Biologics and Beyond: Treatment of Multiple Sclerosis

• Rita Jebrin, PharmD, BCPS
Disclosure Information

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Rita Jebrin, PharmD, BCPS

• I have no financial relationship to disclose.

AND

• I will not discuss off label use and/or investigational use in my presentation.

OR

• I will discuss the following off label use and/or investigational use in my presentation
Learning Objectives

• Describe relapsing-remitting and progressive Multiple Sclerosis (MS)
• Compare the available biological and some oral agents for treating MS
• Review the literature for ocrelizumab use in MS
What is Multiple Sclerosis

- Multiple sclerosis is a chronic, immune-mediated inflammatory demyelinating disease.

- Symptoms may be mild, such as numbness in the limbs, or severe, such as paralysis or loss of vision.
Multiple Sclerosis Diagnosis

• 2017 McDonald diagnostic criteria

• A process that involves:
  ➢ Clinical presentation
  ➢ MRI of the brain and spinal cord
    o Evidence of damage in at least two separate areas of the CNS
  ➢ Cerebrospinal fluid sample
    o Elevated levels of IgG index
    o Oligoclonal bands
    o Certain proteins that are the breakdown products of myelin
MS Lesions
Prevalence

- Affects 64.44 per 100,000 people in Abu Dhabi
- Most patients are diagnosed between the ages of 20 and 50
- Two thirds are women
- More frequently found among people raised in colder climates

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency (n = 284)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>94</td>
<td>33.1</td>
</tr>
<tr>
<td>Female</td>
<td>190</td>
<td>66.9</td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dubai Natives</td>
<td>158</td>
<td>55.6</td>
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<tr>
<td>Immigrants</td>
<td>126</td>
<td>44.4</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16–28 years</td>
<td>84</td>
<td>29.6</td>
</tr>
<tr>
<td>29–35 years</td>
<td>87</td>
<td>30.6</td>
</tr>
<tr>
<td>36–42 years</td>
<td>53</td>
<td>18.7</td>
</tr>
<tr>
<td>43–74 years</td>
<td>60</td>
<td>21.1</td>
</tr>
</tbody>
</table>
**Risk Factors**

- **Genetic**: 2-3% increase chance
- **Lack of sunlight and vitamin D**: more common in countries far from the equator
- **Smoking**: 2X increased risk
- **Viral infections**: Epstein-Barr virus
MS Disease Courses

RRMS

Disability

Time

SPMS

Disability

Time

PPMS

Disability

Time

PRMS

Disability

Time
# MS Disease Modifying Agents

## MS Treatment Options

### INJECTABLE
- Glatiramer acetate (Copaxone®)
- Interferon beta-1a (Avonex®, Plegridy™, Rebif®)
- Interferon beta-1b (Betaseron® and Extavia®)

### ORAL
- Dimethyl fumarate (Tecfidera™)
- Fingolimod (Gilenya™)
- Teriflunomide (Aubagio®)
  - Cladribine (Mavenclad®)

### INFUSION
- Alemtuzumab (Lemtrada™)
- Natalizumab (Tysabri®)
- Ocrelizumab (Ocrevus®)
Finoglimod (Gilenya™)

Mechanism of action: retains lymphocytes in the lymph nodes, thereby preventing those cells from crossing the blood-brain barrier into the central nervous system (CNS) and subsequently preventing inflammation.

Dose: 0.5 mg capsules once daily

Annual Relapse Rate (ARR) decreased by 48%–55%

Common side effects: upper respiratory tract infection, headache, diarrhea and back pain.

Monitoring: ECG for 6 h after the first dose due to transient bradycardia and atrioventricular block.
Cladribine (Mavenclad®)

- Treatment of **highly active relapsing MS**

- **Mechanism of action**: reduces CD4+ and CD8+ cells with reduction in proinflammatory cytokines and serum and cerebrospinal fluid chemokines

- **Dose**: 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year

- Compared to interferon β, the proportion of relapse-free patients was 86% with cladribine vs. 70% with interferon β

- **Common side effects**: infections and malignancies
Disease Modifying Agents
Biological Agents
Mechanism of Action

![Mechanism of Action Diagram](image-url)
Recommendations for Disease Modifying Therapy (DMT)

- **Therapy initiation:** single clinical demyelinating event with ≥ 2 brain lesions consistent with MS (Isolated clinical syndrome)

- **MS with highly active disease:** alemtuzumab, fingolimod, and natalizumab showed a reduction in relapses and MRI measures

- Ocrelizumab is the only DMT that alters disease progression in individuals with primary progressive MS (PPMS)
Natalizumab (Tysabri®)

- Treatment of relapsing-remitting MS

- **Mechanism of action:** Humanized monoclonal IgG4 antibody that selectively binds to the 4-integrin component of adhesion molecules found on lymphocytes, monocytes, and eosinophils

- **Dose:** 300 mg intravenously every 4 weeks

- **ARR** dropped by 68%

- Increases the risk of progressive multifocal leukoencephalopathy (PML)
Alemtuzumab (Lemtrada®)

- Used in the treatment of **relapsing-remitting** MS
- Mechanism of action: depletion of CD52-expressing T cells, B cells, natural killer cells, and monocytes
- **CARE-MS**: compared to interferon beta-1a, alemtuzumab had significantly fewer new enhancing lesions
- Associated with an increased risk of secondary autoimmunity and serious infections
Treatment Dose

• Course 1: 12 mg/day on 5 consecutive days

• Course 2: 12 mg/day on 3 consecutive days, 12 months later
Ocrelizumab (Ocrevus®)

- Used for the treatment of relapsing-remitting and **primary progressive MS**
- Mechanism of action: anti-CD20 monoclonal antibody that targets mature B lymphocytes

**Dosing Schedule**

- **Initial dose:** 300 mg
- 2 weeks later: **300 mg**
- **Subsequent doses:** 600 mg every 6 months
Ocrelizumab Side Effects

Most Common:

- Rash and itching
- Flu-like symptoms (headache, fatigue, low grade fever, chills)
- Sore throat (itchy, scratchy throat)
- Achy joints within hours of the infusion
- More frequent upper respiratory tract infections
# Ocrelizumab Trial

**Objective**  
Evaluate the Efficacy of Ocrelizumab for Primary Progressive MS

<table>
<thead>
<tr>
<th>Patient population</th>
<th>N=732 patients with <strong>primary progressive</strong> multiple sclerosis</th>
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<tbody>
<tr>
<td>Method</td>
<td>Intravenous ocrelizumab (600 mg) or placebo every 24 weeks for at least 120 weeks</td>
</tr>
<tr>
<td>Primary End Point</td>
<td>Percentage of patients with disability progression confirmed at 12 weeks</td>
</tr>
<tr>
<td>Secondary End Point</td>
<td></td>
</tr>
</tbody>
</table>
  - Percentage of patients with disability progression confirmed at 24 weeks  
  - Change in performance  
  - Change in the total volume of brain lesions  
  - Change in brain volume  
  - Change in the Physical Component Summary score of the Medical Outcomes  

Ocrelizumab Trial

12-Wk Confirmed Disability Progression

Hazard ratio, 0.76 (95% CI, 0.59–0.98)
P=0.03

Cumulative Probability of Confirmed Progression (%)

No. at Risk
Placebo: 244 232 212 199 189 180 172 162 153 145 136 120 85 66 46 30 20 7 2
Ocrelizumab: 487 462 450 431 414 391 376 355 338 319 304 281 207 166 136 80 47 20 7

Week
## Cost of MS Medications at CCAD

<table>
<thead>
<tr>
<th>Infusion Therapy</th>
<th>Price per Vial</th>
<th>Price for Treatment Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>38,000 AED/12,000 mg Vial</td>
<td>190,000 AED</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>28,000 AED/300 mg Vial</td>
<td>112,000 AED</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>9,000 AED/300 mg Vial</td>
<td>117,000 AED</td>
</tr>
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Updates in Multiple Sclerosis

• Daclizumab (ZINBRYTA) was removed from the market due to serious adverse events after FDA approval was received

• Ofatumumab (Arzerra®) is under development

• Ublituximab (TG-1101) is under development
Conclusion

• Multiple sclerosis is a disabling disease that can lead to lower quality of life if not approached in the early phases

• Pharmacists play a vital role in counseling patients on the available treatment options for MS and their safety profiles

• Ocrelizumab is the sole DMT agent for the treatment of primary progressive MS
References


• Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis. AUGranqvist M, Boremalm M, Poorghobad A, Svenningsson A, Salzer J, Frisell T, Piehl F SOJAMA Neurol. 2018;75(3):320