Therapeutic Mechanism of Action (MOAs) in MS: Targeting T- and B-cells to Reset the Immune System
Learning Objectives

• Explore emergent concepts in the management of MS, focusing on targeting T- and B-cells including:
  – Risks associated with continuous immunosuppression
  – Action on the inflammatory activity in the CNS compartment

• Review the benefit/risk strategies in selecting therapy for MS patients while assessing treatment regimens that carry acceptable or diminished risk of disease progression

• Identify strategies that simplify patient dosing and side effects to:
  – Increase treatment compliance
  – Improve patients’ quality of life
  – Slow disease progression
Treatment: Immunomodulation Type

Systemic immune compartment

APC, antigen presenting cells; B, B lymphocytes; BBB, blood-brain barrier; Bi, inflammatory B cells; CNS, central nervous system; Tc, T lymphocytes; Te, encephalitogenic T cells; T_{reg}, regulatory T cells. Figure is reproduced with permission from 1. Wiendl H, Kieseier B. Nat Rev Neurol. 2013;9:125-126.
Treatment: General Immunosuppression Type

Systemic immune compartment

APC, antigen presenting cells; B, B lymphocytes; BBB, blood-brain barrier; Bi, inflammatory B cells; CNS, central nervous system; Tc, T lymphocytes; Te, encephalitogenic T cells; T_{reg}, regulatory T cells. Figure is reproduced with permission from 1. Wiendl H, Kieseier B. Nat Rev Neurol. 2013;9:125-126.

Treatment: Immune-selective Intervention – Blockade Type

Systemic immune compartment

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These agents are under clinical investigation and have not been proven to be safe and effective. There is no guarantee they will be approved in the sought-after indication. APC, antigen presenting cells; B, B lymphocytes; BBB, blood-brain barrier; Bi, inflammatory B cells; CNS, central nervous system; Tc, T lymphocytes; Te, encephalitogenic T cells; Treg, regulatory T cells. Figure is reproduced with permission from 1. Wiendl H, Kieseier B. Nat Rev Neurol. 2013;9:125-126.

Variation in the Human Immune System is Largely Driven by Non-heritable Influences

Variation in the Human Immune System is Largely Driven by Non-heritable Influences

- 77% dominated by non-heritable influences
- 58% almost completely determined by external factors
- Parameters become more variable with age - suggesting cumulative influence of environmental exposure

*Individualizing treatments becomes more and more necessary*

MS Immunomodulatory Treatments

Of the 4 compounds in routine MS treatment, each induced unique constellations of immune deviations, which offers perspectives to the challenge of personalized medicine.


NMDS1 and 2: Non Metric Multidimensional Scaling

CON = controls; FTY720 = fingolimod; GA = glatiramer acetate; IFNB = immunomodulatory treatments interferon-β; NAT = natalizumab; UNT = untreated
CNS-Compartmentalized Inflammatory Injury Plays a Key Role in MS

MS therapies vary in their ability to penetrate the blood–brain barrier\(^2\)

CNS, central nervous system

Is there a need for a MS therapy with evidence of direct action on the inflammatory activity in the CNS compartment?

Periphery
- Glatiramer acetate
- Natalizumab
- Teriflunomide
- Alemtuzumab
- Daclizumab

Blood–brain Barrier
- Dimethyl fumarate
- Cladribine
- Ocrelizumab
- Fingolimod
- Laquinimod

CNS
- Cladribine
- Ocrelizumab
- Fingolimod
- Laquinimod

Lymphocyte depletion
Lymphocyte sequestration
Modulation of lymphocyte signalling

*Preclinical evidence suggests that dimethyl fumarate stabilises the blood-brain barrier. *These agents are under clinical investigation and have not been proven to be safe and effective. There is no guarantee they will be approved in the sought-after indication. CNS, central nervous system; IFN, interferon; PI, Prescribing Information; sc, subcutaneous; SmPC, Summary of Product Characteristics. Rebif® EU SmPC; Copaxone® SPC; Aubagio® EU SmPC; Tecfidera® EU SmPC; Tysabri® EU SmPC; Gilenya® EU SmPC; Lemtrada® EU SmPC; Zinbryta® EU SmPC.

# Risks Associated with Prolonged or Continuous Immunosuppression

T cells and B cells play critical roles in MS, and therapies targeting lymphocytes have a clinical effect\(^1\)

<table>
<thead>
<tr>
<th>Nature of immunosuppression(^2)</th>
<th>Likely infectious agents(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil deficits</td>
<td>Bacteria</td>
</tr>
<tr>
<td></td>
<td>Fungi</td>
</tr>
<tr>
<td>Abnormal T cells or monocytes</td>
<td>Viruses</td>
</tr>
<tr>
<td></td>
<td>Parasites</td>
</tr>
<tr>
<td></td>
<td>Fungi (typically yeast forming)</td>
</tr>
<tr>
<td>Disorders of humoral immunity(^3)</td>
<td>Bacteria</td>
</tr>
</tbody>
</table>

**Phase 3 Trials of DMDs in Progressive MS**

When inflammation is compartmentalized in the CNS, drugs that cannot cross the blood–brain barrier have no significant effect on the disease course\(^1\)

<table>
<thead>
<tr>
<th>Agent(^a)</th>
<th>Type of MS</th>
<th>Duration (years)</th>
<th>Primary outcome</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatiramer acetate(^2)</td>
<td>PPMS</td>
<td>3(^b)</td>
<td>Time to sustained progression of accumulated disability&lt;br&gt;HR 0.87 (95% CI, 0.71–1.07)</td>
<td>0.1753</td>
</tr>
<tr>
<td>Fingolimod(^3)</td>
<td>PPMS</td>
<td>3–5</td>
<td>3-month CDP(^c)&lt;br&gt;RR 5.05%; HR 0.95 (95% CI, 0.80–1.12)</td>
<td>0.544</td>
</tr>
<tr>
<td>Ocrelizumab(^4)</td>
<td>PPMS</td>
<td>(~3)</td>
<td>3-month CDP&lt;br&gt;HR 0.76 (95% CI, 0.59–0.98)</td>
<td>0.0321</td>
</tr>
<tr>
<td>Rituximab(^5)</td>
<td>PPMS</td>
<td>2</td>
<td>Time to CDP&lt;br&gt;30.2% (rituximab) vs 38.5% (placebo)</td>
<td>0.1442</td>
</tr>
<tr>
<td>Natalizumab(^6)</td>
<td>SPMS</td>
<td>2</td>
<td>Patients with CDP on (\geq)1 of EDSS, T25FW or 9HPT&lt;br&gt;44% vs 48%; OR 0.86 (95% CI, 0.66–1.13)</td>
<td>0.287</td>
</tr>
<tr>
<td>Siponimod</td>
<td>SPMS</td>
<td>Max 3</td>
<td>Delay in time to confirmed disability progression as measured by EDSS</td>
<td>0.013</td>
</tr>
</tbody>
</table>

No data are available for teriflunomide, dimethyl fumarate, alemtuzumab, daclizumab or cladribine tablets in PMS. \(^a\)Agents not approved anywhere in the world for use in progressive MS; \(^b\)Terminated early for non-efficacy reasons. \(^c\)Composite endpoint including change in EDSS, 9HPT and T25WT. 9HPT, 9-hole peg test; CDP, confirmed disability progression; CI, confidence interval; CNS, central nervous system; DMD, disease-modifying drug; EDSS, Expanded Disability Status Scale; HR, hazard ratio; OR, odds ratio; PPMS, primary progressive MS; RR, risk reduction; SPMS, secondary progressive MS; T25FW, timed 25-foot walk test.

The Crucial Role of B-Cells in MS

B cells and the Brain

CNS, central nervous system; CSF, cerebrospinal fluid; OCB, oligoclonal band.
Involvement of B Cells in the Pathogenesis of Multiple Sclerosis

B Cells Play Key Functional Roles in MS

Figure 3: B cells in the pathophysiology of MS [8-11].
B Cells Express Different Surface Markers Throughout Development


Reduction in Pre-specified Pooled Analysis of Confirmed Disability Progression (CDP) at 12 and 24 Weeks with IFN B-1a

**Time to CDP for ≥12 weeks**

- IFN-β-1a 44 µg (n=829)
- Ocrelizumab 600 mg (n=827)

Proportion of Patients Having CDP (%)

<table>
<thead>
<tr>
<th>Week</th>
<th>IFN-β-1a</th>
<th>Ocrelizumab</th>
</tr>
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<tr>
<td>Baseline</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>12</td>
<td>7.8</td>
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</tr>
<tr>
<td>24</td>
<td>9.2</td>
<td>9.2</td>
</tr>
<tr>
<td>36</td>
<td>11.6</td>
<td>11.6</td>
</tr>
<tr>
<td>48</td>
<td>13.0</td>
<td>13.0</td>
</tr>
<tr>
<td>60</td>
<td>14.4</td>
<td>14.4</td>
</tr>
<tr>
<td>72</td>
<td>15.8</td>
<td>15.8</td>
</tr>
<tr>
<td>84</td>
<td>17.2</td>
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</tr>
<tr>
<td>96</td>
<td>18.6</td>
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Risk reduction: 40%

HR (95% CI): 0.60 (0.45, 0.81); p=0.0006

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**Time to CDP for ≥24 weeks**

- IFN-β-1a 44 µg (n=829)
- Ocrelizumab 600 mg (n=827)

Proportion of Patients Having CDP (%)

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Risk reduction: 40%

HR (95% CI): 0.60 (0.43, 0.84); p=0.0025

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ITT CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; IFN, interferon; OCR, ocrelizumab.

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Actions of Four Key MS Medications

- Alemtuzmab
- Daclizumab
- Ocrelizumab
- Cladribine
Alemtuzumab: A Humanized Monoclonal Antibody Approved for Treatment of Patients with Active RRMS

- A humanized monoclonal antibody that selectively targets CD52, a protein abundant on the surface of B and T lymphocytes¹

- Novel dosing regimen: administered 12 mg/day via intravenous (IV) infusions on 5 consecutive days at baseline and on 3 consecutive days 12 months later²,³

- Approved for adult patients with relapsing-remitting MS (RRMS) with active disease defined by clinical or imaging features⁴

- First approved - EU in 2013⁵

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Daclizumab (CD25) blockade induces a shift of IL-2 signalling from activated T-cells to CD56-bright NK cells

- Activation of T cells induces expression of IL-2 high-affinity receptor and production of IL-21-5
- Levels of bioavailable IL-2 are increased1-6
- CD25 blockade prevents IL-2 consumption by activated T cells and increases IL-2 production (via inhibition of negative feedback)1-5

- Increased levels of IL-2 can induce expansion and activation of CD56bright NK cells through the intermediate affinity receptor1-6

Ocrelizumab in RMS Superior Efficacy, Similar Safety to Rebif

Cladribine

Cladribine was designed by adding 1 chlorine atom to deoxyadenosine, making it largely resistant to degradation by ADA.

Cladribine Enters Cells to be Activated and Exerts Its Effect

Cladribine works by a 4-step mechanism:

• Cladribine enters cell via nucleoside transporter
• Accumulates intracellularly due to ADA resistance
• Cladribine is activated by specific kinases
• Activated Cladribine induces selective lymphocyte reduction

*One of the kinases is deoxycytidine kinase (DCK). The phosphatase is 5’-nucleotidase.
Cladribine Selectivity for Lymphocytes is Due to Preferential Intracellular Activation in B and T Cells

B and T Lymphocytes

High levels of activated cladribine

Other Cells

Low levels of activated cladribine

TREATMENT WITH CLADRIBINE TABLETS LEADS TO SPECIFIC, DISCONTINUOUS REDUCTION IN LYMPHOCYTE COUNTS

Arrows show cladribine tablet dosing. aReductions in absolute lymphocyte counts (lymphopenia) were graded according to the Common Terminology Criteria for Adverse Events: 1, <lower limit of normal to 800/mm³; 2, <800 to 500/mm³; 3, <500 to 200/mm³; 4, <200/mm³. bLymphocyte count data were not available for all patients at every observation. cCentral laboratory reference range. Error bars represent 5–95 percentile range for cell counts at each time point. AE, adverse event; BL, baseline; LA, last assessment; MoA, mechanism of action. Figure reproduced with permission from Giovannoni G et al. N Engl J Med 2010;362:416–26 (supplementary). Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
Significant Reduction in Annualized Relapse Rate vs Placebo Over 2 Years (Primary Endpoint)

A relapse was defined as an increase of 2 points in at least one functional system of the EDSS or an increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement. RR, relative reduction. Intent-to-treat population. Figure reproduced with permission from Giovannoni G et al. N Engl J Med 2010;362:416–26. Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
Significant Delay in Time to 3-month Confirmed Disability Progression

10th percentile time to 3-month disability progression prolonged by ~3 months

Cladribine tablets 3.5 mg/kg
HR vs placebo: 0.67; 95% CI: 0.48, 0.93, p=0.018a

Cladribine tablets 5.25 mg/kg
HR vs placebo: 0.69; 95% CI: 0.49, 0.96, p=0.026a

aThe hazard ratio, 95% CI and p-values were estimated using Cox proportional hazards model with fixed effects for treatment group and region. Intent-to-treat population CI, confidence interval; RR, risk reduction.
Summary

1. In general MS DMTs modify the course of MS by
   - immunomodulation
   - generalised immunosuppression
   - reduced trafficking of T & B cells into the CNS
   - immunodepletion

2. Some DMTs may act within the CNS

3. Recently licensed and emerging DMTs include:
   - Oral cladribine (purine nucleoside analogue)
   - Alemtuzumab (anti-CD52)
   - Daclizumab (anti-CD25)
   - Ocrelizumab (anti-CD20)