Immunology for the Non-Immunologist

Kathleen Costello, MS, ANP-BC, MSCN
National Multiple Sclerosis Society

Scott Newsome, DO, MSCS
Johns Hopkins Multiple Sclerosis Center

Peter Calabresi, MD
Johns Hopkins Multiple Sclerosis Center

Michael Racke, MD
Ohio State University Multiple Sclerosis Center

CMSC Annual Meeting
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Faculty

• Kathy Costello, MS, ANP, MSCN, MSCS
  – VP Healthcare Access
  – National MS Society

• Scott Newsome, DO, MSCS
  – Assistant Professor Neurology and Director of Neurology Outpatient Services
  – Johns Hopkins Medicine

• Peter Calabresi, MD
  – Professor Neurology and Director of the Neuroimmunology Division and the Hopkins MS Center
  – Johns Hopkins Medicine

• Mike Racke, MD
  – Professor and Chair Department of Neurology
  – THE Ohio State University College of Medicine
Session Summary

The immune system is a complex and elegant system that protects us from infection and in addition, prevents autoimmunity. However, when internal and environmental factors interact and disrupt normal immune function, immune mediated and auto-immune conditions can occur. Over the past quarter century much has been learned about the role of the immune system in Multiple Sclerosis and this has led to the identification of multiple immune targets and 13 FDA approved treatments for MS. This program will review normal immune response, our basic understanding of the immunopathology in MS and the mechanisms of action of our current DMT’s. This will be followed a deeper look into more recently discovered inflammatory and degenerative mechanisms that are involved in MS. Current knowledge of gut inflammation and its’ potential role in MS and other autoimmune conditions will be explored as well as the evolution of our knowledge of the immune pathology in MS and the implications for future treatments.

Objectives

Following this session, participants will:

1. Contrast the normal immune response to that seen in multiple sclerosis.
2. Compare the mechanisms of action of the FDA approved disease modifying therapies.
3. Define what is meant by myelin repair.
4. List examples of endogenous and exogenous myelin repair.
5. Discuss therapeutic agents in the research pipeline that may promote repair in MS.
### Agenda Part I:
**Basic Immunology for the Non-Immunologist**
1:15 PM - 2:45 PM

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:15 – 1:45 PM</td>
<td>Kathleen Costello, MS, ANP-BC, MSCN</td>
<td>How does the immune system protect us?</td>
</tr>
<tr>
<td>1:45 – 2:15 PM</td>
<td>Scott Newsome, DO, MSCS</td>
<td>What causes CNS inflammation in MS?</td>
</tr>
<tr>
<td>2:15 – 2:45 PM</td>
<td>Scott Newsome, DO, and Kathleen Costello, MS, ANP-BC</td>
<td>How do the current DMT’s affect the altered immune response in MS?</td>
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<tr>
<td>2:45 - 3:00 PM</td>
<td>Questions?</td>
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### Agenda: Part 2
**Advanced Immunology for the Non-Immunologist**
3:00 PM – 4:30 PM

<table>
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<tr>
<td>3:00 pm – 3:40 PM</td>
<td>Peter Calabresi, MD</td>
<td>Mechanisms of Myelin Repair</td>
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<tr>
<td>3:40 – 4:20 PM</td>
<td>Michael Racke, MD</td>
<td>Exogenous Repair Mechanisms in Multiple Sclerosis</td>
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<tr>
<td>4:20 – 4:30 PM</td>
<td>Questions?</td>
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</tr>
</tbody>
</table>
Disclosures

• Kathleen Costello – None

• Peter Calabresi –
  – Consultant: Vertex
  – Research Grants: MedImmune, Novartis, Biogen

• Scott Newsome –
  – Consultant: Biogen, Novartis, and Genzyme
  – Research Grants: Biogen, Novartis, National MS Society

• Michael Racke –
  – Consultant: Abbvie, Genentech/Roche, EMD Serono, Novartis, TG Therapeutics, Teva Neuroscience
  – Research Grants: National MS Society, National Institutes of Health

PART 1: BASIC IMMUNOLOGY FOR THE NON-IMMUNOLOGIST
The Normal Immune Response

Kathleen Costello, MS, ANP-BC, MSCN, MSCS
National Multiple Sclerosis Society
Purpose of the Immune System

• Prevent infections
• Eliminate established infections

• The immune system does this by identifying pathogens: such as bacteria, viruses, fungi and a coordinated immune response, destroys the pathogen

Important Properties of the Immune System

• Specificity
• Diversity
• Memory
• Ability to distinguish self from non-self
Innate and Adaptive Immunity

• **Innate**
  - Rapid response system
  - No memory
  - Reacts to cells and substances: identifiers of different microbes
  - Can stimulates adaptive immunity

• **Adaptive**
  - Slower to respond
  - Has memory
  - Humoral
    • Recognizes pathogens outside of cells
  - Cell mediated
    • Recognizes pathogens inside of cells

Who’s who in the Immune System?

**Cells**
- Neutrophils
- Monocytes
  - Macrophage
  - Dendritic cells
- NK cells
- T-cells
  - T-helper cells: CD4
  - Cytotoxic T cells: CD8
  - T-regulatory cells
- B-cells

**Surface molecules**
- MHC I and II
- Costimulatory molecules
- Adhesion molecules

**Proteins and messengers**
- Chemokines
- Cytokines
- Interleukins
- Interferons
- Complement
The Justice League of America

The Justice League of the Immune System
Injury

Splinter, causing local bacterial infection
How does it work?

• Innate Immune activity
  – First defense:
    • Stop entry of pathogens into the body by creating barriers to pathogen entry:
      • Respiratory
      • Skin
      • GI tract
    – Activation of cells that destroy the pathogen
    – Involved in inflammation and eradication of infected cells

Macrophages: Sentries of Innate Immunity
Innate Immunity: First Responders
Neutrophils and Monocytes

NK cells
**Innate Immunity**

1. Neutrophils #1
   - Short lived
   - After about 24 hrs

2. Monocytes #2
   - Differentiate into macrophages
     - Powerful phagocytes
     - Stimulate repair mechanisms
     - Produce IL-1, TNF, ROS (H2O2) when activated
     - APC for lymphocyte function in adaptive immunity
     - Become further stimulated by adaptive immune mechanisms

**Neutrophils and Monocytes**

- Both neutrophils and monocytes can directly recognize the characteristic features of microbes
  - Detect features on the cell surface
    - Virus, bacteria, parasite
  - Phagocytosis follows recognition
- But, some microbes that cause human disease are able to resist phagocytosis – can be engulfed but not destroyed
- The innate immune system responders create the “game plan” for the activation and response of the adaptive immune system.
3. NK cells – destroy viral infected cells
   – Cytotoxic lymphocytes that are Killing machines
   – Recognize and destroy infected cells without presentation
     – Injects infected cells with suicide proteins
   – Induce secretion of interferon gamma which activates macrophages

4. Complement activation
   – Complement proteins recognize chemical groups on the surface of an invader and signal other proteins.
     Complement can tag an invader so other cells know it needs to be destroyed. Also complement can bore a hole in an invading cells which will destroy it.

Adaptive Immunity
Adaptive Immunity

• When the actions of the innate immune system are not sufficient to eliminate the pathogens, the adaptive immune system is activated
  – Cell-mediated
    • T-cells
      – Th-1, Th-2, Th-17
  – Humoral
    • B-cells
    • T-cells
    • Antibodies
    • Complement

Activation of Adaptive Immunity

• B-cells recognize pathogens that are in circulation and outside of the cell
  – Able to recognize and make antibodies –
    • An initial and weaker response
  – They are also stimulated to become active by T cells
    • This takes longer, but provides a more robust Ab response
• T-cells recognize pathogens that are presented to them by antigen presenting cells
  – APC’s process a virus and display part of it on the APC cell surface and only in this way can the T-cell recognize the antigen
T-cell Activation

- Antigen presenting cells encounter antigens, engulf them and process them.
- A particle of the antigen is then presented on the APC cell surface on a specific type of surface cell called MHC (major histocompatibility complex)
- CD-4 cells (Th-1, Th-2, Th-17) recognize antigen presented by MHC class II
- CD-8 cells (Cytotoxic T cells) recognize antigen presented by MHC class I
T-cell activation

• *The differentiation into Th-1, Th-2 or Th-17 cells is not a random process*
• It is regulated by the stimuli the naïve T-cell receives with antigen presentation
  – **Th-1** differentiation occurs with stimulation by IL-12 and IFN-γ which are produced by macrophages, dendritic cells. NK cells produce IFN-γ
  – **Th-2** differentiation occurs with stimulation by IL-4
    • As with parasitic infections
  – **Th-17** differentiation occurs with stimulation by IL-6, and IL-1 and IL-23 produced by macrophages and dendritic cells

Adaptive Immunity: B-cell activation

• Pathogen in circulation is recognized by B cell surface receptor
• B cell processes some of the pathogen and displays on MHC for T helper recognition.
• Comstimulation from the T cell is necessary for activation
• T cell then helps to activate the B-cell to become an effector B-cell or plasma cell, an Ab secreting cell.
Different antibodies for different jobs (infections)

- IgM – first Ab made, activates complement, opsonizes pathogen
- IgA – abundant in mucosal surfaces, and protects those surfaces. Resistant to digestive acidity. Coats pathogens so they cannot attach to mucosal wall
- IgG – opsonizes pathogen (binds) and optimizes phagocytosis
- IgE – mast cells bind to IgE causing a signal for the mast cell to degranulate – releasing histamine and other chemicals.
T-Regulatory Cells

Turning off the Immune Activation

- T regulatory cells
  - A subpopulation of T cells
  - Modulate the immune system
    - Shut down the immune responses after they have successfully eliminated invading organisms
  - Maintain tolerance to self antigens
    - To help prevent auto-immunity
Summary

• The immune system is a highly complex system that protects us from pathogens and eliminated those that have caused infection
• The normal functioning immune system has three important features:
  – Specificity
  – Diversity
  – Memory
• And it has the ability to differentiate self from non-self, and leave self alone
• However, if the immune system malfunctions and loses the ability to distinguish self/non-self an autoimmune response may occur

References

What Causes Central Nervous System Inflammation in Multiple Sclerosis?

Scott Newsome, DO, MSCS
Assistant Professor of Neurology
Johns Hopkins School of Medicine
Director, Neurology Outpatient Services
Director, Neurology Infusion Center

Multiple Sclerosis History

• Who was the first person(s) to describe multiple sclerosis (MS)?
  – Carswell in Scotland (1838) and Cruveilhier in France (1835-1842) connected the association of MS symptoms with plaques in the spinal cord and brain
  – Charcot at Salpetriere put together a more definitive description in a series of lectures in 1868 and named the condition “sclerose en plaques”
CNS immunity gone wrong...

- Multiple sclerosis
  - Immune-mediated disease of the central nervous system (CNS) that is characterized by inflammation, destruction of myelin, axonal loss, damage to CNS resident cells, and neurodegeneration
  - Both white and grey matter affected
  - Subtypes of MS likely due to different underlying immune mechanisms

Etiology of MS

- Over 200 Immune Gene SNPs implicated in the risk of MS: HLADR2, IL-2rec, IL-7 rec
- Innate immune response (macrophages)
- Adaptive immune response (T and B lymphocytes)
- Viruses (EBV)
- Vitamin D
- Latitude
- Smoking
- Diet (salt)
- Gut Microbiome
- Obesity

SNP = single nucleotide polymorphism.
Immune Tolerance

- Tolerance = no reactivity to self antigens
- Central tolerance in thymus and bone marrow
- Peripheral tolerance in the periphery
- Failure of tolerance to self antigens
  - autoimmune disease
    - Difficult to eliminate self antigen completely via the normal immune response
    - Tissue damage and chronic inflammation result

What are Antigens

- Antigens are any structural substances which serve as targets for the receptors of an adaptive immune response (T and B lymphocytes)
- Antigens may originate from within the body ("self") or from the external environment ("non-self")
- Self antigens may be myelin proteins, neuronal proteins, and/or astrocytic proteins
Molecular Mimicry and Bystander Activation

- Molecular Mimicry: non-self antigens share homology with self-antigens leading to autoimmune disease
  - Data supporting this concept are weak

- Bystander Activation: systemic immune response against foreign antigen leads to immune response directed against self
  - T cells with dual TCRs identified that could recognize “self” with 1 TCR and “non-self” with another
  - Priming of T cells in the gut in response to specific microbiota could result in autoimmunity

Immune Cells Implicated in CNS Inflammation

- Lymphocytes
- Monocytes
- Microglia
- Dendritic Cells
- T cells
- B cells
- Antibodies
- Macrophages
- Granulocytes
- NK Cells
**Components of autoimmunity**

1. Auto antigen
2. APC activation
3. CD4 help
4. CD8 T cells

- CD4+ and CD8+ T cells specific for myelin antigens circulate harmlessly until activated by environmental stimulus.

- How do myelin-specific T cells escape tolerance and what leads to their activation?
  - Genetics? Environment? Infection?

- What is the phenotype of pathogenic T cells in MS?

- What do these T cells do in the CNS?
Phenotype of Pathogenic T cells in MS
(Helper T cell differentiation)

- **T_{H0}**
  - IL-4/STAT6
  - IFN-γ
  - Pro-inflammatory

- **T_{H1}**
  - IL-12/STAT4
  - IL-4
  - IL-5
  - IL-10
  - IL-13
  - Anti-inflammatory/Allergy

- **T_{H2}**
  - IL-4/STAT6
  - IL-6 + TGF-β

- **T_{H17}**
  - IL-23
  - IL-17
  - Pro-inflammatory

- **T_{reg}**
  - TGF-β
  - Regulatory

B cells

- B cells with myelin-specific BCRs become activated and pass thru blood-brain barrier into CNS
- Secrete antibodies that can mediate damage to axons
- Some patients have presence of B cell follicles in the meninges
- Also may play an important role in repair and remyelination by promoting clearance of myelin debris via opsonization
Monocytes/Macrophages/Microglia and Dendritic cells

- Damage to CNS tissue = activation of CNS resident immune cells
  - MICROGLIAL CELLS
    - Sense changes in CNS and immune regulation
    - upregulate MHC (also known as HLA in humans) and COSTIMULATORY MOLECULES
    - release CYTOKINES and CHEMOKINES, paving the way for the entry of
      - MONOCYTES, lymphocytes and DENDRITIC CELLS (DCs) into the lesion
  - DCs play central role in antigen presentation to invading T cells
  - MACROPHAGES - release proinflammatory cytokines and toxic molecules
    - nitric oxide, interleukin (IL)-1, IL-6, tumor necrosis factor- (TNF-) and matrix metalloproteinases—which cause damage to oligodendrocytes and neurons
Activated microglia/macrophages can be detected in CNS lesions with immunostaining.
Immunopathogenesis of MS

Courtesy of Suhayl Dhib-Jalbut, MD
Immune Steps Leading to Neurological Problems

“Activated” T cells, B cells and monocytes...

cross the blood-brain barrier…

…launch attacks on myelin & nerve fibers...

to obstruct nerve signals.

Inflammation in the CNS Results in Axonal Damage

• Axonal damage and loss are most important determinants of permanent neurological disability

• Axonal damage occurs even in early stages of disease

• Hypotheses for a link between an aberrant inflammatory response in the CNS and axonal damage include:
  – Activation of CD8+ T cells that directly target neurons
  – Vigorous CD4+ T-cell responses that recruit macrophages, leading to release of inflammatory mediators and toxic molecules
  – Binding of antibodies to neuronal surface antigens, followed by COMPLEMENT activation or antibody-mediated phagocytosis of axons
  – MS-specific immune response may trigger a program in CNS resident cells resulting in secondary inflammation-independent neurodegeneration
  – Indirect mechanisms, such as loss of protective myelin, mitochondrial dysfunction, dysregulation of ion channels, or release of glutamate or nitric oxide
Pathology of MS Lesions due to Immune Attack

- Acute and chronic active lesions
  - axons commonly preserved, with presence of macrophages that have taken up myelin debris

- Inactive lesions (gadolinium -)
  - loss of axons and oligodendrocytes with few macrophages present

- Cortical plaques
Perivenular Inflammation Lesions

MS: Gray and white matter lesions
Summary

- Etiology of MS is unknown but immune system plays a central role in disease pathogenesis.

- Persistent acquired immune response in MS may be driven by a small number of antigens—the identity of which is currently unknown—that are presented in the CNS.

- Invasion of the CNS by T cells and B cells may be the initiating event of MS.

- May be secondary to the activation of microglia and macrophages, and the local release of self or foreign antigens.

- Inflammation mediated by T cells, B cells, and macrophages drives demyelination and degeneration in all forms of the disease.
How do the current DMT’s affect the altered immune response in MS

Scott Newsome, DO, MSCS
Assistant Professor of Neurology
Johns Hopkins School of Medicine
Director, Neurology Outpatient Services
Director, Neurology Infusion Center

Kathleen Costello MS, CRNP, MSCN
Vice President Health Care Access
National Multiple Sclerosis Society
Adjunct Assistant Professor of Neurology, Johns Hopkins School of Medicine

Strategies to Block the Immune System’s Attack

Broad-spectrum Immunosuppression

- Nonselective
  - Toxicity

- Selective
  - Antigens unknown or multiple ones!

Antigen-Specific

Slide courtesy of P. Calabresi, MD
**Expanding Landscape of MS Therapeutics**

**FDA-Approved Therapies (Approval time period)**

5. IFNβ-1a [prescribing information]. Rockland, MA: EMD Serono, Inc; 2014.
7. IFNβ-1b [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.

**Injectable Disease-Modifying Therapies**
Interferon β

• **Early findings MoA:** Reduces T-cell activation/proliferation, reduces T-cell secretion of matrix metalloproteinases, inhibits interferon-γ release, limits T-cell migration across blood brain barrier, and reduces expression of HLA.

• **Recent findings MoA:** Interferes with antigen processing, reduces antigen presentation to T-cells, and Th1/Th2 expression.

HLA = human leukocyte antigen; MOA = mechanism of action.

Glatiramer Acetate

• **Early findings MoA:** Th1 to Th2 shift and block MHC peptide antigen.

• **Recent findings MoA:** CNS migration of Th2 cells, modifies antibody production by plasma cells, regulates B-cell properties, cytokine modulation, inhibits antigen presentation to T-cells, and oligodendrocyte precursor cells

CNS = central nervous system; MHC = major histocompatibility complex.
Oral Disease-Modifying Therapies

Fingolimod

- Sphingosine 1-phosphate receptor (S1PR) modulator; S1P1, S1P3, S1P4, S1P5 receptors
- MoA: Functionally antagonizes S1PR blocking lymphocyte egress from secondary lymphoid organs to the peripheral blood circulation.
- Oral medication given daily

Teriflunomide

- Active metabolite of leflunomide
- **MoA:** Mimics DNA building blocks (pyrimidine); interferes with DNA synthesis and inhibits dihydro-orotate dehydrogenase → cytostatic to proliferating B and T cells
  - Reduces T-cell proliferation, activation, and production of cytokines
  - Interferes with the interaction between T-cells antigen-presenting cells
- Oral medication administered daily (7 mg or 14 mg)

Dimethyl Fumarate

- **MoA:** Changes balance of Th1 to Th2 and activates Nrf2 transcriptional pathway (oxidative, metabolic, and inflammatory stress)
- Oral medication given twice a day


Mitoxantrone

- Mainly used to treat leukemia and prostate cancer
- MoA: DNA topoisomerase II inhibitor; suppresses proliferation of T cells, B cells, and macrophages
- Lifetime dose of 140 mg/m²
Natalizumab

- First drug developed in the class of selective adhesion molecule inhibitors
- **MoA**: Humanized monoclonal antibody against alpha-4 (α4) integrin
- α4-integrin is required for WBCs to move into organs

WBC = white blood cell.

Alemtuzumab

- Treats B-cell chronic lymphocytic leukemia
- **MoA**: Targets CD52+ cells (present on mature lymphocytes); depletes B and T cells
- Initial treatment: 12mg/day for 5 consecutive days; subsequent treatment 1 year later: 12mg/day for 3 days

Oral Disease-Modifying Therapy
Side Effects/Monitoring

<table>
<thead>
<tr>
<th>Agent</th>
<th>Minor Side-Effects</th>
<th>Major Side-Effects</th>
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</thead>
<tbody>
<tr>
<td>Fingolimod1</td>
<td>Lymphopenia (absolute lymphocyte count &gt;200), transaminitis</td>
<td>Bradycardia, heart block, hypertension, risk of infections (herpetic), lymphopenia (absolute lymphocyte count &lt;200), transaminitis, macular edema, skin cancer, reactive airway, PRES, PML</td>
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<tr>
<td>Teriflunomide2</td>
<td>Diarrhea, nausea, hair thinning</td>
<td>Transaminitis, lymphopenia, teratogenic (men and women), latent tuberculosis, neuropathy, hypertension</td>
</tr>
<tr>
<td>Dimethyl fumarate3</td>
<td>Flushing, gastrointestinal distress</td>
<td>Transaminitis, leukopenia, PML</td>
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</tbody>
</table>

PRES= posterior reversible encephalopathy syndrome; PML= progressive multifocal leukoencephalopathy.

### Intravenous Disease-Modifying Therapy Side-Effects/Monitoring

<table>
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<tr>
<th>Agent</th>
<th>Minor Side-Effects</th>
<th>Major Side-Effects</th>
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<tbody>
<tr>
<td>Natalizumab¹</td>
<td>Headaches, joint pain, fatigue, wearing off phenomenon</td>
<td>Progressive multifocal leukoencephalopathy, infusion reaction, Herpes infections, liver failure</td>
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<tr>
<td>Mitoxantrone²</td>
<td>Nausea, vomiting, hair thinning, menstrual irregularities</td>
<td>Cardiac toxicity, acute myelogenous leukemia, infections, infertility, liver dysfunction</td>
</tr>
<tr>
<td>Alemtuzumab³</td>
<td>Infusion reactions</td>
<td>Autoimmune thyroid disease, ITP, Goodpasture syndrome, infections (HSV, VZV)</td>
</tr>
</tbody>
</table>

ITP= idiopathic thrombocytopenia purpura; HSV= herpes simplex virus; VZV= varicella zoster virus.


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Emerging Therapies for Multiple Sclerosis
Daclizumab HYP

• Humanized monoclonal antibody against CD25, the high-affinity α-subunit of the IL-2 receptor
• Subcutaneous injection monthly (IV form)
• Two proposed main mechanisms of action
  – Activate/expand CD56<sup>bright</sup> NK cells
  – Inhibit antigen-specific T-cell activation


Daclizumab HYP

• DECIDE trial (Phase III): Daclizumab HYP vs IFN β-1a (N = 1841) for 96 weeks
  – Annualized relapse rate: ↓ 45%
  – Disability progression: 3-month 16% reduction (p = .16) and 6-month 27% reduction (p = .033)
  – MRI: 65% reduction in new gadolinium-enhancing lesions vs IFNβ-1a

Daclizumab Safety
Main Adverse Effects

• Cutaneous events, including severe skin reactions
• Elevated liver enzymes
• Infections
• Secondary autoimmune disorders
• Diffuse lymphadenopathy


Ocrelizumab

• Fully humanized monoclonal antibody targeted against CD20 B cells
• Infusion every 6 months

For educational purposes only.
# Ocrelizumab

**(Phase III RRMS programs)**

- OPERA I ($n = 821$), OPERA II ($n = 835$)

| Clinical Trials | Agent(s) | Relapses | MRI Activity | Disability Progression-
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<tbody>
<tr>
<td>OPERA 1: Hauser S, et al. ECTRIMS October 2015; Barcelona, Spain [PS 190].</td>
<td>Ocrelizumab vs IFN β-1a</td>
<td>ARR: ↓ 46%</td>
<td>Gd+ lesions: ↓ 94% T2 lesions: ↓ 77% Brain Volume: ↓ 23.5%</td>
<td>↓ 43%</td>
</tr>
<tr>
<td>OPERA 2: Hauser S, et al. ECTRIMS October 2015; Barcelona, Spain [PS 190].</td>
<td>Ocrelizumab vs IFN β-1a</td>
<td>ARR: ↓ 47%</td>
<td>Gd+ lesions: ↓ 95% T2 lesions: ↓ 83% Brain Volume: ↓ 23.8%</td>
<td>↓ 37%</td>
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EDSS = Expanded Disability Status Scale.

# Ocrelizumab

**(Phase III PPMS program)**

- Ocrelizumab ($n = 488$), Placebo ($n = 244$)

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Agent</th>
<th>12 Week EDSS</th>
<th>24 Week EDSS</th>
<th>MRI Measures</th>
<th>Timed 25 Foot Walk</th>
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<tbody>
<tr>
<td>ORATORIO: Montalban X, et al. ECTRIMS October 2015; Barcelona, Spain [PS 228].</td>
<td>Ocrelizumab vs placebo</td>
<td>↓ 24%</td>
<td>↓ 25%</td>
<td>T2 LV: placebo ↑ 7.4, Ocrelizumab ↓ 3.4 Brain Volume: ↓ 17.5%</td>
<td>↓ 29%</td>
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LV = lesion volume; PPMS = primary progressive multiple sclerosis.
Anti-CD20 Monoclonal Antibody Safety
Main Adverse Effects

<table>
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<tr>
<th>Drug</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>Rituximab</td>
<td>• Infusion reactions</td>
</tr>
<tr>
<td></td>
<td>• Urinary tract infections</td>
</tr>
<tr>
<td></td>
<td>• Sinusitis</td>
</tr>
<tr>
<td></td>
<td>• PML</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>• Infusion reactions (mainly with first infusion)</td>
</tr>
<tr>
<td></td>
<td>• Opportunistic infections</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>• Infusion reactions</td>
</tr>
<tr>
<td></td>
<td>• Infection</td>
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<tr>
<td></td>
<td>• Neutropenia</td>
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<td></td>
<td>• Anemia</td>
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<td>• Rash</td>
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<td></td>
<td>• Fever</td>
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<td>• Diarrhea</td>
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Advantages and Disadvantages of Anti-CD20 Monoclonal Antibodies

- **Advantages**
  - Efficacious
  - Infrequent delivery
- **Disadvantages**
  - Infusion reactions common
  - Long term effects are unknown
Questions