Multiple Sclerosis: An overview of current and novel therapies

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Abstract

Multiple sclerosis (MS) is believed to be an autoimmune disease of the white matter of the Central Nervous System and typically presents as inflammatory plaques in the brain, spinal cord and optic nerves. Cerebral atrophy and axonal loss may be related to a neurodegenerative process and result in chronic neurological disability.

The condition is diagnosed by clinical symptoms and investigations such as MRI scan confirming that the lesions are separated in time and location. Disease course is unpredictable, ranging from benign to aggressive, with various subtypes with/without relapses and progression. Relapsing remitting MS is the most common presentation.

The treatment of MS has been delineated to include symptomatic control, immunosuppression and immunomodulation. Immunosuppression with corticosteroids is used to treat the acute relapses. On the other hand, immunomodulation is aimed at preventing relapses and changing the course of the disease.

Beta-interferons are currently the disease-modifying treatment of choice as they reduce relapses. Glatiramer acetate also reduces relapse frequency. These drugs are directed at the inflammatory components of MS, but effects on the neurodegenerative components are not confirmed. It is therefore debatable whether these medicines slow down disease progression.

Adverse effects, cost, route and frequency of administration and neutralising antibodies are of concern with interferons. Subsequently, there is research to develop affordable drugs with less adverse effects and more favourable effects on relapses and long-term disability.

Alemtuzumab, a monoclonal antibody, has shown superior efficacy as compared to interferon in clinical trials. Unfortunately, immune thrombocytopenic purpura (rare) and autoimmune thyroid dysfunction may limit the use of this agent in clinical practice.

There is no cure for MS and there are still many unresolved issues pertaining to appropriate treatment. The main challenges are to identify patients who will deteriorate faster and to develop drugs that target the progressive stage.

Introduction

Multiple sclerosis is an incurable and unpredictable chronic disease of the Central Nervous System (CNS) affecting approximately 2.5 million people worldwide. Lesions are spread throughout the CNS and occur at different sites at different times. The white matter of the brain, brain stem and spinal cord, as well as the optic nerves are mostly affected. Neurological defects are typically multiple, associated with a clinical course characterised by remissions and relapses, gradually resulting in disability. Disease progression may also occur in the absence of clinical exacerbations.

Most authors believe MS to be an autoimmune disease with inflammatory and demyelinating features. However, some investigators state that direct proof of an autoimmune cause of MS is lacking and that the aetiology may involve a neurodegenerative process independent of immune and inflammatory mediators. This may especially be the case in the development of chronic disability, where cerebral atrophy and significant axonal loss become prominent.

Nevertheless, studies show that most MS patients have other autoimmune disorders such as autoimmune thyroid disease. Furthermore, inflammatory T and B cells and macro-
phages are seen when examining the MS demyelinating lesions (plaques) and increased IgM and IgG levels are found in cerebrospinal fluid (CSF).2,7,10

Epidemiology and aetiology
Most people affected by MS are between age 20 and 40 at first presentation of the disease and most are women.1,5,10,13 Risk factors appear to involve viral infections, as increased levels of antibodies to Epstein Barr Virus (EBV) were found in serological investigations of MS patients.5,6,9,10 Studies are however conflicting or not convincing.3,7,11 Varicella zoster and other viral infections may trigger acute exacerbations of MS, but additional studies are required to confirm this.9,10

There is also an association between latitude and the risk of MS.5,8,10,14 White populations, particularly those from Northern Europe and Northern America are mostly affected by MS, as compared to people from Asia, Africa and of Indian origin.6,10,14,15 It seems that people staying further away from the equator are more likely to be affected by MS, possibly due to lower vitamin D levels as a result of less exposure to sunlight.5,9,10

Other environmental factors include smoking, especially exposure at a young age,5,10,16 while genetics also seem to contribute to MS.5,6,9,10,16

Pathophysiology
T cell transmigration over the blood brain barrier (BBB) appears to play an important role in MS pathogenesis. Activated T cells and other immune components lead to specific antibody production, e.g. to myelin basic protein and myelin oligodendrocyte glycoprotein, with the myelin sheath, oligodendrocytes and axons becoming the targets of tissue damage.2,3,6,7,9 The affected nerve cannot transfer information from the brain and spine to the rest of the body. The damage can be disabling.13

However, during the inflammatory process there is also an opposing down-regulation of the immune response in order to limit and resolve the MS lesion.2,6,7 In early MS there is a relative increase of CD4+ CD25 T cells, most likely representing a protective regulatory T cell population (Tregs).4 Impaired function of these Tregs may contribute to the chronic and progressive nature of the disease.2,3,4

Symptoms
The initial symptoms experienced are often double or blurred vision, red-green colour alteration or even blindness in one eye.2,13 Optic neuritis is diagnosed where patients present with acute unilateral eye pain followed by visual loss; ophthalmoplegia involves nystagmus and rapid oscillation of the eyes.3,5,13 MS patients often experience tremors, muscle weakness in the extremities and difficulty with coordination and balance; some may present with partial or complete paralysis and/or spasticity. Most people experience sensory feelings of numbness or "pins and needles" and several pain syndromes may occur.5,10,13

Cognitive impairment such as difficulties with attention, concentration and memory, as well as poor judgement occurs in about 50% of patients. Dizziness or light-headedness, fatigue and depression are also common.5,8,10 Bowel and bladder symptoms, e.g. constipation and urinary incontinence or urgency are common in MS, as is sexual dysfunction.3,5,10

Disease patterns of MS
- **Relapsing remitting multiple sclerosis (RRMS)** is regarded as episodic relapses with full or partial recovery within weeks; there is no disease progression between relapses. Acute focal inflammation and associated oedema are characteristic of these attacks.7,10 Approximately 85-90% of MS cases are RRMS.1,3,6,7,8,17
- **Secondary progressive multiple sclerosis (SPMS)** is characterised by RRMS followed by neurodegenerative progression with or without relapses, minor remission and plateaux.3,6,7,8,17 Global inflammation of the brain and meninges with demyelination of the cerebral cortex and diffuse injury of white matter is prominent in SPMS, causing significant neurological disability.10 Most patients with RRMS will enter this phase in about 15-25 years.3,6,7,8,17
- **Primary progressive multiple sclerosis (PPMS):** These patients experience a steady decline in neurological function from the beginning, although temporary minor improvements or plateaux may transpire; acute attacks are not experienced.1,6,8,10,17 The same degenerative changes as those occurring in SPMS appear in the brain.10 PPMS normally manifests in older persons (average age of onset is 40 years) and affects males and females equally.1,6 PPMS patients represent about 10% of cases and have poorer prognosis and more disability compared to patients with RRMS.1,6,10
- **Progressive-relapsing multiple sclerosis (PRMS)** is characterised by progressive disease from the beginning together with sudden relapses, with or without full recovery; progression continues between relapses.3,5,10,17 This is a rare pattern occurring in only about 10-15% of patients with PPMS.1,5

The activity of the disease is highly variable: Benign MS is a syndrome where the patient remains fully functional in all neurologic systems and clinically stable for about 15 years after diagnosis. Approximately 15–20% of patients with RRMS present like this.6,8,10 On the other hand, malignant MS is disease with frequent relapses and virtually no recovery, or rapid progression leading to significant disability, severe neurologic damage or death.1,11,18 Lastly, clinical isolated syndromes (CIS) must be mentioned. The patients in this group experience symptoms similar to MS, but have a negative MRI and/or do not meet the McDonald diagnostic criteria.14,19 CIS may or may not develop into MS.15

Indices used to diagnose and measure MS
There is no single diagnosing measure or test that can confirm MS. One or two tests may be indicative, but are not

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conclusive. There has to be a combination of features to accurately diagnose the condition.15,18,20

- **Clinical.** Initial symptoms include optic neuritis, acute eye pain followed by visual loss, muscle weakness in the extremities and difficulty with coordination and balance.1,5,8 Symptoms are separated by months or years and separated in anatomical location and may be either monofocal (single lesions) or multifocal (more than one lesion).3,18,20

- **MRI** scans are used to exclude other disorders that may imitate MS e.g. neuromyelitis optica, diffuse cerebral sclerosis, metabolic disorders, stroke, spinal cord infarction, essential tremor, HIV1–opportunistic infection, progressive multifocal leukoencephalopathy, systemic lupus erythematosus, etc.1,3,6 The presence of T2 lesions or gadolinium-contrast enhanced lesions can distinguish actively inflamed plaques indicating breakdown of the BBB and is used to confirm clinical episodes or demyelination in the white matter.3,5,11 The T1 lesions (black holes) reflect axonal damage or chronic tissue damage resulting in brain atrophy.3,11,20 MRI is also used to measure MS disease activity and progression.11,20

- **CSF examination** is only required if there is clinical indecision.1,18 The CSF illustrates an increased immunoglobulin level, mostly IgG, in the form of distinct patterns, namely oligoclonal bands.3,5,20

- **Evoked potentials (EP)** are delays in electrical responses to sensory stimulation and happen in damaged tissues of the CNS.5 EP can be measured using visual evoked responses, which are more sensitive, somatosensory or brain stem auditory evoked potentials.3,5,18

- **The McDonald Criteria** are diagnostic criteria for MS recommended by various authority groups, including NASA (Neurological Association of South Africa).14,18 These criteria use clinical presentation together with advanced MRI imaging techniques of the brain or spine lesions to confirm the diagnosis. See www.bmj.com for the 2006 MacDonald criteria.8,14,18,20

The Kurtzke Expanded Disability Status Scale (EDSS) is used to measure disease progression by assigning a severity score (0–10) to the clinical status:3,14,21

- EDSS score 0 refers to normal neurological assessment
- EDSS score 1.0–3.5 indicates neurological impairment that is likely to have partial impact on the daily activities
- EDSS score 4.0 –5.5 reflects ambulatory limitations for distances up to 500m
- EDSS score 6.0–9.5 indicates that the patient requires mobility aids, may require a wheelchair or become confined to bed as the disease deteriorates
- EDSS score 10 refers to death due to MS

### Treatment of MS

There are no standard recommendations for the treatment of MS, because treatment depends on individual clinical situations. Currently, a patient’s prognosis cannot be predicted, i.e. if he/she will experience early progression or benign MS.6,11

**Goals of MS treatment are to:**3,5,8,11

- Manage acute exacerbations
- Prevent relapses
- Slow or stop progression and disability
- Limit side effects and cost of therapy

#### Acute relapses

Management of acute attacks include administration of high dose corticosteroids in order to reduce the severity and duration of these relapses.1,3,8,11,13 The NICE guidelines recommend corticosteroid therapy to hasten the recovery from relapses if the attack is causing distressing symptoms or disability to daily activities.18 The exact mode of action of corticosteroids in MS is not clear, however, anti-inflammatory properties have been proven to quickly resolve the relapse by reducing oedema, stabilising the BBB, decreasing pro-inflammatory cytokines and inducing T cell depletion.1

Typical regimens are:

- IV methylprednisolone 500mg to 1g daily for between 3 to 5 days.1,3,5,8,11,18,22
- High dose oral methylprednisolone 500mg to 2g daily for between 3 to 5 days.1,3,5,18,22

There is no significant long-term effectiveness in terms of reducing exacerbation frequency or disease progression. Side effects of chronic use outweigh any possible benefits.1,3,8,11,13

#### Symptomatic treatment

Numerous therapies are used for treatment of the related symptoms of MS, but many of them “off label”. Refer to Table I. Potential side effects should also be considered.3,23

### Table I: Treatment of secondary symptoms in MS3,5,8,11,13,24

<table>
<thead>
<tr>
<th>Condition/Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Fluoxetine, sertraline, amitriptyline</td>
</tr>
<tr>
<td>Spasticity</td>
<td>Baclofen, diazepam</td>
</tr>
<tr>
<td>Painful spasms</td>
<td>Carbamazepine, gabapentin</td>
</tr>
<tr>
<td>Urinary dysfunction</td>
<td>Oxxybutynin, imiprime</td>
</tr>
<tr>
<td>Tremors</td>
<td>Clonazepam, primidone, propranolol</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Sildenafil, tadalafl, vardenafil</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>Modafinil, amantadine, methylphenidate, selegiline</td>
</tr>
</tbody>
</table>

*Patients need to avoid excessive activity and heat to counter physiological fatigue13
**Disease-modifying therapies**

In the past 15 years MS-specific disease-modifying drugs became available. They have a partial efficacy in RRMS and allow control of disease activity by targeting the inflammatory component of the disease. Regrettably, no drugs have been approved for progressive disease as yet. Novel therapies such as monoclonal antibodies (natalizumab, alemtuzumab) are undergoing clinical trials to explore their role in reducing relapses and slowing down progression of the illness. Impact on progression of disability has not yet been demonstrated. Refer to Table II.

**Intravenous immunoglobulins (IVIG)**

IVIG interfere with myelin damage by blocking monocytes or macrophages and by promoting remyelination. It seems to have immunosuppressive effects in MS at the early stages of optic neuritis by reducing relapse rate and gadolinium-enhancing lesions, but not at the progressive stages. Some trials, however, lacked complete data on clinical and MRI outcomes. Other studies report that the odds ratio of RRMS patients to remain relapse-free after a two year treatment period with IVIG is similar to that of interferons and glatiramer acetate, each compared to placebo. Overall there is inconclusive data and more trials need to be done.

Nevertheless, the European Federation of Neurological Societies (EFNS) recommends that IVIG be considered as a 2nd or 3rd line agent in RRMS when a patient is intolerant to other immunomodulators, and for relapses in pregnant women or in the post-partum period.

**Conventional immunosuppressants**

Non-specific immunosuppressants are also being used to treat MS, with varying results.

- **Azathioprine** is registered for RRMS in Europe and also for autoimmune diseases in South Africa. As stated earlier, MS is believed to be an inflammatory immune-mediated demyelinating disease. The drug has been widely tested in MS and produces a similar reduction as interferon beta in the relative risk of relapse at 2 years (15–30%).

  Both the American Association of Neurologists and NICE concluded that azathioprine has no effect on disease progression. Conversely, in a 2007 Cochrane review, it was concluded that "azathioprine is an appropriate maintenance treatment for patients with multiple sclerosis who frequently relapse and require steroids." From the above it seems that azathioprine’s place in the prevention of MS disability is currently controversial.

- **Methotrexate** – one trial reported no consequence on relapse rate, while the other trial showed beneficial effects of treatment compared to placebo. Results are generally inconclusive.

- **Cyclophosphamide** is a cytotoxic drug. There is conflicting data in trials, as two trials reported delays in progression, but in the other trials where the drug was compared to placebo there was no effect on progression. There was a wide range of side-effects which made the drug unfavourable. Results are generally inconclusive and the use of cyclophosphamide in MS is not recommended.

- **Ciclosporin** – one trial reported no beneficial effect on treatment, while another trial showed positive effects. Nephrotoxicity was significant, but when compared to azathioprine, side effects were less severe. Results are equivocal.

**Novel therapies: alemtuzumab**

**Modes of action of alemtuzumab**

Alemtuzumab is a humanised, monoclonal antibody against CD52, an antigen expressed on T and B lymphocytes, macrophages and monocytes. Pulse administration causes prolonged depletion of T cells and modulation of the lymphocyte cascade. Alemtuzumab also inhibits T cell transmigration over the BBB. Furthermore, the anti-CD52 effect possibly provides a costimulatory signal for CD4+ T cells and subsequently induces Tregs, the protective T cell population.

**Indications of alemtuzumab**

Alemtuzumab is approved in the USA and Europe for fludarabine-refractory B cell chronic lymphocytic leukaemia (BCLL). Alemtuzumab is not registered for MS in these regions.

In South Africa, it is marketed as Mabcampath® (Bayer) and is currently registered for treatment of CLL after failure of other treatments or incomplete response to, or short remission following fludarabine phosphate therapy. Registration for RRMS is pending at the MCC.

**The CAMMS 223 trial**

The CAMMS 223 trial was a single-blinded study of 334 RRMS patients with EDSS of ≤3. Patients were randomised in a 1:1:1 ratio to IFNB-1a (Rebif 44ug) given 3 times a week, alemtuzumab 12mg/day or 24mg/day infused IV over 5 days together with methylprednisolone for 3 days. After one year, participants in the alemtuzumab arms were infused with the same dose over 3 days.

The alemtuzumab arms were suspended after 3 patients experienced ITP (immune thrombocytopaenic purpura) and one died due to haemorrhagic stroke, but the IFNB-1a arm continued with treatment. Due to this, 155 patients (75%) were precluded from receiving the 3rd cycle of alemtuzumab at 24 months.

**Results**

In the one year interim analysis alemtuzumab reduced the relapse rate by 75% (p=0.00267) and the risk of sustained progression of disability by 60% (not significant, p>0.05) compared to IFNB-1a.
### Table II: Disease-modifying therapy

<table>
<thead>
<tr>
<th>Drug/Trade name</th>
<th>Mechanism of action</th>
<th>Dose</th>
<th>Side effects</th>
<th>Precautions</th>
<th>Approval</th>
<th>Place in therapy</th>
</tr>
</thead>
</table>
| **Interferon beta-1a** (Avonex®; Rebif®) | • Anti-inflammatory agent that inhibits BBB opening  
  • Alters immune response by reducing T cell proliferation  
  • Reduces cytokines, adhesion molecules and proteases | | • Flu-like symptoms (malaise, muscle aches, fever)  
  • Headaches  
  • Inflammation at injection site  
  • Psychiatric disorders  
  • Anaemia, leucopaenia, thrombocytopenia  
  • Elevated liver enzymes  
  • Seizure | • Active liver disease  
  • History of significant liver disease  
  • Depression  
  • Suicidal ideation/ attempts  
  • Cardiac disease  
  • Seizure disorder | • Avonex®: RRMS (USA, Europe and SA)4,23  
  • Rebif®: RRMS and SPMS with relapses (USA and Europe)4 | • First line/drugs of choice in RRMS  
  2.4,13,17,27 | • However, not recommended by NICE26 |
| **Interferon beta-1b** (Betaferon®) | • Anti-inflammatory agent that inhibits BBB opening  
  • Alters immune response by reducing T cell proliferation  
  • Reduces cytokines, adhesion molecules and proteases | 250 mcg every 2nd day by SC injection | • Flu-like symptoms  
  • Sweating  
  • Elevation of hepatic transaminase levels  
  • Depression and mental disorders  
  • Hypertension, palpitations and tachycardia  
  • Injection site reactions | • Abortifacient potential  
  • Depression  
  • Bone marrow suppression  
  • Cardiovascular disease  
  • Pulmonary disease  
  • Neuropsychiatric or seizure disorders  
  • Renal or hepatic disease | • RRMS and SPMS with relapses (USA, Europe and SA)4,23 | • First line/drug of choice in RRMS  
  2.4,13,17,27 | • However, not recommended by NICE26 |
| **Glatiramer acetate** (Copaxone®) | • Synthetic polypeptides with four amino acids antigenically similar to myelin basic protein that suppress T cell activation  
  • Express anti-inflammatory cytokines | 20 mg daily by SC injection | • Anxiety, tremor  
  • Arthralgia  
  • Facial oedema, palpitations, chest pain  
  • Nausea  
  • Hypertension  
  • Lymphadenopathy  
  • Dyspnoea  
  • Eosinophilia  
  • Injection site reactions | • Postinjection reactions  
  • Cardiac disease  
  • Renal impairment  
  • Breast feeding mothers23 | • RRMS (USA, Europe and SA)4,23 | • 2nd line therapy  
  • Safer, less side effects1,17 | • However, not recommended by NICE26 |
| **Mitoxantrone HCl** (Novantrone®)* | • Immunosuppressant  
  • Chemotherapeutic drug that delays progression in severe relapses | 12 mg/m² by short IV infusion once every 3 months for a total period of 24 months | • Nausea  
  • Alopecia  
  • Upper respiratory tract infections  
  • Urinary tract infections, menstrual disorder  
  • Transient neutropenia  
  • Cardiac toxicity  
  • Leukaemia1,17 | • Cardiac disorders2 | • RRMS, SPMS with or without relapses (USA and Europe, but not in SA)4,23 | • Last line therapy because of cardiac toxicity  
  • Treatment of advanced MS1,13 |
| **Natalizumab** (Tysabri®)* | • Humanised monoclonal antibody against alpha-4 integrins  
  • Prevents entry of T-cells across BBB | 300 mg IV infusion every 4 weeks | • PML (Progressive Multifocal Leuкоencephalopathy)** | • Not to be used with other immunomodulators or immunosuppressants4,17,26 | • RRMS (USA and Europe, but not in SA)4,23 | • Last line therapy because of PML2 |

* Off label use/not registered in SA  
** PML is an opportunistic virus infection of the CNS caused by the John Cunningham Virus (JCV).4,17,24
In the two year interim analysis alemtuzumab showed a 72% reduction in the relapse rate at low dose (p<0.0001) and 87% at high dose (p<0.0001) compared to IFNB-1a. The decrease in risk of sustained accumulation of disability was 88% with the low dose and 66% with the high dose compared to INFB-1a (both p<0.01). MRI parameters also favoured alemtuzumab-treated patients, but not all differences were significant at 36 months. There was no significant difference between the 12mg/day and 24mg/day alemtuzumab patients on outcome measures or adverse events. Refer to Table III for selected results.

### Table III: CAMMS 223 clinical trial – measure of disability, relapse and radiologic outcomes

<table>
<thead>
<tr>
<th>Outcome at 36 months</th>
<th>Interferon beta-1a (n = 111)</th>
<th>Alemtuzumab 12 mg/day dose (n=112)</th>
<th>Alemtuzumab 24 mg/day dose (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score improved</td>
<td>35 (33.7)</td>
<td>58 (54.2)</td>
<td>65 (60.2)</td>
</tr>
<tr>
<td>Score stayed the same</td>
<td>26 (25.0)</td>
<td>25 (23.4)</td>
<td>23 (21.3)</td>
</tr>
<tr>
<td>Score declined</td>
<td>43 (41.3)</td>
<td>24 (22.4)</td>
<td>20 (18.5)</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with no relapse (%)</td>
<td>51.6</td>
<td>77.0</td>
<td>83.5</td>
</tr>
<tr>
<td><strong>Lesion load on T2 weighted MRI</strong></td>
<td>(n=60)</td>
<td>(n=80)</td>
<td>(n=87)</td>
</tr>
<tr>
<td>Median change from baseline (%)</td>
<td>-13.3</td>
<td>-18.2</td>
<td>-13.5</td>
</tr>
<tr>
<td><strong>Brain volume on T1 weighted MRI</strong></td>
<td>(n=103)</td>
<td>(n=107)</td>
<td>(n=107)</td>
</tr>
<tr>
<td>Median change from baseline (%)</td>
<td>-1.8</td>
<td>-0.9**</td>
<td>0**</td>
</tr>
</tbody>
</table>

* Alemtuzumab significantly better than IFNB-1a
** Alemtuzumab not significantly better than IFNB-1a

### Table IV: Adverse events of interferon beta compared to alemtuzumab

<table>
<thead>
<tr>
<th>Outcome, no of pts (%)</th>
<th>Interferon beta-1a (n=107)</th>
<th>Alemtuzumab 12mg/day dose (n=108)</th>
<th>Alemtuzumab 24mg/day dose (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion–associated reaction</td>
<td>–</td>
<td>106 (98.1)</td>
<td>107 (99.1)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>58 (54.2)</td>
<td>4 (3.7)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Abnormal liver-function test</td>
<td>16 (15.0)</td>
<td>2 (1.9)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Autoimmune–associated event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hyperthyroidism</td>
<td>1 (0.9)</td>
<td>17 (15.7)</td>
<td>15 (13.9)</td>
</tr>
<tr>
<td>• Hypothyroidism</td>
<td>1 (0.9)</td>
<td>8 (7.4)</td>
<td>7 (6.5)</td>
</tr>
<tr>
<td>Depression</td>
<td>19 (17.8)</td>
<td>14 (13.0)</td>
<td>17 (15.7)</td>
</tr>
<tr>
<td>Immune thrombocytopenic purpura</td>
<td>1 (0.9)</td>
<td>2 (1.9)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Neurologic event</td>
<td>71 (66.4)</td>
<td>58 (53.7)</td>
<td>53 (49.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (29.9)</td>
<td>35 (32.4)</td>
<td>32 (29.6)</td>
</tr>
<tr>
<td>Infection–associated event</td>
<td>50 (46.7)</td>
<td>71 (65.7)</td>
<td>71 (65.7)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>29 (27.1)</td>
<td>6 (5.6)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Rash</td>
<td>15 (14.0)</td>
<td>28 (25.9)</td>
<td>27 (25.0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15 (14.0)</td>
<td>5 (4.6)</td>
<td>7 (6.5)</td>
</tr>
<tr>
<td>Digestive disorders</td>
<td>22 (20.6)</td>
<td>10 (9.3)</td>
<td>7 (6.5)</td>
</tr>
</tbody>
</table>

Adverse effects

ITP is a serious adverse effect and was experienced by 6 patients in the alemtuzumab group and one in the IFNB group. The reduced platelet count is caused by an autoimmune reaction and can lead to visible bleeding (purpura) as well as fatal blood loss. Approximately 23% of alemtuzumab-treated patients experienced autoimmune thyroid dysfunction, and about 6.5% of alemtuzumab-treated patients experienced Graves’ disease or hyperthyroidism. Infusion-related adverse events such as fever, rigors and nausea were frequently observed in alemtuzumab-treated patients, but pretreatment with ibuprofen reduced the events. Refer to Table IV for more adverse effects.
The place of alemtuzumab in therapy

Alemtuzumab shows to be effective in early stages of MS pathogenesis by blocking the inflammatory process. It compares favourably on frequency of administration as it is only given over 5 days in 12 months, then over 3 days after 12 months. Due to adverse effects, it is not advised as first line therapy, considering that MS mostly affects young people. It can however be an alternative to failed therapy or in patients who cannot tolerate other drugs.33,37

Other therapies under investigation

- Rituximab2,4,12,17
- Leflunomide /teriflunomide2,17
- Mycophenolate mofetil2,17
- Simvastatin2,12
- Salbutamol2
- Azithromycin, rifampicin, minocycline2
- Oestriol2
- Pioglitazone12
- Immunisation2
- Stem cell transplantation2

Unresolved issues on MS treatment

- There is considerable debate on the long-term effects of immunomodulators in MS, and also on when to start or stop treatment.3,15
- It is not clear when to start treatment as some patients have a benign course and it’s not worth early treatment, while if treatment is delayed, there may be neurological damage that cannot be reversed.11 The rate and pattern of progression cannot be predicted at initial presentation, thus it is difficult to identify patients with an unfavourable prognosis.12,15
- Most guidelines define active RRMS as experiencing at least 2 relapses in the past 2 years and patients with this presentation are eligible for treatment while they can still walk.14,18,19 However, the positive effects of interferon if initiated soon after a single demyelinating event suggestive of MS, was also demonstrated in a number of studies, e.g. the CHAMPS, ETOMS and BENEFIT studies.3,28 Early treatment with glatiramer acetate also resulted in a reduced conversion from clinically isolated syndrome (CIS) to clinically definite MS in the PRECISE trial.3 Some authors believe that this is not powerful evidence to treat CIS at the first opportunity,15,19 but emerging trends are to treat MS (or possible MS) early and aggressively. This approach will most likely eliminate relapses, but whether it will slow or prevent axonal degeneration and accumulation of disability, is the critical issue.27
- Before long-term treatment is implemented, patients need to be counselled about realistic objectives regarding adverse effects and efficacy. Overly optimistic expectations may complicate treatment.11 Criteria related to cessation of treatment should be discussed and agreed upon with the patient before initiating treatment.18
- While on treatment with these drugs, an increase in disability could occur and if significant disease progression takes place, the immunomodulators are generally not indicated.14,18,19
- There is huge controversy over the long-term effects of immunomodulators and whether they actually have an impact on disability.2,3,11,15 A significant benefit of interferons and glatiramer acetate on disease progression and disability has not been demonstrated.13,15
- Direct comparison between interferons are limited. Recent head to head trials failed to show superiority between interferons and do not show significant advantage in using higher doses.3
- Neutralising antibodies (Nabs) limit the effectiveness of IFNB as measured by MRI activity, relapses and disease progression, because Nabs reduce the bioavailability of interferon.11,17 Nabs develop more frequently with IFNB-1b than with IFNB-1a, but may disappear over time with both.2,27,38 The EFNS nevertheless regards Nabs as a major problem with IFNB treatment and recommends that therapy should be discontinued in patients with sustained high titers of these Nabs.38 Dangond states that the long-term clinical significance of Nabs is still unclear and controversial.3
- Comparisons between interferons and other immunomodulators are also sparse. The odds ratios of relapsing remitting MS patients to remain relapse-free after a 2-year period of treatment seem to be similar for IFNB-1a, IFNB-1b, glatiramer acetate, IVIG or azathioprine compared to placebo. Based on indirect comparison, a reduction in relapses of about 30% can be expected with each treatment.3,28
- Glatiramer acetate seems to have the safest adverse effect profile of the immunomodulators3 but long-term data is not yet available.17
- The efficacy and safety of natalizumab beyond 2 years are not known.3
- Safety of alemtuzumab and its role in the development of Graves’ disease must be addressed.2 Clearly, there is a need for treatment that would be more effective than first line agents, but less toxic than natalizumab, alemtuzumab and mitoxantrone.12
- High cost is a limiting factor as long-term treatment has incomplete evidence. The benefit of reducing the frequency and severity of attacks in MS is questionable as to whether it is increasing quality of life, a factor that is
difficult to measure. The NICE guidelines state that interferons and glatiramer acetate are the only disease-modifying treatment options available. However, due to cost-effectiveness issues, the use of these drugs is not recommended by NICE outside of its risk-sharing scheme or clinical trials. It has to be noted that these guidelines have not been updated since 2001/2002.

- Lastly, all the first-line disease-modifying therapies are injectables and are administered frequently. There is a need for drugs that can be given orally or less often in order to improve continuance, but with less toxicity or adverse effects.

Conclusion

Interferons evolved as the mainstay of MS treatment, especially with regards to relapse prevention. However, there is controversy over when to start treatment, as well as their long-term cost-effectiveness. These drugs are only partially effective and may not prevent progression of the disease.

Glatiramer acetate is an immunomodulator and has thus far shown a good safety profile, but long-term data is limited. Mitoxantrone is used in various subtypes of MS, but cardio-toxicity is a problem and the drug is only available abroad.

Novel treatments such as the monoclonal antibodies, alemtuzumab and natalizumab, have shown promising effects. Over a 3-year period, alemtuzumab is clearly more effective than IFNB-1a with regards to prevention of relapse and disability, but its role in ITP and the development of Graves’ disease must be addressed. Natalizumab unfortunately also has safety issues, such as PML.

Without a doubt, there is a need for treatment that would be more effective and convenient than first-line agents, but less toxic than mitoxantrone, natalizumab and alemtuzumab. With better understanding of MS pathogenesis and of which patients will benefit most from which agent, more successful treatment will hopefully be developed in the near future.

References