Relapsing Remitting Multiple Sclerosis: Treatment Update

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Outline

- Why should we treat MS
- Rational for early treatment goals
- Treatment consideration in clinical practice
- DMT overview

The Natural Course of Relapsing-Remitting MS

Despite treatment, approximately one quarter (21-27%) of patients worsened by 2.5 point on the EDSS within 2 years.

Optimize Therapy Before Disability Accumulates

DMT overview

Does Early Treatment of Patients With CIS Delay Development of CDMS?

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment (vs Placebo)</th>
<th>Conversion to CDMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-Up</td>
<td>On Therapy</td>
<td>Placebo</td>
</tr>
<tr>
<td>CHAMPS</td>
<td>Placebo 30 mg IV q4W</td>
<td>3 years</td>
</tr>
<tr>
<td>B10MS</td>
<td>Placebo 44 mg 125 D2/Q2</td>
<td>2 years</td>
</tr>
<tr>
<td>BENEFIT</td>
<td>Placebo 250 mg 2G every other</td>
<td>2 years</td>
</tr>
<tr>
<td>PRO-16</td>
<td>Placebo 20 mg 12G/D</td>
<td>2 years</td>
</tr>
<tr>
<td>MT-816</td>
<td>Placebo 44 mg 125 D2/Q2</td>
<td>2 years</td>
</tr>
<tr>
<td>TOPIC</td>
<td>Placebo 1 mg OD</td>
<td>2 years</td>
</tr>
</tbody>
</table>

Note: CHAMPS Placebo 30 mg IV q4W; B10MS Placebo 44 mg 125 D2/Q2; BENEFIT Placebo 250 mg 2G every other; PRO-16 Placebo 20 mg 12G/D; MT-816 Placebo 44 mg 125 D2/Q2; TOPIC Placebo 1 mg OD.
Current Standard Treatment Outcomes In MS

▪ Reduce relapses; extend time b/w relapses
▪ Reduce severity of relapse
▪ Prevent or reduce the number (lesion burden), size of new lesions on MRI in order to prevent axonal damage in central nervous system (CNS) and mitigate brain atrophy.
▪ Prevent or extend the time to onset of secondary progressive stage
▪ Extend time during which there is no evidence of disease activity (NEDA)

NEDA in Clinical Studies

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>Study Duration, y</th>
<th>Patients With NEDA Status, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE</td>
<td>1</td>
<td>Placebo, 15%; pegylated interferon-beta-1a every 2 weeks, 34%</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>1</td>
<td>Placebo, 15%; natalizumab, 47%</td>
</tr>
<tr>
<td>SELECT</td>
<td>1</td>
<td>Placebo, 11%; dimethyl fumarate, 39%</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>2</td>
<td>Placebo, 7%; natalizumab, 27%</td>
</tr>
<tr>
<td>CARE-MS I</td>
<td>2</td>
<td>SC interferon-beta-1a, 27%; alemtuzumab, 39%</td>
</tr>
<tr>
<td>CARE-MS II</td>
<td>2</td>
<td>SC interferon-beta-1a, 13%; alemtuzumab, 32%</td>
</tr>
<tr>
<td>CLARITY</td>
<td>2</td>
<td>Placebo, 16%; cladribine, 46%</td>
</tr>
<tr>
<td>CLIMB</td>
<td>2</td>
<td>Early MS, 24%; established MS, 33%</td>
</tr>
<tr>
<td>FREEDOMS</td>
<td>2</td>
<td>Placebo, 13%; fingolimod, 33%</td>
</tr>
<tr>
<td>DEFINE</td>
<td>2</td>
<td>Placebo, 15%; dimethyl fumarate, 28%</td>
</tr>
<tr>
<td>Consalo</td>
<td>3</td>
<td>IM interferon-beta-1a alone, 31%; glatiramer acetate alone, 19%; glatiramer acetate and IFN-beta-1a, 31%</td>
</tr>
<tr>
<td>CLIMB</td>
<td>7</td>
<td>Early MS, 46%; established MS, 10%</td>
</tr>
</tbody>
</table>

Choosing the Optimal Individualized Treatment Regimen

▪ Patient factors
▪ Disease factors
▪ Drug factors

NEDA-4

▪ No relapse
▪ No disability progression
▪ No MRI activity
▪ Annualized Brain volume loss less than/equal to 0.4

Therapy selection: Factors to Consider
Identifying Active and Aggressive Disease

**Clinical Factors**
- Male gender
- Older age of onset
- African American/Hispanic
- Onset with disabling symptoms; cerebellar and spinal cord disease
- Poor recovery from relapses
- Multifocal involvement at onset
- Early cognitive dysfunction

**Paraclinical Factors**
- High MRI lesion burden at presentation
- New T2 lesions in the first year of symptom onset
- Brainstem, Cerebellum or Spinal Cord lesions
- Brain/spinal cord atrophy

Neurofilament Light Protein

- Proposed biomarker for MS disease activity
- Structural component of neurons and axons
- Released in CSF after axonal injury
- Elevated during relapse or active lesion
- Levels decrease with effective DMT
- Initial level in CSF may predict disease course
- Studies have shown that it can be detected in serum and it does correlate to CSF levels

FDA Approved disease modifying agents

**Indication:**
- Relapsing Remitting MS (RRMS)
- Clinically Isolated Syndrome (CIS) with high probability to develop clinical definitive MS
- Active Secondary Progressive MS (SPMS)
- Primary Progressive MS (PPMS)

Cells, Molecules, and Therapies.

Injectable | Oral | Intravenous
---|---|---
Avonex (interferon beta-1a) | Aubagio (teriflunomide) | Ocrevus (ocrelizumab)
Plegridy (pegylated interferon-1a) | Tecfidora (dimethyl fumarate) | Tysabri (natalizumab)
Betaseron [interferon beta-1b] | Vumerity (diroximel fumarate) | Lambrada (alemtuzumab)
Extavia (interferon beta-1b) | Bapiertam (monomethyl fumarate) | Novantrone (mitoxantrone)
Reolif (interferon beta 1a) | Gilenya (fingolimod) | Betaseron (interferon beta-1b)
Copaxone (glatiramer acetate) | Mayzent (siponimod) | Kesimpta (ofatumumab)
Glatopa (glatiramer acetate) | Zeposia (ozanimod) | Mavenclad (cladribine)
Kesimpta (ofatumumab) | Nofizzit (natalizumab) | Feltista (copaxone)
### Types of DMTs by Effects to Immune System

<table>
<thead>
<tr>
<th>Type</th>
<th>Approved Therapies</th>
<th>Emerging Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunomodulation</strong></td>
<td>IFNs, glatiramer acetate, dimethyl fumarate, diroximel fumarate, monomethyl fumarate, teriflunomide</td>
<td>NA</td>
</tr>
<tr>
<td><strong>General</strong> Imunosuppression</td>
<td>Mitoxantrone,</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Immune-selective blockade</strong></td>
<td>Natalizumab</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Immune-selective-sequestering</strong></td>
<td>Fingolimod, SIRONIMOD, Ozanimod</td>
<td>Ponemod, Oponesimod</td>
</tr>
<tr>
<td><strong>Immune-selective-depleting</strong></td>
<td>Alemtuzumab, Ofatumumab, Ublituximab</td>
<td></td>
</tr>
</tbody>
</table>

### DMT Overview

**Interferons (beta 1a, beta 1b, pegylated)**
(Avonex, Rebif/Extavla, Betaseron, Plegridy)

<table>
<thead>
<tr>
<th>MOA</th>
<th>Effects on immune cells and mediators</th>
<th>Safety issues</th>
</tr>
</thead>
</table>
| • Activation of IFN on leukocytes                                    | • ↓ migration of inflammatory cells through the BBB  
• ↓ production of pro-inflammatory cytokines  
• ↑ anti-inflammatory cytokines | • ISR  
• Cytopenias  
• LFTs  
• Hepatic injury  
• Depression  
• CHF  
• Seizures |

**Fumarates**

- **Diroximel Fumarate (Vumerity)**
  - Significantly fewer days with individual GI symptoms and Impact Scale (IGISIS)
  - Lower discontinuation rates

- **Monomethyl Fumarate (Bafiertam)**
  - Active metabolite of Vumerity and Tecfidera
  - Lower GI side effects

**Glatiramer acetate (Copaxone, Glatopa)**

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</table>
| • MBP mimetic  
• Competes with MBP antigens to bind with the MHC II            | • Diverts T-cells response away from myelin  
• ↓ production of pro-inflammatory cytokines (TH1)  
• ↑ anti-inflammatory cytokines (Th2)                  | • ISR  
• Post-injection reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, urticaria)  
• Pregnancy Cat:B                                           |

**Dimethyl fumarate (Tecfidera), diroximel fumarate (Vumerity), monomethyl fumarate (Bafiertam)**

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<thead>
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<th>MOA</th>
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</thead>
</table>
| • Activates nuclear factor-like 2 (NF2)                             | • ↓ lymphocyte count by 30%  
• 6% lymph count <0.5x109/L                                           | • Severe and/or persistent lymphopenia  
• Flushing  
• Pruritus, rash  
• GI symptoms (less with newer fumarates)  
• PML                     |

**Monitoring**

- CBC and diff, CMP prior to medication initiation
- Every three months for first year then every 6 months.
- Check baseline VZV IgG titer, hepatitis and TB status
**Teriflunomide (Aubagio)**

**MOA**
- Inhibits proliferation of activated T and B lymphocytes
- Inhibits mitochondrial dihydroorotate dehydrogenase

**Effect on immune cells and mediators**
- $\downarrow$ neutrophils and lymphocytes by 15%
- 12% with lymphocytes, $0.8 \times 10^9/L$

**Safety issues**
- Hepatic injury
- Teratogenicity
- $\uparrow$ blood pressure
- Alopecia
- Intestinal lung disease
- Headache
- GI symptoms
- Latent TB
- Neuropathy

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**Fingolimod (Gilenya), siponimod (Mayzent), ozanimod (Zeposia), ponesimod (Ponvory)**

**MOA**
- S1P receptor modulator on lymphocytes. Preventing egress form secondary lymphoid organs to peripheral circulation
- S1P1 and S1P5 receptor modulator (siponimod, ozanimod)
- S1P1 modulator (ponesimod)

**Effects on immune cells and mediators**
- $\downarrow$ circulating lymphocytes by 20-30%

**Safety issues**
- LFTs
- Hepatic injury
- Bradycardia
- New generation S1P receptor modulators (selective affinity for S1P1 and S1P5 receptor) less prone to cause bradycardia due to utilization of drug titration
- Macular edema
- $\uparrow$ blood pressure
- PRES
- Pulmonary events
- Infections (HSV, Cryptococcus)
- Skin cancer
- PML

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**Monitoring**

- CBC and diff, CMP prior to medication initiation.
- Check baseline VZV IgG titer, hepatitis and TB status
- CBC with diff, LFTs (monthly for the first 6 months), patients must use reliable contraception, wash out (if needed).
- Women who wish to become pregnant must stop therapy and undergo accelerated elimination procedure (cholestyramine or activated charcoal for 11 days).

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**New S1P modulators**

- Shorter half life
- Minimizes cardiac issues – does not bind to S1P3 with high affinity also slow drug titration less cardiac effects
- Selective sphingosine 1-phosphate (S1P)-1 and 5 receptor.
  - May cross blood-brain-barrier and decrease production of TNF alpha, IL-6, IL-17 by astrocytes and microglia, this can lead to less demyelination modulation reduces accumulation of neurological impairment and slows progression of brain atrophy.

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**Ozanimod**

- Contraindicated in patients taking MOA inhibitors
- Monoamine oxidase (MOA) is an enzyme that is responsible for breakdown of tyramine
- Ozanimod metabolites inhibit MOA that may result in higher levels of tyramine and hypertensive crisis
- Patients need to avoid food and beverages that would result in a total of more than 150 mg daily of tyramine while on ozanimod.
### Monitoring

- Eye and skin examinations (macular edema and basal cell carcinoma) yearly
- Varicella-Zoster Virus IgG prior to starting medication if negative vaccinate 2-4 weeks prior to starting med, PFTs (if clinically indicated)
- EKG prior to starting treatment with all
- CBC with diff, LFTs every 6 months.
- Treatment interruption >12-14 days need repeat of first dose observation (fingolimod)

### Monoclonal Antibodies

- **Natalizumab**
  - Target: CD49, α4-integrin, leukocytes
- **Alemtuzumab**
  - Target CD52, T cells, B cells, APC
- **Ocrelizumab**
  - Humanized mAb, Target CD20, mature B cells
- **Ofatumumab**
  - Humanized mAb, Target different site of CD20, mature B cells

### Natalizumab

**MOA**
- Inhibits VLA-4 integrins
- Prevents leukocyte migration across the BBB

**Effects on immune system**
- ↑ circulating leukocytes except neutrophils

**Safety profile**
- PML
- Hypersensitivity reactions
- Hepatic injury
- Infections (HSV, meningitis, hep b)

### Factors that Increase PML Risk

- Anti-JCV antibody positive status
- Receiving an immunosuppressant (such as mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil) prior to receiving natalizumab
- Natalizumab treatment duration (especially >2 years)
- Titer index over 0.9
- Serum JV Ab check every 6 months (<2 yr tx); every 3 months > 2yrs of tx

### Alemtuzumab

**MOA**
- Targets CD52 on lymphocytes
- Depletes T and B cells, monocytes, macrophages and dendritic cells

**Effects on immune system**
- Rapid ▲ of circulating T and B Cells
- Long lasting effects on adaptive immunity

**Safety issues**
- Infusion reactions
- Thyroid dysfunction-30%
- ITP- 1% one death in trial
- Glomerulonephritis-0.1%
- Infections (herpes, fungal, listeria, monocida)
- Cancer Risk: thyroid, melanoma and lymphoma.

### Safety Considerations with Alemtuzumab

**Warnings**
- Infusion reaction
  - >60% of patients in clinical trials experienced infusion reactions, 2% serious. Rash, headaches, influenza-like symptoms: less common transient recurrence of previous MS symptoms
- Autimmune thyroid disease (20%)
- Autimmune Thrombocytopenia (10%)
- Glomerular nephropathies (3.3%)
- Malignancies: Melanoma (0.3%), Lymphoma
- Infections
- Pneumonitis

**Monitoring and Precautions**
- Restricted distribution under the REMS program
- Monthly blood tests
- TSH every 2 months.
- Obtain thyroid function tests prior to initiating treatment and every 3 months until 6 months after the last infusion.
- Monitor CBC prior to treatment and monthly until 48 months after last infusion.
- Monitor serum creatinine prior to treatment and monthly.
- Conduct baseline and yearly skin exams for melanoma.
- Delay treatment initiation in patients with active infections.
- Do administer live viral
### Ocrelizumab

**MOA**
- Targets CD20 on B lymphocytes
- Antibody and cell mediated cytotoxicity

**Effect on immune cells**
- Depletion of pre-B cells, mature B cells and memory B cells
- Lymphoid stem cells and plasma cells are unaffected

**Safety issues**
- Infusion reactions
- Infection (URI, PML)
- Neoplasm?
- Breast

### Ofatumumab (Kesimpta)

**MOA**
- Targets CD20 on B lymphocytes
- Antibody and cell mediated cytotoxicity

**Effect on immune cells**
- Depletion of pre-B cells, mature B cells and memory B cells
- Lymphoid stem cells and plasma cells are unaffected

**Effect on immune system**
- Injection site reaction
- Headache
- Myalgia
- Fever
- Fatigue
- Infection
- URI
- Hep B reactivation
- PML

**Safety issues**
- Malignancy
- Hematologic malignancies
- Ovarian carcinoma
- Pancreatic carcinoma
- Malignant melanoma (1.1% vs 0.5% placebo)
- URI
- Headache
- Lymphopenia
- Infections (TB, VZV, PML (none), liver problems and heart failure

### Cladribine (Mavenclad)

**MOA**
- Purine analog that prevents DNA replication and reduces T and B cells.
- In cells phosphorylated into its toxic form by another enzyme deoxycytidine kinase, (DCK).
- Cells that have high concentration of DCK (T, B and NK cells) accumulate phosphorylated cladribine.

**Effect on immune system**
- Depletes 80% of peripheral B cells,
- 40-50% of total T-cells.
- Also affects NK Cells

**Safety issues**
- Malignancy
- Hematologic malignancies
- Ovarian carcinoma
- Pancreatic carcinoma
- Malignant melanoma (1.1% vs 0.5% placebo)
- URI
- Headache
- Lymphopenia
- Infections (TB, VZV, PML (none), liver problems and heart failure

### Cladribine

- One or two pills depending on weight
- Two treatment weeks per year one month apart and repeated again on second year.
- 2 year treatment courses: 1.75 mg/kg/course divided into 2 treatment cycles
- Not to exceed 3.5 mg/kg cumulative dosage
- #mg tablet taken daily for 4 to 5 consecutive days, repeated one month later for another week - repeat cycle one year later.

**Tests prior to treatment**
- CBC and diff
- TB status
- HIV status
- VZV status
- Vaccination recommended for VZV IgG negative patients
- Pregnancy test

**Monitoring**
- Measure lymphocyte counts before each treatment course and at 2 and 6 months after each treatment course
- Absolute lymph count must be > 800 cells/mm3 before year 2 of treatment
- HSV prophylactic treatment if lymphocytes drop to 200
- Prescautions to prevent pregnancy must be maintained for at least 6 months after treatment (of either partner)
 Mitoxantrone (Novantrone)

**MOA**
- Intercalates with DNA causing strand breaks
- Inhibits DNA repair via inhibition of topoisomerase II leading to cytotoxicity

**Effects on immune cells**
- Reduction of leukocytes, mainly neutrophils and most lymphocyte subsets except for naive and activated T lymphocytes

**Safety Issues**
- Menstrual disorders
- Blue/Green urine
- Hair loss
- UTI/ URI
- Mouth sores
- Irregular heart beat
- Cardiotoxicity; CHF can happen years after cessation of therapy
- Acute myeloid leukemia

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 Stem Cell Transplant

- Autologous hematopoietic stem cell transplant (HSCT)
  - Immunosuppression followed by infusion of autologous stem cell
  - "Re-booting of immune system"
  - Stem cells derived form bone marrow or blood are stored and the rest of the individual’s immune cells are depleted by chemotherapy then stem cells re-introduced.
  - Potent durable benefits
  - Young, mild to mod disability and highly active MS benefit

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 BEAT-MS

- Best Available Therapies (BAT) versus Autologous Hematopoietic Stem Cell Transplant (AHSCT) for Multiple Sclerosis
- Comparing BAT vs AHSCT over 72 months in RRMS and continued MS disease activity despite treatment with DMTs
- BAT agents: natalizumab, alemtuzumab, ocrelizumab or rituximab
- Prospective 1:1 randomized controlled trial of 156 participants
- Age less than 55, EDSS less than 5.5
- Primary Endpoint: MS release free survival

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 Efficacy of DMTs for MS

<table>
<thead>
<tr>
<th>DMT</th>
<th>ARR reduction*</th>
<th>MRRI**</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN beta 2b</td>
<td>31% vs placebo</td>
<td>↓ 0.3 % lesion area</td>
</tr>
<tr>
<td>IFN beta 1a IM</td>
<td>31% (PTX vs placebo)</td>
<td>↓ 0.4 % lesion area</td>
</tr>
<tr>
<td>IFN beta 1a SC</td>
<td>34% (PET vs placebo)</td>
<td>↓ 0.4 % lesion area</td>
</tr>
<tr>
<td>PegIFN beta 1a</td>
<td>36% vs placebo</td>
<td>↓ 0.4 % lesion area</td>
</tr>
<tr>
<td>Gilasaximab</td>
<td>29% vs placebo</td>
<td>↓ 0.4 % lesion area</td>
</tr>
<tr>
<td>Omnituzumab</td>
<td>49% vs placebo</td>
<td>↓ 0.4 % lesion area</td>
</tr>
<tr>
<td>Terifluodone</td>
<td>36% vs placebo</td>
<td>↓ 0.4 % lesion area</td>
</tr>
<tr>
<td>fingolimod</td>
<td>54% vs placebo</td>
<td>↓ 0.4 % lesion area</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>65% vs placebo</td>
<td>↓ 0.4 % lesion area</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>55% evaluable (6% female)</td>
<td>↓ 0.4 % lesion area</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>69% vs placebo</td>
<td>↓ 0.4 % lesion area</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>47% evaluable</td>
<td>↓ 0.4 % lesion area</td>
</tr>
</tbody>
</table>

* Efficacy: relapse definition / diagnostic criteria / population / comparator
** Efficacy metrics
PTX: Placebo
FRI = FLAIR lesion positive (enhancing lesions)

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 Approaches to MS Treatment

- Escalation of chronic immunomodulatory/- suppressive treatment
- Induction and reconstitution, followed up by treatment of residual (innate) inflammation
- 3 principles: safety, efficacy and tolerability
- Optimize neurologic reserve, cognition and physical function by reducing disease activity
Reasons to Consider Switching Treatment

- Breakthrough disease activity
  - More than three lesions on MRI
  - More than one relapse in first year of treatment
  - Disability progression with EDSS
- JCV ab seroconversion
- Poor adherence
- Intolerable and severe medication side effects

Temporal effect on the immune cell system

<table>
<thead>
<tr>
<th>Near term</th>
<th>Mid term</th>
<th>Long Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day to week</td>
<td>Week to month</td>
<td>Month to Year</td>
</tr>
<tr>
<td>INF beta 1B</td>
<td>Fingolimod</td>
<td>Alemtuzumab</td>
</tr>
<tr>
<td>INF beta 1a</td>
<td>Siponimod</td>
<td>Ocrelizumab</td>
</tr>
<tr>
<td>Peginterferon</td>
<td>Ozanimod</td>
<td>Cladribine</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Natalizumab</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>Teriflunomide (w/o accelerated elimination)</td>
<td></td>
</tr>
<tr>
<td>Teriflunomide (with accelerated elimination)</td>
<td>Ofatumumab</td>
<td></td>
</tr>
</tbody>
</table>

When to STOP DMT in MS

- DISCO MS-PICORI study= DISContinuation of MS DMT
- Randomized controlled prospective study for individuals with MS age 55 or older.
- Participants will be randomized to one of the 2 groups: one continue with DMT and one discontinue medications.
- Estimated completion by February 2022.

Pregnancy Considerations

- Glatiramer acetate pregnancy Class B
- Interferons, FDA updated for Plegridy and Avonex in 4/2020
  - No longer contains Pregnancy category C due to human pregnancy registry.
- No washout period necessary for GA or interferons
- Dimethyl fumarate and Tysabri no wash out period required
- Must stop S1P modulators 3 months prior to conception
- Must stop Cladribine 6 months prior to conception
- Must stop Ocrelizumab and ofatumumab 6 months prior to conception (12 months in Europe)
- Teriflunomide use accelerated elimination to lower serum levels to below 0.03 mg/L

COVID-19 and Multiple Sclerosis

- SARS-CoV-2 triggers the innate immune system, on which DMTs have little effect
- DMTs should be continued
- Most DMTs do not increase risk of severe COVID-19 infection, with some exceptions
  - Possible: alemtuzumab, cladribine, ocrelizumab, rituximab
- Having MS does not make it likely to become severely ill or die
- Susceptible to severe disease similar subgroups to those observed with general population
  - >60, men, A.A or S. Asian, HTN, DM, heart/lung disease, obesity, patients with higher disability

COVID-19 vaccine and MS

- Recommendations from NMSS
  - COVID-19 vaccine is inactive and safe
  - Most DMTs should be continued as they will not affect response to vaccine
  - Some DMTs (alemtuzumab, cladribine, B-cell depleting drugs) may decrease the mounted response to vaccine
- Coordinate timing of vaccine with timing of DMT
  - If not on DMT already ideal to start oral/infusions (DMTs) 2-4 weeks after second dose of vaccine
  - If already on DMT for ocrelizumab or rituximab consider vaccine 12 weeks after last dose
  - Ocrelizumab no longer listing delayed after last dose for vaccine, wait 2-4 weeks post vaccine to resume next injection.
  - Cladribine no longer listing ideal timing for vaccine while on medication but consider wait 2-4 weeks post vaccine to resume
  - For IV steroids wait 5 days after
Repertoire of DMTs for patients with RRMS has increased over the recent years
- MOA and duration of effect on immune system need to be considered when selecting and changing DMTs
- Different routes of administration and dosing
- Different safety and efficacy profiles
- Greater opportunities for individualized treatment

Treatment needs to fit the needs of a given patient and their disease activity
- Adherence to treatment
- Comorbidities, family planning, age, safety
- Patient education

References
- Wynn et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Neurol 2011;76:1074