed in 4 % of the control patients (median 4 ng/ml), 91 % of patients with superficial siderosis (75 ng/ml), 73 % of patients with a subarachnoid hemorrhage (59 ng/ml), 10 % of patients with relapsing-remitting MS (5 ng/ml), 11 % of patients with primary progressive MS (6 ng/ml), 23 % of patients with secondary progressive MS (5 ng/ml), and 23 % of patients with meningoencephalitis (5 ng/ml). In MS, there was no significant change of CSF ferritin levels over the 3-year follow-up period. The authors concluded that these findings do not support an etiologic role for CCSVI-related parenchymal iron deposition in MS.

Doepp et al (2011) stated that CCSVI was proposed as the causal trigger for developing MS. However, current data are contradictory and a gold standard for venous flow assessment is missing. These investigators compared structural magnetic resonance venography (MRV) and dynamic extracranial color-coded duplex sonography (ECCS) in a cohort of patients with MS. They enrolled 40 patients (44 +/- 10 years). All underwent contrast-enhanced MRV for assessment of internal jugular vein (IJV) and azygos vein (AV) narrowing, graded into 3 groups: 0 % to 50 %, 51 % to 80 %, and greater than 80 %. Extracranial color-coded duplex sonography (analysis of blood flow direction, cross-sectional area (CSA), and blood volume flow (BVF)) in both IJV and vertebral veins (VV) occurred in the supine and upright body position. Magnetic resonance venography identified 1 AV narrowing. Internal jugular vein analysis yielded 12 patients for group 1 (30 %), 19 patients for group 2 (48 %), and 9 patients for group 3 (22 %). By ECCS criteria, 4 patients (10 %) presented with venous drainage abnormalities. Jugular BVF was different only between groups 1 and 3 (616 +/- 133 versus 381 +/- 213 ml/min, p = 0.02). No other parameters in supine position and none of the parameters in the upright body position, apart from the IJV-BVF decrease in groups 1 and 3 (479 +/- 172 versus 231 +/- 144 ml/min, p = 0.01), were different. The authors concluded that these ECCS data contradict the postulated 100 % prevalence of CCSVI criteria in MS. Magnetic resonance venography seems more sensitive to detect IJV narrowing compared to ECCS. A measurable hemodynamic effect only exists in vessel narrowings greater than 80 %. They stated that these combined data argue against a causal relationship of venous narrowing and MS, favoring the rejection of the CCSVI hypothesis and underline the plea to all clinicians to omit any intervention to remove "stenosis" by dilatation or stent implantation.
Zecca and Gobbi (2011) stated that the so called "CCSVI theory" has recently emerged, supporting the concept of cerebrospinal venous drainage impairment as the cause of MS. Since the first publication on this topic with a claimed 100% specificity and sensitivity of the condition for MS diagnosis, CCSVI theory has generated a scientific and mass media debate with a great hope for the miracle of a new possible endovascular treatment of MS ("liberation procedure"). These investigators critically summarized the available evidence on CCSVI discussing inconsistent and incomplete replication of the original results by different groups, methodological limits and potential therapeutic implications. The authors concluded that the available data are insufficient to establish conclusively a clear relationship between MS and CCSVI and do not support the role of CCSVI as the primary cause of MS. They stated that until credible scientific evidence replicates the original results, any proposed invasive treatments of CCSVI should be discouraged.

The Canadian Agency for Drugs and Technologies in Health's update on the "Investigation of Chronic Cerebrospinal Venous Insufficiency for the Treatment of Multiple Sclerosis" (CADTH, 2012) states that "[i]t is not yet established whether chronic cerebrospinal venous insufficiency (CCSVI) contributes to MS disease activity, and there have been conflicting data as to the frequency of this condition in people with MS. Recent results from a large clinical trial suggest that CCSVI may be the result of the disease rather than a cause. It is hoped that findings from ongoing studies will provide clarity regarding the need for pan-Canadian therapeutic clinical trials".

Endovascular procedures such as angioplasty with or without stenting has been studied for the treatment of patients with MS. Kostecki et al (2011) prospectively evaluated the mid-term results (6 month follow-up) of the endovascular treatment in patients with CCSVI and MS. A total of 36 patients with confirmed MS and CCSVI underwent endovascular treatment by the means of the uni- or bi-lateral jugular vein angioplasty with optional stent placement. All the patients completed 6 month follow-up. Their MS-related disability status and quality of life were evaluated 1, 3 and 6 months post-operatively by means of the following scales: Expanded Disability Status Scale (EDSS), Multiple Sclerosis Impact Scale (MSIS-29), Epworth Sleepiness Scale (ESS), Heat Intolerance scale (HIS) and Fatigue Severity Scale (FSS). For patency and re-stenosis rate assessment, the control US duplex Doppler examination was used. Six months after the procedure, re-stenosis in post-percutaneous transluminal angioplasty (PTA) jugular veins was found in 33% of cases. Among 17 patients who underwent stent implantation into the jugular vein, re-stenosis or partial in-stent thrombosis was identified in 55% of the cases. At the 6 month follow-up appointment, there was no significant improvement in the EDSS or the ESS. The endovascular treatment of the CCSVI improved the quality of life according to the MSIS-29 scale but only up to 3 months after the procedure (with no differences in the 6 month follow-up assessment). Six months after the jugular vein angioplasty (with or without stent placement), a statistically significant improvement was observed only in the FSS and the HIS. The authors concluded that endovascular treatment in patients with MS and concomitant CCSVI did not have an influence on the patient’s neurological condition; however, in the mid-term follow-up, an improvement in some quality-of-life parameters was observed.

Kipshidze et al (2011) noted that in recent observational studies performed on patients from distinctive gene pools, the prevalence of CCSVI in MS ranged from 56% to 100%. Endovascular treatment (PTA) with or without stenting of CCSVI was reported to be feasible with a minor complication rate. In 4 patients with different forms of MS, venography was performed that revealed stenosis of the proximal region of the jugular vein (right or left). Percutaneous transluminal balloon angioplasty was performed in all patients. There were no complications and mean stenosis was reduced after PTA from 59.75% to 36.75%. Follow-up included clinical observations and MRI. In all the cases these researchers observed positive remission of the disease, the first ever documented case of MRI index improvement. PTA seems to be an effective treatment for patients with CCVI and MS. The authors concluded that randomized studies are needed to establish the effectiveness of this new treatment for MS.
A position statement by the Society of Interventional Radiology, endorsed by the Canadian Interventional Radiology Association (Vedantham et al, 2010) considered the published literature to be inconclusive on whether CCSVI is a clinically important factor in the development and/or progression of MS, and on whether balloon angioplasty and/or stent placement are clinically effective in patients with MS.

The Ontario Health Technology Advisory Committee (2010) stated that "OHTAC has undertaken a preliminary evidence review of the safety and effectiveness of endovascular treatments for chronic cerebrospinal venous insufficiency in patients with multiple sclerosis and is unable to make any recommendation at this time due to the paucity of available evidence. OHTAC regards this treatment as experimental at this time".

The National Institute for Health and Clinical Excellence (2012) has concluded: "Current evidence on the efficacy of percutaneous venoplasty for chronic cerebrospinal venous insufficiency (CCSVI) for multiple sclerosis (MS) is inadequate in quality and quantity. Therefore, this procedure should only be used in the context of research."

Reekers et al (2011) stated that "many interventional radiologists, who are directly approached by MS patients, contact the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) for advice. Worldwide, several centers are actively promoting and performing balloon dilatation, with or without stenting, for CCSVI. Thus far, no trial data are available, and there is currently no randomized controlled trial (RCT) in progress. Therefore, the basis for this new treatment rests on anecdotal evidence and successful testimonies by patients on the Internet. CIRSE believes that this is not a sound basis on which to offer a new treatment, which could have possible procedure-related complications, to an often desperate patient population."

In a pilot, case-control study, Zamboni et al (2012) examined if PTA of duplex-detected lesions, of the internal jugular and/or azygous veins, was safe, burdened by a significant re-stenosis rate, and whether there was any evidence that treatment reduced MS disease activity. These researchers studied 15 patients with relapsing-remitting MS and duplex-detected CCSVI. Eight patients had PTA in addition to medical therapy (immediate treatment group (ITG)), whereas 7 had treatment with PTA after 6 months of medical therapy alone (delayed treatment group (DTG)). No adverse events occurred. At 1 year, there was a re-stenosis rate of 27 %. Overall, PTA was followed by a significant improvement in functional score compared with baseline (p < 0.02). The annualized relapse rate was 0.12 % in the ITG compared with 0.66 % in the DTG (p = NS). Magnetic resonance imaging blindly demonstrates a trend for fewer T2 lesions in the ITG (p = 0.081), corresponding to a 10 % decrease in the ITG compared with a 23 % increase in the DTG over the first 6 months of the study. The authors concluded that the findings of this study further confirmed the safety of PTA treatment in patients with CCSVI associated with MS. They stated that the results, despite the significant rate of re-stenosis, are encouraging and warrant a larger multi-center double-blinded, randomized study.

van der Voort and colleagues (2010) determined if myxovirus resistance protein A (MxA) mRNA is related to clinical disease activity in MS. Baseline MxA mRNA levels were measured in a prospective cohort of 116 untreated patients with early MS and were related to clinical relapses and MRI at baseline and at follow-up. Low levels of MxA mRNA were associated with the occurrence of relapses (p = 0.002) and contrast-enhancing lesions (CELS) on baseline MRI (p = 0.045). In addition, high baseline MxA mRNA levels were related to a longer time to a first new relapse (hazard ratio [HR]: 0.59; 95 % CI: 0.35 to 1.00; p = 0.044). Adding the absence of CELs to high MxA mRNA, the predictive value increased (HR: 0.35; 95 % CI: 0.17 to 0.74; p = 0.006), clearly showing a cumulative value for combining both factors. The authors concluded that MxA mRNA is related to clinical exacerbations, the number of CELs on MRI, and is indicative for the time to a subsequent relapse. They stated that if confirmed (by larger studies), MxA mRNA has potential as a biomarker for clinical disease activity in MS.

The gMS®Pro EDSS Test is a panel of biomarkers specific to identifying patients who will progress towards higher EDSS scores despite treatment. It was developed to help physicians identify which patients with
clinically isolated syndrome (CIS) or newly diagnosed MS will have a higher likelihood of progressing towards meaningful disabilities despite treatment. Physicians may want to consider more aggressive treatment for these patients. In addition, the gMS®Pro EDSS test is targeted for use for diagnosed MS patients and potential MS patients who have had their first neurological event and will be starting therapeutic treatment for MS. However, there is a lack of evidence regarding the clinical value of this test.

Gensicke et al (2012) stated that natalizumab was the first monoclonal antibody to be approved for the treatment of MS. Several other monoclonal antibodies are in development and have demonstrated promising efficacy in phase II studies. They can be categorized according to their mode of action into compounds targeting (i) leukocyte migration into the CNS (natalizumab); (ii) cytolytic antibodies (rituximab, ocrelizumab, ofatumumab, alemtuzumab); or (iii) antibodies and recombinant proteins targeting cytokines and chemokines and their receptors (daclizumab, ustekinumab, atacicept, tabalumab [Ly-2127399], secukinumab [AIN457]).

Kuhle et al (2011) examined if CSF levels of neurofilament heavy chain protein (NfH(SMI35)) correlate with disability, disease activity, or specific stages of MS. An electrochemiluminescence immunoassay was used to retrospectively measure NfH(SMI35) in CSF of patients with clinically isolated syndrome (CIS) (n = 63), RRMS (n = 39), secondary progressive multiple sclerosis (SPMS) (n = 25), primary progressive multiple sclerosis (PPMS) (n = 23), or controls (n = 73). Cell count and CSF levels of immunoglobulin and albumin were also measured. CSF levels of NfH(SMI35) increased with age in controls (r(s) = 0.50, p < 0.0001) and CIS (r(s) = 0.50, p < 0.0001); this effect was less pronounced in RRMS (r(s) = 0.35, p = 0.027) and absent in SPMS/PPMS. After age correction, NfH(SMI35) levels were found to be higher in all disease stages compared to control. Relapses were associated with higher CSF NfH(SMI35) values compared with stable disease. NfH(SMI35) levels correlated with EDSS scores in patients with CIS and RRMS (r(s) = 0.33, p = 0.001), and during relapse (r(s) = 0.35, p = 0.01); the correlation was most prominent in RRMS during relapse (r(s) = 0.54, p = 0.01). This was not the case for any of the other CSF markers examined. The authors concluded that neuronal loss is a feature of aging, and the age-dependent increase of CSF NfH(SMI35) suggests that this loss accelerates over time. For MS, increased NfH(SMI35) levels reflect the super-imposed presence of further neurodegenerative processes. Evaluation of NfH(SMI35) levels is likely to provide a useful surrogate for measuring the rate of neurodegeneration in MS. Furthermore, the dissociation of NfH(SMI35) levels with biomarkers of inflammation suggests that the mechanisms responsible for their production are at least partly independent. One major drawback of this study was the use of EDSS to measure disability; it is imprecise and not a good overall measure of MS. More work is needed for CSF levels of neurofilament to become a useful biomarker for MS.

In an editorial that accompanied the afore-mentioned study, Giovannoni and Nath (2011) stated that "[e]levated CSF Nf is a simple indicator of axonal damage, and is predictive of severity and poor recovery from acute attacks and the development of long-term disability in patients with MS. We would encourage the MS community to take these observations on board and to insist on the inclusion of this valuable biomarker in all future clinical trials".

On May 10, 2012, the FDA issued an alert on potential dangers of an experimental procedure sometimes called “liberation therapy” or the “liberation procedure” to treat CCSVI. The alert noted that some researchers believe that CCSVI, which is characterized by a narrowing (stenosis) of veins in the neck and chest, may cause MS or may contribute to the progression of the disease by impairing blood drainage from the brain and upper spinal cord. However, studies exploring a link between MS and CCSVI are inconclusive, and the criteria used to diagnose CCSVI have not been adequately established. The experimental procedure uses balloon angioplasty devices or stents to widen narrowed veins in the chest and neck. However, the FDA has learned of death, stroke, detachment and migration of the stents, damage to the treated vein, blood clots, cranial nerve damage and abdominal bleeding associated with the experimental procedure. Balloon angioplasty devices and stents have not been approved by the FDA for use in treating CCSVI. The FDA also is notifying physicians and clinical investigators who are planning or conducting clinical trials using medical devices to
treat CCSVI that they must comply with FDA regulations for investigational devices. Any procedures conducted are considered significant risk clinical studies and require FDA approval, called an investigational device exemption. In February 2012, the FDA sent a warning letter to an investigator who was conducting a clinical study of CCSVI treatment without the necessary approval. The investigator voluntarily closed the study. The FDA stated that it will continue to monitor reports of adverse events associated with “liberation therapy” or the “liberation procedure” and keep the public informed as new safety information becomes available.

In a Cochrane review, van Zuuren et al (2012) evaluated the effects of percutaneous transluminal angioplasty for the treatment of CCSVI in people with MS. These investigators searched the following databases up to June 2012: The Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group Specialized Register, CENTRAL in The Cochrane Library 2012, Issue 5, MEDLINE (from 1946), EMBASE (from 1974), and reference lists of articles. They also searched several online trials registries for ongoing trials; RCTs assessing the effects of percutaneous transluminal angioplasty in adults with MS that have been diagnosed to have CCSVI were selected for analysis. The searches retrieved 159 references, 6 of which were to ongoing trials. Based on assessment of the title or abstract, or both, the authors excluded all of the studies, with the exception of 1 that was evaluated following examination of the full text report. However, this study also did not meet the inclusion criteria and was subsequently excluded. No RCTs met the inclusion criteria. The authors concluded that there is currently no high-level evidence to support or refute the safety or effectiveness of percutaneous transluminal angioplasty for treatment of CCSVI in people with MS. They stated that clinical practice should be guided by evidence supported by well-designed RCTs: closure of some of the gaps in the evidence may be feasible at the time of completion of the 6 ongoing clinical trials.

Zhornitsky et al (2013) noted that MS is more common among women than men; and MS often goes into remission during pregnancy, when prolactin (PRL) levels are known to be high. In an animal model of demyelination, PRL promoted myelin repair, suggesting it has potential as a re-myelinating therapy in MS. In this systematic review, these investigators examined the known associations between PRL and MS, in order to elucidate its potential role in the pathophysiology and treatment of MS. A systematic search was performed in the electronic databases PubMed and EMBASE, using the keywords "prolactin" AND "multiple sclerosis". The inclusion criteria were met by 23 studies. These studies suggested that elevated PRL may be more common in MS patients than in controls. Hyper-prolactinemia may also be associated with clinical relapse in MS, especially among patients with hypothalamic lesions or optic neuritis; however, it is unknown if this is a cause or consequence of a relapse. The authors concluded that overall most people with MS have normal PRL levels; and the impact of PRL on MS outcomes remains unclear.

Huang et al (2013) stated that dysregulated levels of interleukin-1 (IL-1) were observed in patients with MS. These investigators performed a meta-analysis of 16 case-control studies involving 3,482 cases and 3,528 controls to evaluate this association. No association was found between the IL-1α -889 (rs1800587), IL-1α +4,845 (rs17561), IL-1β -511 (rs16944), IL-1β +3,953 (rs1143634), IL-1ra variable number tandem repeat (VNTR) polymorphisms and MS risk. However, in subgroup analyses for the IL-1ra VNTR polymorphism, these researchers found that individuals carrying the 2 allele had a 32 % increased risk for bout-onset MS (relapsing remitting and secondary progressive MS) when compared to the LL homozygotes (OR = 1.32, 95 % CI: 1.06 to 1.66, p (z) = 0.014). The authors concluded that common variants in the IL-1 region are not associated with MS risk but these findings suggested that the IL-1ra VNTR polymorphism might be associated with bout-onset MS subtype.

The FDA has approved alemtuzumab (Lemtrada) for the treatment of patients with relapsing forms of multiple sclerosis (MS) (Genzyme, 2014). Because of its safety profile, the FDA labeling states that use of Lemtrada should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.
Alemtuzumab is a monoclonal antibody that targets CD52, a protein abundant on T and B cells (Genzyme, 2014). Circulating T and B cells are thought to be responsible for the damaging inflammatory process in MS. Alemtuzumab depletes circulating T and B lymphocytes after each treatment course. Lymphocyte counts then increase over time with a reconstitution of the lymphocyte population that varies for the different lymphocyte subtypes.

The FDA approval of alemtuzumab is based on two pivotal randomized Phase III open-label rater-blinded studies comparing treatment with alemtuzumab to high-dose subcutaneous interferon beta-1a (Rebif) in patients with relapsing remitting MS who were either new to treatment (CARE-MS I) or who had relapsed while on prior therapy (CARE-MS II) (Genzyme, 2014).

In CARE-MS I, alemtuzumab was significantly more effective than interferon beta-1a at reducing annualized relapse rate (0.18 for alemtuzumab and 0.39 for interferon beta-1a (p<0.0001) (Genzyme, 2014; Cohen, et al., 2012). The difference observed in proportion of patients with disability progression at year two did not reach statistical significance (8 percent for alemtuzumab and 11 percent for interferon beta-1a (p=0.22)). The percent of patients remaining relapse-free at year two for alemtuzumab was 78 percent versus 59 percent for interferon beta-1a (p<0.0001). The percent change in T2 lesion volume from baseline did not reach statistical significance (-9.3 for alemtuzumab and -6.5 for interferon beta-1a, p=0.31).

In CARE-MS II, alemtuzumab was significantly more effective than interferon beta-1a at reducing annualized relapse rates (0.26 for alemtuzumab and 0.52 for interferon beta-1a, p<0.0001) (Genzyme, 2014; Coles, et al., 2012). The proportion of patients with confirmed six-month disability progression was significantly lower for alemtuzumab (13 percent for alemtuzumab versus 21 percent for interferon beta-1a, p=0.0084). The percent of patients remaining relapse-free at year two for alemtuzumab was 65 percent versus 47 percent for interferon beta-1a (p<0.0001). The percent change in T2 lesion volume from baseline did not reach statistical significance (-1.3 for alemtuzumab and -1.2 for interferon beta-1a, p=0.14).

The FDA-approved labeling of Lemtrada includes a boxed warning noting a risk of serious, sometimes fatal autoimmune conditions, serious and life-threatening infusion reactions and also noting alemtuzumab may cause an increased risk of malignancies including thyroid cancer, melanoma and lymphoproliferative disorders (Genzyme, 2014). Lemtrada is contraindicated in patients with Human Immunodeficiency Virus (HIV) infection.

Lemtrada is only available through the Lemtrada REMS (Risk Evaluation and Mitigation Strategy) restricted distribution program (Genzyme, 2014). This program has been developed to ensure that access to Lemtrada is only through certified prescribers, healthcare facilities and specialty pharmacies and to also ensure that patients are enrolled in the REMS program. The program is intended to help educate healthcare providers and patients on the serious risks associated with alemtuzumab and the appropriate periodic monitoring required to support the detection of these risks for 48 months after the last infusion. The REMS is based on a developmental risk management program that was used in the Phase 2 and Phase 3 trials and allowed for early detection and management of some of the serious risks associated with alemtuzumab.

Alemtuzumab for multiple sclerosis has a dosing and administration schedule of two annual treatment courses (Genzyme, 2014). The first treatment course is administered via intravenous infusion on five consecutive days, and the second course is administered on three consecutive days, 12 months later.

The most common side effects of alemtuzumab are rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid gland disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting (Genzyme, 2014). Other serious side effects associated with alemtuzumab include autoimmune thyroid disease, autoimmune cytopenias, infections and pneumonitis.
Serious and life-threatening autoimmune conditions such as immune thrombocytopenia (ITP) and anti-glomerular basement membrane disease can occur in patients receiving alemtuzumab (Genzyme, 2014). The FDA-approved labeling recommends complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts at periodic intervals in patients who receive alemtuzumab. The labeling states that alemtuzumab is associated with serious and life-threatening infusion reactions. The labeling states that alemtuzumab can only be administered in certified healthcare settings that have on-site access to equipment and personnel trained to manage anaphylaxis and serious infusion reactions.

Siddiqui et al (2014) reported the results of the investigation of safety and effectiveness of venous angioplasty in patients with MS with findings of extra-cranial venous anomalies, considered hallmarks of CCSVI, in a 2-phase study. Phase 1 was an open-label safety study (10 patients); phase 2 was sham-controlled, randomized, and double-blind (10 sham procedure, 9 treated). All study patients fulfilled venous hemodynamic screening criteria indicative of CCSVI. Assessment was at 1, 3, and 6 months post-procedure with MRI, clinical, and hemodynamic outcomes. Primary end-points were safety at 24 hours and 1 month, venous outflow restoration greater than 75% at 1 month, and effect of angioplasty on new lesion activity and relapse rate over 6 months. Secondary end-points included changes in disability, brain volume, cognitive tests, and quality of life. No peri-operative complications were noted; however, 1 patient with history of syncope was diagnosed with episodic bradycardia requiring placement of a pacemaker before discharge. Doppler evidence-based venous hemodynamic insufficiency severity score (VHISS) was reduced greater than 75% compared to baseline in phase 1 (at 1 month) but not phase 2. In phase 2, higher MRI activity (cumulative number of new contrast-enhancing lesions [19 versus 3, p = 0.062] and new T2 lesions [17 versus 3, p = 0.066]) and relapse activity (4 versus 1, p = 0.389) were identified as non-significant trends in the treated versus sham arm over 6 months. Using analysis of co-variance, significant cumulative new T2 lesions were related to larger VHISS decrease (p = 0.028) and angioplasty (p = 0.01) over the follow-up. No differences in other end-points were detected. The authors concluded that venous angioplasty is not an effective treatment for MS over the short-term and may exacerbate underlying disease activity. This is a Class I study demonstrating that clinical and imaging outcomes are no better or worse in patients with MS identified with venous outflow restriction who receive venous angioplasty compared to sham controls who do not receive angioplasty.

In an editorial that accompanied the afore-mention study, Bourdette and Cohen (2014) stated that “Clinical trials of venous angioplasty for MS are placing participants at risk of complications without a reasonable hope of benefit”.

There are inconsistent reports of an association between methylenetetrahydrofolate reductase (MTHFR) mutations and MS, but no established clinical utility of such testing. Currently, there are no studies demonstrating that manipulation of diet and vitamins in persons with this mutation can either prevent or delay progression of MS.

Alatab et al (2011) stated that both genetic and inflammatory factors are suspected in the etiology of MS. Of genetic factors, the MTHFR C677T polymorphism has been associated with increased levels of plasma homocysteine, a neuronal excitotoxic amino acid. Sclerotic patients also have elevated levels of plasma and CSF homocysteine. In this study, the association between C677T polymorphism and MS was tested by recruiting 230 healthy and 194 multiple sclerotic age- and gender-matched patients. The MTHFR C677T polymorphism and the serum levels of inflammatory mediators IL-1β, tumor necrosis factor- alpha (TNF-α), and C-reactive protein (CRP) were measured. The levels of TNFα, CRP, and IL-1β were significantly higher in sclerotic patients. T allele was 1.7 times more present in this group. In patient's group, the levels of all inflammatory mediators were higher in T/T compared to 2 other genotypes. Evaluation of the age of onset of disease revealed that subjects with T allele developed the MS disease, almost 4 years sooner than other genotype. The authors concluded that having T allele of C677T in MS might be accompanied with higher levels of serum inflammatory mediators and a vulnerability to earlier age of onset of disease. Moreover, they stated that further studies are needed to elucidate the underlying mechanisms.
Fekih Mrissa et al (2013) stated that MS is a chronic neurological disease characterized by CNS inflammation and demyelination of nerve axons. These researchers investigated a possible association between the methylenetetrahydrofolate reductase (MTHFR) gene and MS in Tunisian patients. The genotyping of 2 missense variants of the MTHFR gene, C677T and A1298C was performed in 80 MS patients and 200 healthy controls. No significant differences were found in the frequency of the MTHFR C677T polymorphism between MS patients and healthy controls. However, the genotype prevalence of the missense variant MTHFR A1298C was significantly different between patients and controls (A/C: 55 % versus 7 %, p<10(-3); C/C: 13.75 % versus 0 %, p < 10(-3), respectively). The authors concluded that although these preliminary findings suggested no association between the MTHFR C677T variants and MS, there is evidence to suggest a significant association between the MTHFR A1298C polymorphisms and MS.

Ineichen et al (2014) noted that MTHFR is necessary for the synthesis of methionine and S-adenosylmethionine, which is necessary for CNS (re-)myelination. The MTHFR variant c.1298A>C was associated with the development of RRMS in a German population. These researchers examined if further genetic variants of methionine metabolism are associated with the development or the clinical course of RRMS. Therefore, genomic DNA of 147 serial German RRMS patients and 147 matched healthy controls was genotyped for 5 polymorphic variants of methionine metabolism. Statistical analyses were performed using multi-variate binary and linear regression analyses. They showed that the insertion allele of cystathionine beta-synthase (CBS) c.844_855ins68bp and the G-allele of reduced folate carrier 1 (RFC1) c.80G>A were associated with an earlier age of onset of MS, suggesting gene-dose effects (median age of onset in years: 25-26-32; standardized regression coefficient beta: 0.216; p = 0.030, and 29-31-35 years; beta: 0.282; p = 0.005, respectively). The authors concluded that mutant variants of CBS and RFC1 may be associated with the age of RRMS onset. They stated that since methionine metabolism can be manipulated by supplementation of vitamins and amino acids, these data provided a rationale for novel ideas of preventive and therapeutic strategies in RRMS.

Furthermore, UpToDate reviews on “Diagnosis of multiple sclerosis in adults” (Olek, 2014a), “Clinical features of multiple sclerosis in adults” (Olek, 2014b), and “Treatment of relapsing-remitting multiple sclerosis in adults” (Olek, 2014 c), and “Pathogenesis and epidemiology of multiple sclerosis” (Olek, 2014 d) do not mention the use of MTHFR testing.

An UpToDate review on “Treatment of progressive multiple sclerosis in adults” (Olek, 2014e) states that “Few clinical trials have studied intravenous immune globulin (IVIG) in progressive forms of MS, and these have shown little or no benefit …. Based primarily on the latter study, treatment with IVIG for progressive MS cannot be recommended”.

In a Cochrane review, He and colleagues (2013) evaluated the safety and effectiveness of rituximab, as monotherapy or combination therapy, versus placebo or approved disease-modifying drugs (DMDs) (IFN-β, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab) to reduce disease activity for people with RRMS. The Trials Search coordinator searched the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group Specialised Register (August 9, 2013). These investigators checked the references in identified trials and manually searched the reports (2004 to August 2013) from neurologic associations and MS societies in Europe and America. They also communicated with researchers who were participating in trials on rituximab and contacted Genentech, BiogenIdec and Roche. All randomized, double-blind, controlled parallel group clinical trials with a length of follow-up equal to or greater than 1 year evaluating rituximab, as monotherapy or combination therapy, versus placebo or approved DMDs for patients with RRMS without restrictions regarding dosage, administration frequency and duration of treatment were selected for analysis. These researchers used the standard methodological procedures of The Cochrane Collaboration. Two review authors independently assessed trial quality and extracted data. Disagreements were discussed and resolved by consensus among the review authors. Principal investigators of included studies were contacted for additional data or confirmation of data.
One trial involving 104 adult RRMS patients with an entry score less than or equal to 5.0 on the EDSS and at least 1 relapse during the preceding year was included. This trial evaluated rituximab as monotherapy versus placebo, with a single course of 1,000 mg intravenous rituximab (on day 1 and day 15). A significant attrition bias was found at week 48 (24.0 %). Patients receiving rituximab had a significant reduction in total number of gadolinium-enhancing lesions at week 24 (mean number 0.5 versus 5.5; relative reduction 91 %) and in annualized rate of relapse at week 24 (0.37 versus 0.84); but not at week 48 (0.37 versus 0.72). Disability progression was not included as an outcome in this trial. More patients in the rituximab group had adverse events within the 24 hours after the first infusion (78.3 % versus 40.0 %), such as chills, headache, nausea, pyrexia, pruritus, fatigue, throat irritation, pharyngo-laryngeal pain, and most were mild-to-moderate events (92.6 %). The most common infection-associated adverse events (greater than 10 % in the rituximab group) were nasopharyngitis, upper respiratory tract infections, urinary tract infections and sinusitis. Among them, only urinary tract infections (14.5 % versus 8.6 %) and sinusitis (13.0 % versus 8.6 %) were more common in the rituximab group. One ongoing trial was identified. The authors concluded that there is insufficient evidence to support the use of rituximab as a disease-modifying therapy for RRMS because only 1 RCT was included. The quality of the study was limited due to high attrition bias, the small number of participants, and short follow-up. The beneficial effects of rituximab for RRMS remain inconclusive. However, short-term treatment with a single course of rituximab was safe for most patients with RRMS. Mild-to-moderate infusion-associated adverse events were common, as well as nasopharyngitis, upper respiratory tract infections, urinary tract infections and sinusitis. These researchers stated that the potential benefits of rituximab for treating RRMS need to be evaluated in large-scale studies that are of high quality along with long-term safety.

Furthermore, an UpToDate review on “Treatment of relapsing-remitting multiple sclerosis in adults” (Olek, 2014c) states that “In a preliminary randomized trial of 104 adult patients with RRMS, treatment with intravenous rituximab (1000 mg) given on days 1 and 15 was associated with a significant reduction in both total and new gadolinium-enhancing lesions on brain MRI at 24 weeks when compared with placebo. In addition, rituximab treatment was associated with a significant reduction in the proportion of patients who had a clinical relapse by week 24. While these results are promising, further clinical trials are needed to establish the long-term effectiveness and safety of rituximab for RRMS. Rare cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients treated with rituximab. However, it is unknown if rituximab increases the risk of PML, since rituximab is often used to treat patients who have an underlying risk factor for PML”.

Nolan et al (2013) examined if fingolimod, an oral sphingosine-1-phosphate receptor modulator approved for treatment of MS, generally leads to increased retinal tissue volume. In this longitudinal observational study, these researchers compared changes in macular volume on spectral-domain OCT between consecutive patients with MS who initiated fingolimod and a matched reference cohort of patients with MS never exposed to the drug. The primary reference cohort was matched based on time interval between OCT examinations. A secondary reference cohort was matched based on age and disease duration. Change in macular volume within each group was analyzed using the paired-t test. Change in macular volume between groups was examined using multiple linear regressions. Macular volume increased by a mean of 0.025 mm$^3$ (95 % confidence interval [CI]: +0.017 to +0.033, p < 0.001) in the 30 patients with MS who initiated fingolimod over a mean follow-up time of 5 months (SD 3). Macular volume did not significantly change over a mean follow-up time of 6 months (SD 4) in a comparison group of 30 patients with MS never treated with fingolimod (mean change of -0.003 mm$^3$, 95 % CI: -0.009 to +0.004, p = 0.47). Overall, 74 % of eyes in the fingolimod-treated group exhibited an increase in macular volume versus 37 % of eyes in the comparison group. The authors concluded that initiation of fingolimod in MS is associated with a modest, relatively rapid increase in macular volume.

Zarbin et al (2013) reported outcomes of ophthalmic evaluations in clinical studies of patients receiving fingolimod for MS. Analysis done on pooled safety data (n = 2,615, all studies group) from 3 double-masked, randomized, parallel-group clinical trials (phase 2 core and extension greater than 5 years, and phase 3...
FREEDOMS and TRANSFORMS core and extension studies). Patients aged 18 to 55 years (18 to 60 years in phase 2 study) diagnosed with relapsing-remitting MS were included. Patients with diabetes mellitus or ME at screening were excluded. Participants received fingolimod (0.5/1.25 mg), placebo, or interferon beta for the respective study durations. Ophthalmic examination included detailed eye history (at screening), visual acuity (VA) assessment, dilated ophthalmoscopy, OCT, and fluorescein angiography (FA). Extensive ophthalmic monitoring was performed for all patients. While being studied, patients with abnormal findings on dilated ophthalmoscopy and OCT compatible with ME were further studied by FA. All locally diagnosed ME cases were centrally reviewed by the retina specialist (M.A.Z.) on the Data and Safety Monitoring Board. Among 2,615 patients assessed, 19 confirmed ME cases were observed in fingolimod-treated groups (0.5 mg: n = 4, 0.3 %; 1.25 mg: n = 15, 1.2 %). Most patients (n = 13, 68 %) presented with blurred vision, decreased VA, or eye pain. Macular edema was diagnosed within 3 to 4 months of treatment initiation in most cases (n = 13, 68 %); 2 patients had late onset (greater than 12 months) ME. Of the 19 patients with ME, 5 (26 %), all treated with fingolimod 1.25 mg, had a history of uveitis compared with 26 (1 %) in the all studies group. In most cases (n = 16, 84 %), ME resolved after discontinuing the study drug; 11 patients required topical anti-inflammatory medications. No patient had further vision deterioration. The authors concluded that fingolimod 0.5 mg is associated with a low incidence of ME in MS studies. Patients with a history of uveitis may be at an increased risk of developing ME. An ophthalmic examination before initiating fingolimod therapy and regular follow-up eye examinations during fingolimod therapy are recommended.

A review on "Macular edema associated with fingolimod" (Jain and Bhatti, 2012) published in EyeNet (by the American Academy of Ophthalmology) stated that "The initial evaluation of patients taking fingolimod should include a complete ophthalmic examination, including dilated fundus examination. A macular contact lens may assist in the assessment of macular thickening. The use of OCT as a screening tool is not mandatory. In our practice, we are more likely to obtain a baseline OCT in patients with uveitis, diabetic retinopathy, recent intraocular surgery or optic nerve pallor. Also, we perform Amsler grid testing and teach patients how to perform the test at home. We occasionally will perform FA, particularly in patients with diabetic retinopathy and possible macular edema. Repeat ophthalmic examination should be performed at three to four months, as most cases of FAME [fingolimod-associated macular edema] develop within this time period. Patients with visual symptoms, abnormal Amsler grid testing, decreased best-corrected visual acuity or macular thickening on clinical examination should undergo OCT and/or FA. We perform follow-up surveillance at six months and annually thereafter. We advise our patients to return sooner if they experience any visual symptoms". 

Appendix

Specific Phobia: DSM 5 Diagnostic Criteria:

I. A market fear or anxiety about a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood). Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, or clinging.
II. The phobic object or situation almost always provokes immediate fear or anxiety.
III. The phobic object or situation is actively avoided or endured with intense fear or anxiety.
IV. The fear or anxiety is out of proportion to the actual danger posed by the specific object or situation and to the sociocultural context.
V. The fear, anxiety, or avoidance is persistent, typically lasting for 6 months or more.
VI. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
VII. The disturbance is not better explained by the symptoms of another mental disorder, including fear, anxiety, and avoidance of situations associated with panic-like symptoms or other incapacitating symptoms (as in agoraphobia); objects or situations related to obsessions (as in obsessive-compulsive
disorder); reminders of traumatic events (as in posttraumatic stress disorder); separation from home or attachment figures (as in separation anxiety disorder); or social situations (as in social anxiety disorder).


Table: Expanded Disability Status Scale (EDSS):

The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>No disability, minimal signs in one FS</td>
</tr>
<tr>
<td>1.5</td>
<td>No disability, minimal signs in more than one FS</td>
</tr>
<tr>
<td>2.0</td>
<td>Minimal disability in one FS</td>
</tr>
<tr>
<td>2.5</td>
<td>Mild disability in one FS or minimal disability in two FS</td>
</tr>
<tr>
<td>3.0</td>
<td>Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking</td>
</tr>
<tr>
<td>3.5</td>
<td>Moderate disability in one FS and more than minimal disability in several others. No impairment to walking</td>
</tr>
<tr>
<td>4.0</td>
<td>Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m</td>
</tr>
<tr>
<td>4.5</td>
<td>Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m</td>
</tr>
<tr>
<td>5.0</td>
<td>Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m</td>
</tr>
<tr>
<td>5.5</td>
<td>Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m</td>
</tr>
<tr>
<td>6.0</td>
<td>Requires a walking aid - cane, crutch, etc. - to walk about 100m with or without resting</td>
</tr>
<tr>
<td>6.5</td>
<td>Requires two walking aids - pair of canes, crutches, etc. - to walk about 20m without resting</td>
</tr>
<tr>
<td>7.0</td>
<td>Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day</td>
</tr>
<tr>
<td>7.5</td>
<td>Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorized wheelchair</td>
</tr>
<tr>
<td>8.0</td>
<td>Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms</td>
</tr>
<tr>
<td>Score</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>8.5</td>
<td>Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions</td>
</tr>
<tr>
<td>9.0</td>
<td>Confined to bed. Can still communicate and eat</td>
</tr>
<tr>
<td>9.5</td>
<td>Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow</td>
</tr>
<tr>
<td>10.0</td>
<td>Death due to MS</td>
</tr>
</tbody>
</table>

CPT Codes / HCPCS Codes / ICD-9 Codes

**CPT codes covered when selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>36514</td>
<td>Therapeutic apheresis; for plasma pheresis [not covered for chronic or secondary progressive MS (maintenance therapy)]</td>
</tr>
<tr>
<td>90283</td>
<td>Immune globulin (IgIV), human, for intravenous use</td>
</tr>
</tbody>
</table>

**CPT codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>35476</td>
<td>Transluminal balloon angioplasty, percutaneous; venous</td>
</tr>
<tr>
<td>36522</td>
<td>Photopheresis, extracorporeal</td>
</tr>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation per collection; allogenic</td>
</tr>
<tr>
<td>38206</td>
<td>autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
</tbody>
</table>
38230   Bone marrow harvesting for transplantation; allogenic
38240   Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
82728   Ferritin
83520   Immunoassay, analyte quantitative; not otherwise specified [if reported for neutralizing antibodies against interferon beta]
83540   Iron
84146   Prolactin
86376   Microsomal antibodies (eg, thyroid or liver-kidney), each
86382   Neutralization test, viral [if reported for neutralizing antibodies against interferon beta]
87253   Virus isolation; tissue culture, additional studies or definitive identification (eg, hemabsorption, neutralization, immunofluorescence stain), each isolate [if reported for neutralizing antibodies against interferon beta]
92540   Basic vestibular evaluation, includes spontaneous nystagmus test with eccentric gaze fixation nystagmus, with recording, positional nystagmus test, minimum of 4 positions, with recording, optokinetic nystagmus test, bidirectional foveal and peripheral stimulation, with recording, and oscillating tracking test, with recording
92541 - 92548 Vestibular function tests, with recording (e.g., ENG, PENG), and medical diagnostic evaluation
92550   Tympanometry and reflex threshold measurements
92558   Evoked otoacoustic emissions, screening (qualitative measurement of distortion product or transient evoked otoacoustic emissions), automated analysis
92567   Tympanometry (impedance testing)
92568 - 92569 Acoustic reflex testing
92570   Acoustic immittance testing, includes tympanometry (impedance testing), acoustic reflex threshold testing, and acoustic reflex decay testing
92587 - 92588 Evoked otoacoustic emissions
93886   Transcranial Doppler study of the intracranial arteries; complete study
96912   Photochemotherapy; psoralens and ultraviolet A (PUVA)
96913   Photochemotherapy (Goeckerman and/or PUVA) for severe photoresponsive dermatoses requiring at least four to eight hours of care under direct supervision of the physician (includes application of medication and dressings)
99183   Physician or other qualified health care professional attendance and supervision of hyperbaric oxygen therapy, per session
Modifier 7A APOE, commonly called apolipoprotein E (cardiovascular disease or Alzheimer's disease)

Other CPT codes related to the CPB:

88271 - 88275 Molecular cytogenetics
99601 - 99602 Home infusion/specialty drug administration
96365 - 96368 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug)
96372 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular

Interleukin-1 gene polymorphisms testing:

No specific code

HCPCS codes covered if selection criteria are met:

J1561 Injection, immune globulin, (Gamunex/Gamunex-C/Gammaked), nonlyophilized (e.g., liquid), 500 mg
J1566 Injection, immune globulin, intravenous, lyophilized (e.g. powder), not otherwise specified, 500 mg [for relapsing remitting multiple sclerosis-not chronic progressive-when standard approaches have failed, become intolerable, or are contraindicated]
J1568 Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g. liquid), 500 mg
J1569 Injection, immune globulin, (Gammagard liquid), nonlyophilized, (e.g., liquid), 500 mg
J1595 Injection, glatiramer acetate, 20 mg [for relapsing remitting multiple sclerosis]
J1826 Injection, interferon beta-1a, 30 mcg
J1830 Injection, interferon beta -1b, 0.25 mg (code may be used for Medicare when drug administered under direct supervision of a physician, not for use when drug is self-administered) [covered for relapsing, remitting multiple sclerosis in persons with a contraindication, allergy, intolerance or failure of a one-month trial of Avonex, Copaxone, or Rebif]
J2323 Injection, natalizumab, 1 mg [covered for relapsing, remitting multiple sclerosis in persons with a contraindication, allergy, intolerance or failure of a one-month trial of Avonex, Copaxone, or Rebif]
J7500 Azathioprine, oral, 50 mg
J7501 Azathioprine, parenteral, 100 mg
J9065 Injection, cladribine, per 1 mg
J9070 Cyclophosphamide, 100 mg
J9293 Injection, mitoxantrone HCl, per 5 mg
Q3027 Injection, interferon beta-1a, 1 mcg for intramuscular use
S9338 Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem
S9490 Home infusion therapy, corticosteroid infusion; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
S9559 Home injectable therapy, interferon, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem

**HCPCS codes not covered for indications listed in the CPB:**

C1725 Catheter, transluminal angioplasty, nonlaser (may include guidance, infusion/perfusion capability)
C1874 Stent, coated/covered, with delivery system,
C1876 Stent, noncoated/noncovered, with delivery system,
C1885 Catheter, transluminal angioplasty, laser
C2625 Stent, noncoronary, temporary, with delivery system
E0218 Water circulating cold pad with pump
E0691 - E0694 Ultraviolet light therapy system, includes bulbs/lamps, timer and eye protection; treatment area 2 sq ft or less, 4 ft panel, 6 ft panel, or ultraviolet multidirectional light therapy system in 6 ft cabinet, includes bulbs/lamps, timer and eye protection
E0761 Non-thermal pulsed high frequency radiowaves, high peak power electromagnetic energy treatment device
J0800 Injection, corticotropin, up to 40 units
J0833 Injection, cosyntropin, not otherwise specified, 0.25 mg
J2315 Injection, naltrexone, depot form, 1 mg
J7502 Cyclosporine, oral, 100 mg
J7505 Muromonab-CD3, parenteral, 5mg
J7513 Daclizumab, parenteral, 25 mg
J7515 - J7516 Cyclosporine, oral, 25 mg or parenteral, 250 mg
J8530 Cyclophosphamide, oral, 25 mg
J8610 Methotrexate, oral, 2.5 mg
J9015  Aldesleukin, per single use vial

J9212 - J9216  Injection interferon alfacon-1, recombinant, 1 mcg, interferon, alfa-2A, recombinant, 3 million units, interferon, alfa-2B, recombinant, 1 million units, interferon alfa-N3 (human leukocyte derived), 250,000 IU, or interferon gamma-1B, 3 million units

J9250 - J9260  Methotrexate sodium, 5 mg or Methotrexate sodium, 50 mg

S0090  Sildenafil citrate, 25 mg

S2150  Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: perehesis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

S3852  DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

Other HCPCS codes related to the CPB:

J0881  Injection, darbepoetin alfa, 1 mcg (non-ESRD use)

J0885  Injection, epoetin alfa, (for non-ESRD use), 100 units

J0888  Injection, epoetin beta, 1 microgram, (for non-ESRD use)

ICD-9 codes covered if selection criteria are met:

340  Multiple sclerosis [acute exacerbation] [relapsing/remitting]

ICD-9 codes not covered for indications listed in the CPB:

V42.82  Organ or tissue replaced by transplant, peripheral stem cells

Other ICD-9 codes related to the CPB: [results of acute exacerbation that may require hospital admission] :

323.61  Infectious acute disseminated encephalomyelitis (ADEM)

323.81  Other causes of encephalitis

335.23  Pseudobulbar palsy

341.8  Other demyelinating diseases of central nervous system [clinically isolated syndrome]

344.00 - 344.09  Quadriplegia and quadripareisis

344.89  Other specified paralytic syndrome

345.00 - 345.91  Epilepsy and recurrent seizures

368.11  Sudden visual loss

780.01  Coma
780.39 Other convulsions
784.0 Headache
787.01 - 787.03 Nausea and vomiting
995.27 Other drug allergy
995.29 Unspecified adverse effect of other drug medicinal and biological substance allergy
[intolerance of one-month trial of Avonex, Copaxone, or Rebif]

**Alemtuzumab (Lemtrada):**

No specific code

The above policy is based on the following references:


207. Olek MJ. Pathogenesis and epidemiology of multiple sclerosis. UpToDate Inc., Waltham, MA. Last reviewed December 2014d.


212. Novartis AG. Sandoz receives FDA approval for Glatopa as the first generic competitor to MS therapy Copaxone 20mg. Media Releases. Holzkirchen, Germany: Novartis; April 16, 2015.