Disease Modifying Drugs in Multiple Sclerosis: New Treatment Algorithm

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Disclosures

• I have received honoraria for lectures from Biogen, Novartis and Merck
Contents

• Overview about multiple sclerosis (MS)

• Introduction to MS therapies

• Pharmacology in MS

• First-line disease modifying drugs (DMDs)

• Second-line disease modifying drugs (DMDs)

• New treatment algorithm
Multiple Sclerosis is the most common neurological disorder in young Caucasian adults\(^1\)

- MS is a chronic autoimmune disease of the CNS
- MS affects up to 2.5 million people worldwide\(^1\)
- Caucasians are at greater risk\(^2\)
  - 60 to 140 per 100,000 for Northern EU, USA, Canada, Australia and New Zealand
  - up to 20 per 100,000 in Central and South America
  - 5 per 100,000 in Asia
- Women are up to three times as likely to develop MS as men\(^3\)
- MS generally affects people in the prime of their life – onset typically begins between 20 to 40 years of age\(^4,5\)

Global prevalence of MS per 100,000 population\(^2\)

CNS, central nervous system; MS, Multiple Sclerosis
Epidemiology of MS in Lebanon

- No formal epidemiological study is available in Lebanon to determine the exact prevalence and incidence of MS.

- It is estimated, according to different governmental agencies covering MS therapies, that around 1300-1400 Lebanese patients are currently under treatment and that they account for around two thirds of the total number of MS patients in Lebanon which are estimated to be around 2000 patients.

- With a Lebanese population of around 4.2 million according to the WHO report in 2009, an approximate prevalence of MS in Lebanon would be around 40-45 per 100,000.
MS Pathogenesis

Genetic background: Both HLA and non-HLA genes

autoreactive T - cells

Demyelination-Axonal degeneration

- Release of cytokines
- Recruitment of MΦ
- NO
- IFN-γ
- TNF-α

- Antibodies
- Adhesion
- Transmigration
- Local reactivation
- Activation, differentiation, clonal expansion

Trigger-
Vit D
Smoking
EBV
Obesity - BMI
Multiple Sclerosis: Three Components

Inflammation

Demyelination

Axonal Loss

Potential Triggers for MS

- Infectious agent
- Genetic predisposition
- Environmental

Abnormal immunologic response → MS
Four multiple sclerosis subtypes have been identified, based on the clinical disease course.

- **Relapsing–remitting (40 to 50%)**: Acute relapses with full or partial recovery; stable in between.
- **Secondary progressive (30 to 40%)**: Begins with relapsing–remitting, followed by progression with or without relapses.
- **Primary progressive (10 to 15%)**: Progression from onset, no relapses, continuous or stepwise progression.
- **Progressive relapsing (<5%)**: Progression from onset with few relapses.
Clinical Symptoms

- **Optic nerve**
  - Visual disturbance

- **Brainstem**
  - Speech disorders
  - Difficulties in swallowing
  - Double vision

- **Cerebrum**
  - Fatigue
  - Reduced concentration

- **Cerebellum**
  - Speech disorders
  - Coordination disorders
  - Tremor, vertigo

- **Spinal cord**
  - Sensory dysfunction
  - Tension
  - Muscle stiffness
  - Intestinal and bladder disorders
  - Sexual disorders
MS is a disabling disease (diagnosis between 25 and 35)

10 Years*

Progressive MS

25 Years*

Requiring a Cane

30 Years*

Confined to Wheelchair

*mean time for development
The Treatment of MS

• No known cure for MS at this time
  • Therapies that may slow disease

• Starting treatment early
  • One of the important factors in managing MS
  • Better chances of minimizing nerve damage and halting progression

• Evidence supports the need for early treatment
  • CNS damage occurs very early even before symptoms appear
  • May shorten length and decrease severity of exacerbations
  • May also modify the disease course
  • Can extend remissions
Goals of Therapy

- To modify the disease course by
  - Reducing the number and severity of relapses
  - Reducing accumulation of lesions
  - Slowing the progression of disability

- To treat relapses on a short-term as-needed basis
  - Relieving symptoms and ameliorating risk factors associated with an acute exacerbation
  - No proven impact on disease activity

- To manage symptoms associated with the disease
  - Several drugs to alleviate fatigue, tremor, pain, spasticity, stiffness, urinary problems, depression, etc.
  - No direct impact on disease activity
Current and Future MS Therapies

**ORAL THERAPIES**
- Fingolimod
- Teriflunomide
- Laquinimod*
- Azathioprine†
- Beta-interferons
- Natalizumab
- Glatiramer acetate
- Mitoxantrone¶

**IV, IM, SC THERAPIES**
- Alemtuzumab
- Ocrelizumab§
- Daclizumab§
- PEG IFNβ§

Dates are approximate as approval dates vary between different countries; for drugs beyond 2014, approval dates are estimated, based on current regulatory status. *Not yet approved by the FDA; negative opinion adopted by CHMP in January 2014, opinion being re-examined as of 21 February 2014. †Not currently approved by the EMA or FDA. ‡Approved by the EMA, rejected by the FDA in December 2013. §Not yet approved by FDA or EMA. ¶Not currently approved by the EMA.

Product labelling (including indications, safety information and monitoring requirements) may vary by country; for more detailed information, refer to your local prescribing information for recommendations and contraindications for each DMT.
Pharmacology in Multiple Sclerosis
Many Immune Cell Types Contribute to Damage in MS

Proinflammatory cytokines
Chemokines
Proteases and histamines
Reactive nitrogen/oxygen species
Cytotoxic granules

Different DMDs Unlocking Various Pathways

**Pleiotropic Effects**

- **IFNs**
  - Activation of 100+ IFN-response genes

- **Dimethyl fumarate**
  - Activation of 700+ nrf2 responsive genes and HCAR2

- **Glatiramer acetate**
  - Modulation of Th1:Th2 balance
  - Activation of 700+ nrf2 responsive genes and HCAR2

- **Teriflunomide**
  - Limits pyrimidine availability for rapid cell division

**Targeted Cell Lysis**

- **Alemtuzumab**
  - Lysis of immune cells including mature T and B lymphocytes

- **Ocrelizumab/Rituximab**
  - Lysis of B lymphocytes

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All mechanisms of action shown here are only proposed mechanisms, based on currently available best evidence. BBB, blood–brain barrier; HCAR2, hydroxycarboxylic acid receptor 2; NK, natural killer cell; nrf2, nuclear factor (erythroid-derived 2)-like 2; S1P1, sphingosine-1-phosphate receptor; Th, T-helper cell; CD, cluster of differentiation; CNS, central nervous system; IL interleukin.

Different DMDs Unlocking Various Pathways

**Anti-Migratory**
- **Fingolimod**
  - Decreased IL-2 use by T cells
  - Increased available IL-2
- **Natalizumab**
  - 
  - S1P1
  - Periphery
  - BBB

**Expanding Regulatory Cells**
- **Daclizumab**
  - Decreased IL-2 use by T cells
  - Increased available IL-2
  - Expansion of immunoregulatory CD56bright NK cells

All mechanisms of action shown here are only proposed mechanisms, based on currently available best evidence. BBB, blood–brain barrier; HCAR2, hydroxycarboxylic acid receptor 2; NK, natural killer cell; nrf 2, nuclear factor (erythroid-derived 2)-like 2; S1P1, sphingosine-1-phosphate receptor; Th, T-helper cell; CD, cluster of differentiation; CNS, central nervous system; IL interleukin.

First-line Therapies
Interferons and Glatiramer Acetate

- All FDA approved for the treatment of relapsing-remitting MS
- Injection Frequency and Route of Administration of DMTs

IFNβ-1a
Once-a-week
IM injection

IFNβ-1a
3x/week
SC injection

IFNβ-1b
Every-other-day
SC injection

Glatiramer acetate
qd SC injection

Days of month

1 14 28
Safety, Tolerability and Monitoring

• Minimizing flu-like symptoms
  - Gradual dose escalation
  - Co-medication with ibuprofen or acetaminophen
  - Evening administration
  - Reassurance that symptoms usually diminish over a few months

• Injection-site reactions
  - Optimum training
  - Clean injection technique
  - Site rotation
  - Dry needle
  - Injection at 90 degrees
  - Use of autoinjector
  - Gentle message
  - Use of warm/cool gel packs

• Safety Monitoring
  - CBC with differential
    - At baseline, 1 month, then Q3 months for 1 year and Q6 months thereafter

  - LFTs
    - At baseline, 1 month, then Q3 months for 1 year and Q6 months thereafter

  - TSH
    - Every 6 months in patients with a history of thyroid dysfunction
    - Once yearly or in case of weight loss/gain without any change in diet or physical activity
Teriflunomide selectively and reversibly inhibits DHODH, a key mitochondrial enzyme in de novo pyrimidine synthesis required by rapidly dividing B and T cells\textsuperscript{1,2}.

Through this cytostatic effect, teriflunomide has the potential to limit over-activation of the immune responses that can contribute to MS disease activity\textsuperscript{1,2}.

Protective immunity is not compromised by teriflunomide\textsuperscript{3}.

In preclinical studies, teriflunomide was not genotoxic, mutagenic, or clastogenic\textsuperscript{4}.

The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood.

Teriflunomide is the principal active metabolite of leflunomide (70% conversion)

- Leflunomide is FDA-approved in adults for the treatment of active rheumatoid arthritis: nearly 2.3 million patient-years of use with long-term safety data

**Teriflunomide Adverse Events Profile**

**Table 3. Adverse Events.**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N = 360)</th>
<th>Teriflunomide, 7mg (N = 368)</th>
<th>Teriflunomide, 14 mg (N = 358)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one adverse event</td>
<td>315 (87.5)</td>
<td>328 (89.1)</td>
<td>325 (90.8)</td>
</tr>
<tr>
<td>Any adverse event leading to discontinuation of study medication</td>
<td>29 (8.1)</td>
<td>36 (9.8)</td>
<td>39 (10.9)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>46 (12.8)</td>
<td>52 (14.1)</td>
<td>57 (15.9)</td>
</tr>
<tr>
<td>Any event leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Most common adverse events †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>98 (27.2)</td>
<td>94 (25.5)</td>
<td>93 (26.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>64 (17.8)</td>
<td>81 (22.0)</td>
<td>67 (18.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32 (8.9)</td>
<td>54 (14.7)</td>
<td>64 (17.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51 (14.2)</td>
<td>47 (12.8)</td>
<td>52 (14.5)</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase level ‡</td>
<td>24 (6.7)</td>
<td>44 (12.0)</td>
<td>51 (14.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (7.2)</td>
<td>33 (9.0)</td>
<td>49 (13.7)</td>
</tr>
<tr>
<td>Hair thinning or decreased hair density</td>
<td>12 (3.3)</td>
<td>38 (10.3)</td>
<td>47 (13.1)</td>
</tr>
<tr>
<td>Influenza</td>
<td>36 (10.0)</td>
<td>34 (9.2)</td>
<td>43 (12.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>47 (13.1)</td>
<td>39 (10.6)</td>
<td>41 (11.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>35 (9.7)</td>
<td>27 (7.3)</td>
<td>37 (10.3)</td>
</tr>
<tr>
<td>Pain in arms or legs</td>
<td>47 (13.1)</td>
<td>26 (7.1)</td>
<td>33 (9.2)</td>
</tr>
</tbody>
</table>

- CBC and LFTs at baseline, at 3-month and Q6months
- Screen patients for latent tuberculosis infection with tuberculin skin test
Dimethyl Fumarate: A Twice-Daily Oral Immunomodulator approved for the treatment of RRMS

DMF/MMF Activate Both Anti-Oxidant and Anti-Inflammatory Responses Through Activation of Nrf2

- Availability of long-term safety data distinguishes BG-12 from other new MS therapies.
- Fumaderm has been registered for treatment of psoriasis since 1994, with no serious adverse events reported until recently.

### Common Adverse Events

<table>
<thead>
<tr>
<th>AE, % (n)</th>
<th>Placebo (n=408)</th>
<th>BG-12 240 mg BID (n=410)</th>
<th>BG-12 240 mg TID (n=416)</th>
<th>Total BG-12 (N=826)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued study drug</td>
<td>55 (13)</td>
<td>65 (16)</td>
<td>68 (16)</td>
<td>133 (16)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (&lt;1)</td>
<td>10 (2)</td>
<td>6 (1)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>MS relapse</td>
<td>31 (8)</td>
<td>5 (1)</td>
<td>10 (2)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (&lt;1)</td>
<td>5 (1)</td>
<td>8 (2)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>1 (&lt;1)</td>
<td>5 (1)</td>
<td>6 (1)</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>5 (1)</td>
<td>6 (1)</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>5 (1)</td>
<td>6 (1)</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Abdominal pain lower</td>
<td>0</td>
<td>3 (&lt;1)</td>
<td>7 (2)</td>
<td>10 (1)</td>
</tr>
</tbody>
</table>

Selmaj K et al. Presented at ECTRIMS; October 10–13, 2012; Lyon, France. P484.
Second-line Therapies
Once-Daily Oral fingolimod prevents lymphocyte to egress from lymph nodes

Oral fingolimod
Autoaggressive lymphocytes remain in the lymph nodes, away from the CNS

Oral fingolimod down-modulates S1P1 receptor
lymphocytes are unable to egress

CNS, central nervous system; S1P, sphingosine 1-phosphate
Fingolimod Adverse Events Profile

- Transient, usually asymptomatic, **bradycardia** associated with first dose: < 40 bpm in 24% of males and 8% of females

- < 5% **AV block** associated with first dose: 1% for 20-50 year olds and 8% for 50-80 year olds

- Mild increase (2-3 mm Hg) in **blood pressure**

- <1% reversible **macular edema** usually within first 3 months

- Few cases of cancer – numbers too small to determine causality

- Asymptomatic, reversible increases in liver enzymes

- Possible increase in risk of certain viral infections, particularly herpes virus

- Two fatal **herpes virus infections** on high dose
Safety Monitoring of Fingolimod

• **Baseline Tests**
  - CBC
  - Liver function tests and bilirubin levels
  - Varicella Zoster antibodies
  - Ophthalmic exam
  - EKG
  - Pregnancy test
  - CBC, LFTs, bilirubin levels at 1-month, 3-month then every 3 month
  - Ophthalmic exam at 3-month of therapy

• **First Dose**
  - Patients vital signs (blood pressure and heart rate) should be monitored for 6 hours after the first oral dose is administered to detect any decrease in heart rate
  - If a patient interrupts fingolimod therapy for > 2 weeks and then resume treatment, monitoring of vital signs for 6 hours is again necessary
Natalizumab: a Humanized Monoclonal Antibody that Could Intervene at Multiple Points in the Inflammatory Process

- Given intravenously (IV) over 60 minutes
- 300mg every 4 weeks
- ONLY given by physicians and infusion centers under a special restricted management program

1. Leukocyte migration from blood to tissue
2. Leukocyte priming and activation
3. Modulation of leukocyte apoptosis
Natalizumab Adverse Events

• Allergic reaction
  - Typically occur within 2 hours of infusion
  - Dizziness, fever, rash, nausea, low blood pressure, difficulty breathing

• Headache, fatigue, joint pain

• Depression

• Increase risk of infections
  - Urinary tract infections
  - Lower respiratory infections

• Increase risk of PML

• Liver abnormalities

• Irregular or loss of menstrual cycle
Risk of PML in Natalizumab

• **Progressive multifocal leukoencephalopathy (PML)**
  - Estimated risk ~ 2:1000
  - 207 PML cases with 44 deaths out of 98,000 patients treated worldwide as of February 2012
  - 3 major risk factors for PML:
    • Duration of treatment: > 2 years
    • Prior treatment with immunosuppressive agents
    • Positive serum JC virus antibodies

- Available **ONLY** under a special restricted distribution program – Risk management program: TOUCH Prescribing Program

*In clinical practice generally used as second line or in aggressive RRMS*

Alemtuzumab Proposed Mechanism of Action: Targeting of T and B cells

- Alemtuzumab is a monoclonal antibody directed at the CD52 surface antigen expressed highly on T and B lymphocytes\(^1,3\)
- Innate immune cells that express lower levels of CD52 are minimally or transiently impacted by alemtuzumab treatment\(^1,3\)

The mechanism by which alemtuzumab exerts its therapeutic effects in MS is not fully elucidated

Alemtuzumab Labels

• **FDA label:**
  Alemtuzumab is a CD52-directed cytolytic monoclonal antibody indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

• **EMA label:**
  Alemtuzumab is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.
### Alemtuzumab Safety Profile

- A total of 1486 patients have been treated with alemtuzumab in the phase II, III trials and the extension study, representing 6740 total patient-years of follow up\(^1\)-\(^3\)

<table>
<thead>
<tr>
<th>Identified Risks</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-associated reactions (IARs)(^2)</td>
<td>• The most common adverse event were mild-to-moderate IARs, which were manageable with appropriate pretreatment and symptomatic treatment</td>
</tr>
<tr>
<td>Infections(^3)-(^5)</td>
<td>• Infections were common with LEMTRADA treatment; most were predominantly mild to moderate and responded to conventional treatment</td>
</tr>
<tr>
<td>Autoimmune AEs(^1),(^6),(^7)</td>
<td>• A comprehensive monitoring programme was implemented for early detection of autoimmune AEs</td>
</tr>
<tr>
<td>Thyroid disorders(^6)</td>
<td>• Protocol-specified safety monitoring and education allowed for early detection and effective management of thyroid AEs</td>
</tr>
<tr>
<td>Immune thrombocytopenia (ITP)(^1)</td>
<td>• Most patients responded to first-line therapy and some ITP events were self-limiting</td>
</tr>
<tr>
<td>Nephropathy(^7)</td>
<td>• Glomerulonephritis was rare and all cases in the MS clinical programme were detected by the safety monitoring programme with good clinical outcomes</td>
</tr>
</tbody>
</table>

\(^*\)December 31, 2013 cut-off.

## Alemtuzumab Monitoring Program

### Monitoring: Recommended laboratory tests

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test</th>
<th>Prior to treatment</th>
<th>Every month</th>
<th>Every 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune thrombocytopenic purpura (ITP)</td>
<td>Complete blood count with differential</td>
<td>☒</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>Nephropathies, including anti-GBM disease</td>
<td>Serum creatinine levels</td>
<td>☒</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinalysis with microscopy</td>
<td>☒</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>Thyroid function, such as TSH levels</td>
<td>☒</td>
<td></td>
<td>☒</td>
</tr>
</tbody>
</table>

- Remind patients to be vigilant for **symptoms** of autoimmunity, seek immediate medical help for concerns
- Following **48-month** period after last infusion, base testing on clinical findings suggestive of autoimmunity

Monitoring for 48 months helps ensure that benefits of therapy outweigh risks, detect early signs of autoimmunity
B Cells in the Pathophysiology of MS

Antigen presentation[a,b]

T cell

CD20⁺ B cell

Cytokine production[b,c]

Autoantibody production[d]

Ectopic lymphoid follicle-like aggregates[c,d]

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Ocrelizumab: Selective Depletion of CD20+ B cells

FDA label of Ocrelizumab

“Ocrelizumab is a CD20-directed cytolytic antibody indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis”
## Ocrelizumab: Adverse Events over 96 Weeks

<table>
<thead>
<tr>
<th>N (%)</th>
<th>IFNβ-1a 44 µg (n=826)</th>
<th>Ocrelizumab 600 mg (n=825)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of patients with ≥1 AE</strong></td>
<td>688 (83.3)</td>
<td>687 (83.3)</td>
</tr>
<tr>
<td><strong>IRRs</strong></td>
<td>80 (9.7)</td>
<td>283 (34.3)</td>
</tr>
<tr>
<td><strong>General disorders and administration-site conditions</strong></td>
<td>396 (47.9)</td>
<td>173 (21.0)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>177 (21.4)</td>
<td>38 (4.6)</td>
</tr>
<tr>
<td>Injection-site erythema</td>
<td>127 (15.4)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>45 (5.4)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td>433 (52.4)</td>
<td>482 (58.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>87 (10.5)</td>
<td>125 (15.2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>84 (10.2)</td>
<td>122 (14.8)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>29 (3.5)</td>
<td>42 (5.1)</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td>IFNβ-1a 44 µg (n=826)</td>
<td>Ocrelizumab 600 mg (n=825)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>252 (30.5)</td>
<td>224 (27.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>124 (15.0)</td>
<td>93 (11.3)</td>
</tr>
<tr>
<td><strong>Malignancies</strong></td>
<td>2 (0.2)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>MCL</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>SCC</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Renal cancer</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
</tr>
</tbody>
</table>

Hauser et al. ECTRIMS 2015 Abstract 190
Ocrelizumab: Serious Adverse Events reported ≥ 1% of Patients

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Placebo (n=239)</th>
<th>Ocrelizumab 600 mg (n=486)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patients with ≥1 SAE</td>
<td>53 (22.2)</td>
<td>99 (20.4)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>14 (5.9)</td>
<td>30 (6.2)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>9 (3.8)</td>
<td>18 (3.7)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>3 (1.3)</td>
<td>10 (2.1)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>6 (2.5)</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>General disorders and administration-site conditions</td>
<td>3 (1.3)</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3 (1.3)</td>
<td>5 (1.0)</td>
</tr>
</tbody>
</table>

- Thirteen malignancies were reported:
  - 2 (0.8%) in the placebo arm: 1 cervix adenocarcinoma in situ and 1 basal cell carcinoma
  - 11 (2.3%) in the ocrelizumab arm: 4 breast cancers, 1 endometrial adenocarcinoma, 1 anaplastic lymphoma, 1 histiocytoma, 1 metastatic pancreas cancer, and 3 basal cell carcinomas

Montalban et al. NEJM 2017; 376:209-220
New Treatment Algorithm
New MENACTRIMS Algorithm for the Treatment of MS

Non-aggressive RRMS patients

IFN B
GA*
Ter
DMF

Patients with contraindications or AE to IFN-B, GA, TER, DMF

Fingolimod

Agressive RRMS patients

≥ 2 disabling relapses in past year AND active MRI

Fingolimod, Natalizumab Alemtuzumab
Ocrelizumab
(Based on risk stratification)

Suboptimal Response: Consider Therapy Escalation

Fingolimod, Natalizumab Alemtuzumab
Ocrelizumab
(Based on risk stratification)

Natalizumab Alemtuzumab
Ocrelizumab
(Based on risk stratification)

Fingolimod, Natalizumab Alemtuzumab
Ocrelizumab
(Based on risk stratification)

Suboptimal Response: Consider Therapy Escalation

Rescue Therapy: Rituximab – Cyclophosphamide – Mitoxantrone – Autologous hematopoietic stem cell transplantation
Optimizing MS Outcomes: A Stepwise Approach

- “Treat early”
- “Understand available DMTs”
- “Choose treatments individually”
- “Monitor vigilantly”
- “Switch confidently”

Yes

- MS prognosis
- Lifestyle and goals
- Shared goals for therapy
- Patient’s preferences?
- Your choice?
- Potential future impact of chosen therapy?

No

- Evidence of disease activity?
- Tolerability/safety?
- Adherence?
- Inhibitory markers?

**Individual measures:**

- Evidence of disease activity?
- Tolerability/safety?
- Adherence?
- Inhibitory markers?