Multiple Sclerosis

Definition

Multiple sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system that is a leading cause of disability in young adults.

MS is characterized pathologically by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. Axonal injury is also a prominent pathologic feature, especially in the later stages.

The pattern of MS:

Is categorized into several clinical subtypes as follows:

-Clinically isolated syndrome (CIS), representing the first attack of MS.

-Relapsing-remitting MS (RRMS): Approximately 85% of cases.

-Secondary progressive MS (SPMS).

-Primary progressive MS (PPMS).

(CIS): Presents as a monophasic clinical episode with patient-reported symptoms and objective findings that reflect a focal or multifocal inflammatory demyelinating event in the central nervous system.

(RRMS): characterized by clearly defined attacks (also known as relapses or exacerbations) with full or incomplete recovery. There is minimal disease progression during the periods between disease relapses.

(SPMS): characterized by an initial relapsing-remitting MS disease course followed by gradual worsening with or without occasional relapses, usually occurs 10 to 20 years after disease onset.

(PPMS): is characterized by progressive accumulation of disability from disease onset with occasional plateaus.
Symptoms/ Signs

Manifestations of multiple sclerosis

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Total (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory in limbs</td>
<td>31</td>
</tr>
<tr>
<td>Visual loss</td>
<td>16</td>
</tr>
<tr>
<td>Motor (subacute)</td>
<td>9</td>
</tr>
<tr>
<td>Diplopia</td>
<td>7</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>5</td>
</tr>
<tr>
<td>Motor (acute)</td>
<td>4</td>
</tr>
<tr>
<td>Balance problems</td>
<td>3</td>
</tr>
<tr>
<td>Sensory in face</td>
<td>3</td>
</tr>
<tr>
<td>Lhermitte sign (electric shock-like sensations that run down the back and/or limbs upon flexion of the neck)</td>
<td>2</td>
</tr>
<tr>
<td>Vertigo</td>
<td>2</td>
</tr>
<tr>
<td>Bladder problems</td>
<td>1</td>
</tr>
<tr>
<td>Limb ataxia</td>
<td>1</td>
</tr>
<tr>
<td>Acute transverse myelopathy</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Polysymptomatic onset</td>
<td>14</td>
</tr>
</tbody>
</table>

Diagnosis

Evidence provided by MRI of the brain and spine, CSF evaluation (presence of increased oligoclonal bands and increased IgG), evoked potentials, and optic coherence tomography, used in conjunction with the physical examination and history, aids in establishing the diagnosis of MS. MRI, the most valuable diagnostic tool, produces images of the brain and spine that reflect damage that is characteristic of MS plaques in multiple areas of the CNS.
Non Pharmacologic therapy

A. Rehabilitation:
Physical therapists, occupational therapists, and speech therapists, and may work with the patient on compensatory techniques to manage cognitive problems.

B. Physical therapy:
Provide assessment of gross motor skills and assessment and training in appropriate assistive devices to improve mobility in patients with MS. They evaluate and train the patient in appropriate exercise programs to decrease spasticity, maintain range of motion, strengthen muscles, and improve coordination.

Treatment of RRMS

DISEASE-MODIFYING THERAPY (DMT)

Disease-modifying therapies have shown beneficial effects in patients with relapsing MS, including reduced frequency and severity of clinical attacks. These agents appear to slow the progression of disability and the reduce accumulation of lesions within the brain and spinal cord.

* recommend starting DMT as soon as possible for all patients with RRMS.

Approach to choosing (DMT) – The choice of a specific agent should be individualized, considering the patient's disease activity, comorbidities, risk factors, and values and preferences. Our suggested approach to initial treatment is as follows:
MONITORING RESPONSE TO THERAPY:

A. By clinical follow-up with careful attention to possible manifestations of MS disease activity including acute attacks (relapses).
B. Development of new MS lesions on brain magnetic resonance imaging (MRI)
C. Onset or progression of sustained disability.

REFRACTORY DISEASE:

For patients initially treated with Drug (X) who have an inadequate response, we suggest the following options:

<table>
<thead>
<tr>
<th>Drug (X)</th>
<th>Alternative 1</th>
<th>Alternative 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta (IFNB) drugs</td>
<td>Oral DMT such as Dimethyl Fumarate, Teriflunomide, or Fingolimod</td>
<td>Infusion DMT monotherapy Natalizumab or Ocrelizumab</td>
</tr>
<tr>
<td>Or Glatiramer acetate</td>
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<tr>
<td>Natalizumab</td>
<td>Oral DMT such as Fingolimod, Siponimod, Ozanimod, Dimethyl Fumarate, and Teriflunomide</td>
<td>Monthly intravenous Glucocorticoid bolus, typically 1000 mg of Methylprednisolone</td>
</tr>
<tr>
<td>Oral Agent</td>
<td>Different Oral Agent</td>
<td>Infusion therapy or Injection therapy</td>
</tr>
<tr>
<td>For patients who are poor responders to all first-line DMTs</td>
<td>- Rituximab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Intravenous Methylprednisolone 1000 mg monthly</td>
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<tr>
<td></td>
<td>- Intravenous Immune globulin</td>
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<tr>
<td></td>
<td>- Intravenous pulse Cyclophosphamide with pulse Methylprednisolone.</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
- Alemtuzumab is usually reserved for patients with highly active RRMS who have had an inadequate response to two or more first-line DMTs.
- Hematopoietic stem cell transplantation is being evaluated at a few centers for refractory RRMS.
- For women with MS who are planning a pregnancy or who become pregnant, Prior to attempting pregnancy, a washout period for most DMTs is advised.

INFUSION THERAPIES

Include:
1. Natalizumab
2. Alemtuzumab
3. Ocrelizumab
4- Rituximab (off-label)
5- Mitoxantrone, is seldom used because of cardiac toxicity and limited evidence of benefit.

### INFUSION THERAPIES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
<th>Pregnancy</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>MS, Relapsing</td>
<td>IV: 300 mg infused over 1 hour every 4 weeks</td>
<td>there are no dosage adjustments</td>
<td>there are no dosage adjustments</td>
<td>crosses the placenta</td>
<td>Headache, fatigue, depression, Skin rash, Nausea, abdominal distress, Influenza, Arthralgia, U&amp;L respiratory tract infection, etc.</td>
</tr>
</tbody>
</table>

**MOA** is a recombinant monoclonal antibody directed against the alpha-4 subunit of integrin molecules, thereby blocking integrin association with vascular receptors and limiting adhesion and transmigration of leukocytes.

**Monitoring**

Symptoms of hepatotoxicity, hypersensitivity reactions during and for 1 hour after infusion, symptoms of (persistent antibody-positivity, meningitis and encephalitis, acute retinal necrosis.), Radiographic signs of PML periodically, Baseline brain MRI scan, if PML is suspected, obtain gadolinium-enhanced brain MRI scan and CSF analysis for JC viral DNA.

**Note**

- Advantage: a highly effective drug for the treatment of RRMS.
- Disadvantage: its use is associated with the development of progressive multifocal leukoencephalopathy (PML), a potentially disabling and fatal complication.
- Discontinuation of natalizumab can be associated with a severe rebound of MS disease activity, sometimes leading to permanent accrual of disability.

*The risk of PML is increased with the duration of natalizumab therapy.*

<table>
<thead>
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<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocrelizumab</td>
<td>MS, Relapsing</td>
<td>IV: 300 mg on day 1, followed by 300 mg 2 weeks later; subsequent doses of 600 mg are administered once every 6 months</td>
<td>there are no dosage adjustments</td>
<td>there are no dosage adjustments</td>
<td>Potential placental transfer of human IgG increasing as pregnancy progresses.</td>
<td>Skin infection, Decreased serum immunoglobulins, Infection, Upper respiratory tract infection, etc.</td>
</tr>
</tbody>
</table>

**MOA** is a recombinant human anti-CD20 (a B-cell marker) monoclonal antibody that binds to a different, but overlapping, CD20 epitope than rituximab, another anti B cell monoclonal antibody.
Monitoring
- Hepatitis B virus screening prior to therapy initiation.
- Monitor for infusion reactions.
- Monitor for signs/symptoms of infection, malignancy, and progressive multifocal leukoencephalopathy.

Note
- Premedicate with methylprednisolone (100 mg IV) 30 minutes prior to each infusion, and an antihistamine (e.g., diphenhydramine) 30 to 60 minutes prior each infusion; may also consider premedication with acetaminophen.

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<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>MS, Relapsing</td>
<td>Lemtrada: IV: 12 mg daily for 5 consecutive days (total 60 mg), followed 12 months later by 12 mg daily for 3 consecutive days (total 36 mg).</td>
<td>there are no dosage adjustments</td>
<td>there are no dosage adjustments</td>
<td>Potential placental transfer of human IgG increasing as pregnancy progresses.</td>
<td>Headache, fatigue, insomnia, paresthesia, Skin rash, Thyroid disease, Nausea, diarrhea, Lymphocytopenia, Infection, Infusion-related reaction, ect</td>
</tr>
</tbody>
</table>

MOA is a humanized monoclonal antibody that causes depletion of CD52-expressing T cells, B cells, natural killer cells, and monocytes.

Monitoring
- Campath: CBC, platelets, signs and symptoms of infection; CD4+ lymphocyte counts, FSH, monitor BP
- Lemtrada: CBC, Infection, tuberculosis screening, TSH

Note
- Antiemetics may be recommended to prevent nausea and vomiting.

### ORAL THERAPIES

- Include:
  1- dimethyl fumarate
  2- diroximel fumarate,
  3- monomethyl fumarate
  4- teriflunomide
  5- fingolimod
  6- siponimod
  7- ozanimod
  8- cladribine.
### INFUSION THERAPIES

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</tr>
</thead>
<tbody>
<tr>
<td><strong>Dimethyl fumarate</strong></td>
<td>MS, Relapsing</td>
<td>Oral: Initial: 120 mg twice daily; after 7 days, increase to the maintenance dose: 240 mg twice daily</td>
<td>there are no dosage adjustments</td>
<td>there are no dosage adjustments</td>
<td>Information related is limited, In general not initiated during pregnancy, except in females at high risk of multiple sclerosis activity.</td>
<td>flushing, diarrhea, nausea, abdominal pain, Infection, decrease lymphocyte counts, elevated serum aminotransferase and bilirubin levels ect</td>
</tr>
</tbody>
</table>

**MOA**
Have neuroprotective and immunomodulatory properties

**Monitoring**
CBC, Liver function test, urinalysis, MRI, signs/symptoms of hypersensitivity

**Note**
- Oral formulation of dimethyl fumarate (BG-12) significantly reduced relapse rates and reduces the rate of disability progression.
- Taking the medication with food can decrease the rate of gastrointestinal upset.
- Should be discontinued this drug if lymphocytopenia develops.
- Developed progressive multifocal leukoencephalopathy (PML), including those with and without lymphocytopenia.

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<tbody>
<tr>
<td><strong>Diroximel fumarate</strong></td>
<td>MS, Relapsing</td>
<td>Oral: Initial: 231 mg twice daily; after 7 days, increase to the maintenance dose: 462 mg twice daily</td>
<td>Mild: there are no dosage adjustments</td>
<td>There are no dosage adjustments, Discontinue treatment if diroximel fumarate-induced hepatic injury is suspected.</td>
<td>Information related is limited, In general not initiated during pregnancy, except in females at high risk of multiple sclerosis activity.</td>
<td>flushing, abdominal pain, diarrhea, and nausea, Infection, ect uncommon, anaphylaxis, angioedema, opportunistic infections (eg, PML, herpes zoster virus),</td>
</tr>
</tbody>
</table>
**MOA**

Hypothesized to regulate cell signaling pathways, causing beneficial immune and neuroprotective effects, is an oral fumarate that is rapidly metabolized to monomethyl fumarate, its major active metabolite. It is postulated to have fewer gastrointestinal symptoms compared with dimethyl fumarate.

**Monitoring**

CBC with lymphocyte count, serum aminotransferase, alkaline phosphatase, and total bilirubin levels.

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### INFUSION THERAPIES

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Monomethyl fumarate</strong></td>
<td><strong>MS, Relapsing</strong></td>
<td>Oral: Initial: 95 mg twice daily; after 7 days, increase to the maintenance dose: 190 mg twice daily.</td>
<td>there are no dosage adjustments</td>
<td>there are no dosage adjustments</td>
<td>In general not initiated during pregnancy, except in females at high risk of multiple sclerosis activity.</td>
<td>Flushing, abdominal pain, diarrhea, and nausea, Infection, etc uncommon, anaphylaxis, angioedema, opportunistic infections (eg, PML, herpes zoster virus), lymphopenia, and liver injury</td>
</tr>
<tr>
<td><strong>MOA</strong></td>
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<td></td>
<td>Is thought to exert neuroprotective effects in patients with multiple sclerosis by activating the nuclear erythroid 2-related factor 2 (nuclear factor erythroid-derived 2-like 2; Nrf2) transcriptional pathway</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td></td>
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<td></td>
<td>Complete blood count with lymphocyte count, serum aminotransferase, alkaline phosphatase, and total bilirubin levels.</td>
</tr>
</tbody>
</table>

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### INFUSION THERAPIES

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Dose</th>
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<th>Hepatic Impairment</th>
<th>Pregnancy</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Teriflunomide Aubagio®</strong></td>
<td><strong>MS, Relapsing</strong></td>
<td>Oral: 7 mg or 14 mg once daily</td>
<td>there are no dosage adjustments</td>
<td>there are no dosage adjustments</td>
<td>Information related is limited, In general it initiated during pregnancy, except in females at high risk of multiple sclerosis activity.</td>
<td>Diarrhea, nausea, hair thinning, elevated alanine aminotransferase (ALT) levels, etc</td>
</tr>
</tbody>
</table>
MOA is the active metabolite of leflunomide that inhibits pyrimidine biosynthesis and disrupts the interaction of T cells with antigen presenting cells.

Monitoring
CBC, Liver function test, urinalysis, MRI, signs/symptoms of hypersensitivity

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**INJECTABLE THERAPIES**

Include:
A. Interferon beta (IFNB) Preparations
   1- Interferon beta-1B.
   2- Interferon beta-1a.
   3- Pegylated interferon beta-1a.
B. Glatiramer Acetate

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**INFUSION THERAPIES**

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Hepatic Impairment</th>
<th>Pregnancy</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interferon beta-1B</strong> Betaferon®</td>
<td>MS, Relapsing</td>
<td>SubQ: Initial: 0.0625 mg (2 million units [0.25 mL]) every other day.</td>
<td>there are no dosage adjustments</td>
<td>there are no dosage adjustments</td>
<td>interferon beta-1b may be considered until pregnancy is confirmed, and in select cases.</td>
<td>Peripheral edema, Skin rash, lymphocytopenia, Antibody development, Inflammation at injection site, injection site reaction, headache, hypertonia, insomnia, pain, asthenia, myalgia, Flu-like symptoms, Fever. ect</td>
</tr>
</tbody>
</table>

MOA
Mechanism in the treatment of MS is unknown; however, immunomodulatory effects attributed to interferon beta-1b include enhancement of suppressor T cell activity, reduction of proinflammatory cytokines, down-regulation of antigen presentation, and reduced trafficking of lymphocytes into the central nervous system.

Monitoring
- Complete blood chemistries (including platelet count)
- Liver function tests are recommended at 1, 3, and 6 months following initiation of therapy and periodically thereafter.
- Thyroid function in patients with history of thyroid dysfunction or as clinically necessary.
- Monitor for flu-like symptoms, allergic or anaphylactic reactions, injection-site reactions, worsening of cardiac symptoms (in HF patients); and for sign/symptoms of depression.
Flu-like symptoms are also common and may be treated with ibuprofen, acetaminophen, and glucocorticoids.

*Interferon beta-1a*  Recombinant human interferon beta-1a is available in several different formulations, including intramuscular, subcutaneous, and pegylated preparations.

### INFUSION THERAPIES

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Interferon beta-1a</strong></td>
<td>MS, Relapsing</td>
<td>IM: 30 mcg once weekly. SUQ: Target dose is either 22 or 44 mcg 3 times weekly; doses should be separated by at least 48 hours</td>
<td>there are no dosage adjustments</td>
<td>Use with caution in patients with active liver disease, alcohol abuse, ALT &gt; 2.5 x ULN, or a history of significant liver disease.</td>
<td>Interferon beta-1b may be considered until pregnancy is confirmed, and in select cases, use may be continued during pregnancy.</td>
<td>Headache, fatigue, increased serum ALT, increased serum AST, Immunologic: Antibody development, Injection site reaction, Myalgia, Visual disturbance, Flu-like symptoms, depression</td>
</tr>
<tr>
<td>Avoneks® IM</td>
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<tr>
<td>Rebif® SUQ</td>
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</tbody>
</table>

**MOA**  Mechanism in the treatment of MS is unknown; however, immunomodulatory effects attributed to interferon beta-1a include enhancement of suppressor T cell activity, reduction of proinflammatory cytokines, down-regulation of antigen presentation, and reduced trafficking of lymphocytes into the central nervous system.

**Monitoring**  - Thyroid function tests, CBC with differential, transaminase levels, blood chemistries
- Symptoms of autoimmune disorders
- Signs/symptoms of psychiatric disorder (including depression and/or suicidal ideation)
- Signs/symptoms of new onset/worsening cardiovascular disease
- Signs/symptoms of thrombotic microangiopathy (new-onset hypertension, thrombocytopenia, renal impairment).

**NOTES**  - The higher dose of interferon beta-1a was associated with an increased rate of adverse effects
- Flu-like symptoms are also common and may be treated with ibuprofen, acetaminophen, and glucocorticoids
### INFUSION THERAPIES

<table>
<thead>
<tr>
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</thead>
</table>
| Pegylated interferon beta-1a  | relapsing forms of MS (e.g., relapsing-remitting MS [RRMS]) | Gradually titrate to recommended dosage of 125 mcg every 14 days according to schedule  
1 (First day of therapy): 63mcg  
15 (14 days later): 94mcg  
19 and every 14 days thereafter: 125mcg | there are no dosage adjustments | No specific dosage recommendations. | Category C use during pregnancy only when potential benefits justify possible risks to fetus | Injection site erythema, flu-like symptoms, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, arthralgia. |

### MOA
Mechanism in the treatment of MS is unknown; however, immunomodulatory effects attributed to interferon beta-1a include enhancement of suppressor T cell activity, reduction of proinflammatory cytokines, down-regulation of antigen presentation, and reduced trafficking of lymphocytes into the central nervous system.

### Monitoring
- complete blood count, liver function, and thyroid function
- symptoms of autoimmune disorders
- signs/symptoms of psychiatric disorder (including depression and/or suicidal ideation)
- signs/symptoms of new onset/worsening cardiovascular disease
- Signs/symptoms of thrombotic microangiopathy (new-onset hypertension, thrombocytopenia, renal impairment).

### NOTES
- Flu-like symptoms are also common and may be treated with ibuprofen, acetaminophen, and glucocorticoids

IFNB treatment should be stopped immediately for patients who develop thrombotic microangiopathy.
## INFUSION THERAPIES

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<thead>
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</thead>
<tbody>
<tr>
<td>Glatiramir Copaxone®</td>
<td>MS, relapsing</td>
<td>SubQ: 20 mg once daily or 40 mg 3 times per week administered at least 48 hours apart</td>
<td>there are no dosage adjustments</td>
<td>there are no dosage adjustments.</td>
<td>glatiramir may be considered until pregnancy is confirmed, and in select cases, use may be continued during pregnancy</td>
<td>include local injection site reactions and, less commonly, transient systemic post injection reactions such as chest pain, flushing, dyspnea, palpitations, and/or anxiety. Development of IgG antibodies, infection Serious adverse effects due to glatiramer are uncommon, but cases of possible hepatotoxicity have been reported</td>
</tr>
</tbody>
</table>

**MOA**

Immunomodulatory mechanism of action for glatiramer involves binding to major histocompatibility complex molecules and consequent competition with various myelin antigens for their presentation to T cells. In addition, glatiramer is a potent inducer of specific T helper 2 type suppressor cells that migrate to the brain and lead to bystander suppression; these cells also express anti-inflammatory cytokines.

**Monitoring**

Monitor for postinjection reactions (eg, self-resolving flushing, chest tightness, dyspnea, and palpitation)

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### ❖ OTHER TREATMENTS

**Azathioprine**: under investigation

**CCSVI treatment**: Venous angioplasty and venous stent placement have been proposed as a treatment for chronic cerebrospinal venous insufficiency (CCSVI), a controversial condition that has been disproven as having a role in the development of MS; CCSVI is characterized by putative anomalies of cerebrospinal veins that interfere with venous drainage from the brain. Invasive treatments for CCSVI...
are not beneficial, and there are reports of harm with such treatments. Therefore, we do not recommend using endovascular venoplasty or stenting procedures to treat patients with MS for presumed CCSVI.

**Cyclophosphamide**: under investigation.

**Dalfampridine**: a potassium channel blocker, may improve walking speed in some patients with MS but is not considered disease-modifying.

**Glucocorticoids** — Monthly IV glucocorticoid bolus, typically 1000 mg of methylprednisolone, is used at many institutions for the treatment of primary or secondary progressive MS alone or in combination with other immunomodulatory or immunosuppressive medications.

**Intravenous immune globulin** — Although data are equivocal, there is no compelling evidence that intravenous immune globulin (IVIG) is effective for patients with RRMS.

**Laquinimod**: under investigation.

**Mitoxantrone**: is approved for use in both relapsing-remitting and progressive forms of MS. However, because of cardiac toxicity, an increased risk of ovarian failure, male infertility, chromosomal aberrations, and promyelocytic leukemia, along with the limited evidence of benefit, mitoxantrone should not be used to treat MS unless potential benefits greatly outweigh the risks.

**Stem cell transplantation**: The goal of autologous hematopoietic stem cell transplantation (HSCT) is eliminating and replacing the patient's pathogenic immune system to achieve long-term remission of MS. Stem cell transplantation is also under investigation as a treatment for patients with progressive forms of MS.

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**References**:
4. Lexicomp

Prepared by Pharm D students: Mariam Tahrawi, Anood Shbelat.
Supervised by clinical pharmacist: Eshraq Al-Abweeny.