Shifting the Treatment Paradigm for Multiple Sclerosis: Advances in Pathophysiology and Emergence of Novel Disease-Modifying Therapies

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Learning Objectives

• Describe the pathophysiology of MS as it relates to T- and B-cell behavior and mechanisms of action of MS therapies

• Assess mechanisms of emerging MS DMTs and how to integrate these therapies into treatment regimens to enhance patient outcomes

• Discuss how advanced understanding of MS pathophysiology may translate into new and emerging therapeutic options for progressive forms of MS

Please review the faculty disclosures and accreditation information on the accompanying webpage.
Pathophysiologic Mechanisms of MS
Paradigm Shifts in Understanding of MS

• MS was thought to be primarily a T-cell disease; we now recognize the importance of both B- and T-cell mechanisms

• Recognition of a variety of immune cell types involved in MS pathology offers potential for more targeted treatments

• Understanding of immune-cell interaction in the periphery and CNS suggests that triggering activities may occur on both sides of the BBB

CNS = central nervous system; BBB = blood-brain barrier.
Unanswered Questions in MS Pathology

• What is the inciting event that leads to the immune cascade resulting in MS?
• Does this occur in the CNS or periphery?
• Rather than activated immune cells crossing the BBB, could an event originating in the meninges trigger a breach in the BBB that allows immune cells to cross over and interact with antigens?
Activity of T Cells in Periphery and CNS

DC = dendritic cell; Treg = regulatory T cell.
T Cells in MS Pathogenesis

**Th1 cells**

- Promote cellular immunity directed against intracellular pathogens
- \( \text{Th1} \uparrow \) during relapse (proinflammatory)
  \( \text{Th2} \uparrow \) during remission (anti-inflammatory)
- T-cell subsets determine whether they will have a helper or suppressor function

Th1 Mechanisms

IFN = interferon; Ig = immunoglobulin; IL = interleukin.
Th17 cells\(^1\):
- Distinct Th subset producing IL-17; critical role in autoimmune response
- Accumulation in MS vs controls: active MS lesions, CSF, peripheral circulation (esp. during acute relapse)

T-regulatory cells (Tregs)\(^2\):
- In non-MS: control autoreactive T cells; may have protective effect
- In MS: dysregulation or impaired maturation of Tregs
- Tregs, dendritic cells are potential therapeutic targets in MS

CSF = cerebrospinal fluid.
Personalized Medicine in MS

- Personalized medicine is desirable in MS because it is a heterogeneous disease
- Expanding treatment armamentarium increases opportunity to tailor therapy to patient
- Biomarkers are needed to better stratify patients

Role of B Cells in MS Pathophysiology
B-Cell Mechanisms in MS

• Found mainly in active MS lesions
• Cytokine production:
  – Activation/effector
  – Proinflammatory, anti-inflammatory
  – Regulatory
• Interaction with T cells:
  – Presentation of antigen by B cells is necessary for triggering autoimmunity against myelin oligodendrocyte glycoprotein

B-Cell Mechanisms in MS (cont’d)

BCR = B-cell receptor; LT = lymphotoxin; MHC = major histocompatibility complex; TCR = T-cell receptor; TNF = tumor necrosis factor.

Early Rituximab Data Established Viability of B-Cell Depletion in MS

P values represent comparisons at baseline and 12, 16, 20, and 24 weeks

Does Depletion of B Cells “Reset” Immune System in MS?

• Antigen presentation by B to T cells fosters proinflammatory milieu associated with MS activity
• Bystander activation by B cells to T cells may explain association between MS relapses and systemic infections
• Goal of therapy is not just to reduce lymphocyte counts but also to adjust immune balance
• Reset immune system toward an anti-inflammatory environment by modulating B-cell activity (“rebooting” immune system)
Measuring Response to B-Cell Therapies

With recovery¹,²:

• Immature B cells predominate in periphery
• Proinflammatory Th1, Th17 responses decreased in periphery and CSF
• Repopulated B cells do not appear to have increased IL-6 expression

“Resetting” the Immune System: B-Cell Depletion

With recovery:

• Depleting peripheral B-cell population maintains immune surveillance

• Pro-B cells and antibody-producing plasmablasts/plasma cells are unaffected by CD20 depletion

Newer and Novel Mechanisms of MS Disease-Modifying Therapies
Anti-CD20 Monoclonal Antibodies

- B-lymphocyte antigen CD20: glycoprotein on surface of all B cells\(^1\)
- 3 anti-CD20 monoclonal antibodies (mAbs) under study for treatment of MS\(^2\):
  - Rituximab (chimeric human/mouse IgG1)
  - Ocrelizumab (humanized IgG1)
  - Ofatumumab (fully human IgG1)

What Are the Goals of Induction Therapies in MS?

• Rapid onset of action
• Significant impact on disease activity
• Durable mechanism of action
• Long-term influence on immune regulation/modulation
• Acceptable safety profile with respect to immune activity (fighting infections, viruses)
Ocrelizumab Phase II Data (Gd+ Lesions)

Gd+ = gadolinium-enhancing.
Ocrelizumab: Phase III Trials

**OPERA I and II**¹
- Relapsing-remitting MS (N=800 each)
- Ocrelizumab 2 x 300 mg IV, followed by 600 mg IV every 24 weeks *vs*
- IFN-beta-1a 44 mcg SC 3 x weekly
- Primary outcome: annualized relapse rate at 96 weeks

**ORATORIO**²
- Primary progressive MS (N=732)
- Ocrelizumab 600 mg IV every 24 weeks vs placebo
- Age 18-55 years; EDSS 3.0-6.5, abnormal CSF
- Primary outcome: time to sustained progression

EDSS = Expanded Disability Status Scale.
Ocrelizumab Phase III Results

RRMS (OPERA I and II)\(^1\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Interferon-β-1a</th>
<th>Ocrelizumab</th>
<th>Reduction</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annualized relapse rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPERA I</td>
<td>0.292</td>
<td>0.156</td>
<td>46%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OPERA II</td>
<td>0.290</td>
<td>0.155</td>
<td>47%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Gadolinium-enhancing lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPERA I</td>
<td>0.286</td>
<td>0.016</td>
<td>94%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OPERA II</td>
<td>0.416</td>
<td>0.021</td>
<td>95%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

PPMS (ORATORIO)\(^2\) Reduced proportion of patients with:

- Confirmed disability progression at 12 weeks by 24% vs placebo (25% by 24 weeks, \(P=0.0365\))
- Worsening on Timed 25-Foot Walk Test by 29% vs placebo (\(P=0.0404\))
- Whole-brain volume loss over 120 weeks, by 17.5% vs placebo (\(P=0.0206\))

PPMS = primary progressive MS; RRMS = relapsing-remitting MS.
Goals for Long-Term Follow-Up Studies of CD20 Therapies

- Crossover trials will move patients into most effective treatment group
- No long-term IFN comparator group
- Sustained benefits over time:
  - Brain atrophy
  - New lesion acquisition
  - Relapse activity
  - EDSS progression
NEDA (“No Evidence of Disease Activity”)

• Is NEDA an aspirational outcome?
• Useful outcome in clinical trials to show the maximum potential efficacy of a therapy
• Percentage of patients achieving NEDA in a real-world setting is unknown

Ofatumumab: Phase II Data

MIRROR Study
• RRMS, N=232

Subcutaneous dosing:
• Phase II study compared every 12 weeks and every 4 weeks

Overall Objective:
• Determine MRI efficacy and tolerability/safety of SC ofatumumab doses of 3, 30, and 60 mg vs placebo

Primary Endpoint:
• Cumulative number of new T1 Gd+ brain lesions over 12 weeks, vs placebo
Ofatumumab: Cumulative T1 Lesions (Phase II)

Alemtuzumab: Anti-CD52

- CD52: glycoprotein present on surface of normal T and B lymphocytes, monocytes, dendritic cells
- Alemtuzumab: humanized mAb directed against CD52 cell-surface protein
- Depletes mainly T and B lymphocytes
- To a lesser degree, depletes monocytes, macrophages, dendritic cells, NK cells

NK cells = natural killer cells.
Alemtuzumab: Anti-CD52 (cont’d)

- Rapid depletion of peripheral lymphocytes and monocytes\(^1\)
- Alemtuzumab depletes CD52-bearing T cells, but does not affect hematopoietic stem cells\(^2\)
- Monocytes return to pre-treatment levels within 1 month; B cells recover in 3 months\(^1\)
- Potential for reconstitution of immune response is preserved\(^2\)

T- and B-Cell Reconstitution After Alemtuzumab

*P<0.05; **P<0.01.

Alemtuzumab Efficacy in MS

Alemtuzumab significantly reduced clinical disease activity in patients who relapsed on prior therapy

- Alemtuzumab significantly reduced annualized relapse rate (ARR) and risk of 6-month sustained accumulation of disability (SAD) by an additional 49.4% and 42% beyond SC IFN-β-1a, respectively, in patients who relapsed on prior therapy
- Benefits on clinical disease activity were similar regardless of type, duration, or number of prior treatments

6-month SAD defined as EDSS score increase ≥1.0 point for ≥6 months (or ≥1.5 points when baseline EDSS = 0).

Targeting Therapeutic Selection in MS

- How can we determine appropriate patient selection for B-cell–depleting therapies?
- Are there groups of patients who do not benefit from these treatment strategies?
- Should we be treating earlier with more aggressive therapies?
- Does stopping immune system activity early in disease prevent long-term progression?
ACR/EULAR Definition of Remission in Rheumatoid Arthritis

• Boolean-based definition: At any time point, a patient must satisfy all of the following:
  – Tender joint count ≤1
  – Swollen joint count ≤1
  – CRP ≤1 mg/dL
  – Patient Global Assessment ≤1

• Index-based definition: At any time point, a patient must have:
  – Simplified Disease Activity Index (SDAI) ≤3.3

Treating Progressive Forms of MS: Impact of Newer Mechanisms
### Revised Phenotype Classification (Lublin 2013)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Disease</td>
<td>Relapses, new/increasing neurologic dysfunction, full or partial recovery</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>Steadily increasing dysfunction or disability without unequivocal recovery</td>
</tr>
<tr>
<td>Worsening Disease</td>
<td>Documented increase in neurologic dysfunction due to relapses or progressive disease</td>
</tr>
<tr>
<td>Confirmed Progression or Worsening</td>
<td>Increase of neurologic dysfunction confirmed through a defined time interval (eg, 3, 6, 12 months)</td>
</tr>
</tbody>
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Determining Active vs Inactive Inflammation in Progressive MS

- Disease burden may continue to advance in some people with MS despite lack of Gd+ lesion activity
- Some patients with progressive forms of MS have continued inflammatory activity
- This subpopulation of patients showed benefit from rituximab in early trials
- New data on B-cell therapies in patients with progressive MS will elucidate the role of lymphocyte depletion in these phenotypes
Educating Patients About Disease Mechanisms and Management
Role of Patient Education on Therapeutic Mechanisms

• Many MS patients are well informed; discussing pathophysiology/mechanism of action is increasingly important

• Risks of particular mechanisms are important part of discussion:
  – Importance of adherence to monitoring protocols
  – Importance of follow-up to therapies

• Therapeutic decisions may be based on response to previous treatments and on individual perceptions of risk vs benefit
This completes this activity, “Shifting the Treatment Paradigm for Multiple Sclerosis: Advances in Pathophysiology and Emergence of Novel Disease-Modifying Therapies.”

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