B cell-depletion therapy in MS: Background, clinical applications, and safety

Gregory F. Wu, MD, PhD
St. Louis VA Medical Center &
Washington University in St. Louis
August 29, 2018
PVA Summit, Dallas, TX
Disclosures

- **Research support:** NIH, Doris Duke Foundation, Biogen
- **Consultant:** EMD Serono, Genzyme, Department of Justice
- **Off-label medication usage:** Rituximab
Learning Objectives

1. Define the key pathophysiologic mechanisms of B cells in MS
2. Identify experimental models to explore the therapeutic potential for B cell-targeted treatment in MS
3. Review the role of antibodies, cytokines and antigen presentation as mechanisms of B cell-mediated immune responses in MS
Clinico-pathologic characterization of MS

Clinically Isolated Syndrome

Disability

Time
Clinico-pathologic characterization of MS

Relapsing Remitting MS

Disability

Time
Clinico-pathologic characterization of MS

Relapsing Remitting MS

Disability

Time
Clinico-pathologic characterization of MS

Secondary Progressive MS

Disability vs. Time

OBSERVATIONS ON ATTEMPTS TO PRODUCE ACUTE DISSEMINATED ENCEPHALOMYELITIS IN MONKEYS

BY THOMAS M. RIVERS, M.D., D. H. SPRUNT, M.D., AND G. P. BERRY, M.D.
(From the Hospital of The Rockefeller Institute for Medical Research)

PLATES 1 TO 3

(Received for publication, February 21, 1933)

During convalescence from certain diseases, notably smallpox, vaccinia, and measles, and during or following vaccination against rabies, an occasional patient develops symptoms and signs referable to the central nervous system. A careful study (1-3) of the brains and cords of individuals who have died because of such involvement of the nervous system has revealed a characteristic pathological picture, acute disseminated encephalomyelitis, of which perivascular demyelination is a striking feature. The etiology of this malady is unknown in spite of the fact that considerable experimental work has been done to disclose it. Inasmuch as vaccine virus is suitable for a variety of experiments, many of the investigations (4-10) have dealt with vaccinal infections of the brain in rabbits and monkeys. At present, as a result of these investigations two main views are held regarding the relation of vaccine virus to postvaccinal encephalomyelitis, namely, (1) that it is the etiological agent and can induce the disease under experimental conditions, (2) that there is no clinical, pathological, or experimental evidence to show that it is directly responsible for the malady. In view of this difference of opinion, we decided to conduct some experiments on vaccinal infections in monkeys in the hope of obtaining information concerning the effect of the active agent on the central nervous system. We made no effort to repeat any work that had been previously reported, yet some of our control animals were handled in a manner similar to that employed by other investigators. Consequently, our results in many instances are comparable with those already recorded in the literature.
### TABLE III

Summary of the Results of Experiment XI in Which Monkeys Received Repeated Injections of Emulsion and Extracts of Normal Rabbit Brains

<table>
<thead>
<tr>
<th>Monkey No.</th>
<th>No. of injections of brain emulsions</th>
<th>No. of injections of brain extracts</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>5</td>
<td>9</td>
<td>Negative. Used in Experiment XII</td>
</tr>
<tr>
<td>27</td>
<td>5</td>
<td>9</td>
<td>“      “      “      XII</td>
</tr>
<tr>
<td>28</td>
<td>24</td>
<td>26</td>
<td>Died suddenly after 50th injection. Brain and cord negative</td>
</tr>
<tr>
<td>29</td>
<td>52</td>
<td>41</td>
<td>Negative. Used in Experiment XIII</td>
</tr>
<tr>
<td>30</td>
<td>46</td>
<td>38</td>
<td>Developed a tendency to hold chin on left shoulder, ataxia, and weakness. Sacrificed. Section showed involvement of midbrain, pons, cerebellum, and medulla, with perivascular demyelination</td>
</tr>
<tr>
<td>31</td>
<td>28</td>
<td>24</td>
<td>Developed ataxia, general weakness, and paresis of left leg and arm. Sacrificed. Section through right parietal and temporal lobes showed marked involvement of white matter with perivascular demyelination. Tract degeneration in cord</td>
</tr>
<tr>
<td>32</td>
<td>52</td>
<td>41</td>
<td>Negative. Used in Experiment XIII</td>
</tr>
<tr>
<td>33</td>
<td>52</td>
<td>41</td>
<td>“      “      “      XIII</td>
</tr>
</tbody>
</table>
Experimental Autoimmune Encephalomyelitis (EAE)
Experimental Autoimmune Encephalomyelitis (EAE)

- Days post Tamoxifen
- Mean EAE scores (SEM)

Parker Harp et al, submitted
Evaluation of EAE


Parker Harp et al. submitted
Pathogenesis of Multiple Sclerosis
Mechanisms of B Cell Participation in the Pathophysiology of MS
## Comparison of EAE Models

<table>
<thead>
<tr>
<th></th>
<th>Mutiple Sclerosis</th>
<th>Marmoset EAE</th>
<th>Rhesus EAE</th>
<th>Rodent EAE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathologic Features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>Focal</td>
<td>Mainly focal</td>
<td>Mainly focal</td>
<td>Diffuse in some models, focal in others</td>
</tr>
<tr>
<td>Remyelination</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Strain/model dependent</td>
</tr>
<tr>
<td><strong>Immunopathology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ T cell transferability</td>
<td>Not testable</td>
<td>Yes, to chimeric twin</td>
<td>Yes, autologous</td>
<td>Yes</td>
</tr>
<tr>
<td>B cell/antibody involvement</td>
<td>Plasma cells, Ig/C deposits in lesions</td>
<td>Plasma cells, Ig/C’ deposits in lesions, anti-MOG enhances demyelination</td>
<td>Not investigated</td>
<td>Controversial: anti-MOG pathogenic in some models</td>
</tr>
</tbody>
</table>

B Cells in Primate EAE

Haanstra et al. The Journal of Immunology, 2013, 190: 000-000.

B Cells in Murine EAE

μMT mice lack B cells

B Cells in Murine EAE

B Cell Cytokine Production

IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases

Ping Shen¹, Toralf Roch¹†, Vicky Lampropoulou¹, Richard A. O’Connor², Ulrik Stervbo¹, Ellen Hilgenberg³, Stefanie Ries³, Van Duc Dang¹, Yarúa Jaimes¹, Capucine Daridon¹,³, Rui Li⁴, Luc Jouneau⁵, Pierre Boudinot⁵, Siska Wilanthi¹, Imme Sakwa¹, Yusei Miyazaki⁴, Melanie D. Leech², Rhoanne C. McPherson², Stefan Wirtz⁶, Markus Neurath⁶, Kai Hoehlig¹, Edgar Meinl⁷, Andreas Grützkau¹, Joachim R. Grün¹, Katharina Horn¹, Anja A. Kühl⁸, Thomas Dörner¹,³, Amit Bar–Or⁴, Stefan H. E. Kaufmann⁹, Stephen M. Anderton² & Simon Fillatreau¹
B Cell Cytokine Production

Shen et al. Nature Feb 23, 2014 online
B cell depletion therapy ameliorates autoimmune disease through ablation of IL-6-producing B cells

Tom A. Barr,1,2, Ping Shen,2, Sheila Brown,1,2 Vicky Lampropoulou,3 Toralf Roch,4 Sarah Lawrie,6 Boli Fan,7 Richard A. O’Connor,2,3,4 Stephen M. Anderton,2,3,4 Amit Bar-Or,6,7 Simon Fillatreau,5 and David Gray1,2

1Institute of Immunology and Infection Research and 2Centre for Immunology, Infection and Evolution, School of Biological Sciences, and 3Medical Research Council Centre for Inflammation Research and 4Centre for Multiple Sclerosis Research, University of Edinburgh, Edinburgh EH9 3JL, Scotland, UK
5Deutsches Rheuma-Forschungszentrum, a Lorenz Institute, 13125 Berlin, Germany
6Neurimmunology Unit and 7Experimental Therapeutics Program, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec H3A 2B4, Canada

B Cell Cytokine Production

Antibodies & EAE

**Figure A**

- **TCR^{1640} serum**
- **NTL serum**
- **8.18C5-mAb**

**Days post serum transfer**

Mean clinical score vs. Days post serum transfer

**Figure B**

- **Mouse IgG2a**
- **Anti-CD20**

Mean clinical score vs. Age (Wk)

% Incidence vs. Age (Wk)

Pöllinger et al. JEM. Vol. 206 No. 6 1303-1316
Autoantibody-boosted T-cell reactivation in the target organ triggers manifestation of autoimmune CNS disease

Anne-Christine Flach, Tanja Litke, Judith Strauss, Michael Haberi, César Cordero Gómez, Markus Reindl, Albert Saiz, Hans-Jörg Fehling, Jürgen Wienands, Francesca Odoardi, Fred Lühder, and Alexander Flügel

Institute of Neuroimmunology and Institute for Multiple Sclerosis Research, University Medical Centre Göttingen, D-37073 Göttingen, Germany; Clinical Department of Neurology, Medical University of Innsbruck, A-6020 Innsbruck, Austria; Service of Neurology, Hospital Clinic, University of Barcelona, Institut d’Investigacions Biomèdiques August Pi i Sunyer Casanova, E-08028 Barcelona, Spain; Institute for Immunology, University of Ulm, D-89081 Ulm, Germany; Institute for Cellular and Molecular Immunology, University Medical Centre Göttingen, D-37073 Göttingen, Germany; and Max-Planck-Institute for Experimental Medicine Göttingen, D-37075 Göttingen, Germany
Antibodies & EAE

Antibodies & EAE

Molnarfi et al, JEM 2013. 210:2921
Antibodies & EAE

i

ii

iii
Antibodies & EAE
B Cell Antigen Presentation

Meningeal Lymphoid Structures in EAE

Parker Harp et al, unpublished
Meningeal Lymphoid Structures in MS
Meningeal Lymphoid Structures in EAE


Pikor et al., 2015, Immunity 43, 1160-1173
Anti-CD52 antibody treatment depletes B cell aggregates in the central nervous system in a mouse model of multiple sclerosis

Micha Simon†, Rojda Ipek†, György A. Homola, Damiano M. Rovituso, Andrea Schampel, Christoph Kleinschnitz, and Stefanie Kuerten†,*
<table>
<thead>
<tr>
<th>Pathology</th>
<th>EAE</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of demyelination</td>
<td>Predominantly, perivenous sleeves of myelin loss in spinal cord and brain</td>
<td>Demyelination not restricted to perivenous regions of white matter; extensive demyelination of cerebral cortex in the absence of inflammation is common</td>
</tr>
<tr>
<td>Location of lesions</td>
<td>Dependent on the autoantigen used for induction; inflammation dominates in lumbar regions in MBP and PLP EAE and brainstem in MOG EAE</td>
<td>Periventricular areas, cortical mantle, brainstem, optic nerves, and upper cervical cord; lesions are uncommon in thoracic and lumbar regions</td>
</tr>
<tr>
<td>Phenotype of cellular infiltrate</td>
<td>CD4+ T cells (MBP and PLP EAE) activated macrophages and few CD8+ T cells</td>
<td>Activated macrophages and CD8+ T cells of a restricted clonotype</td>
</tr>
<tr>
<td>Cytokine predominance</td>
<td>TH1 bias in MBP and PLP EAE; TH2 bias worsens MOG EAE</td>
<td>Variable; no clear cytokine preponderance</td>
</tr>
<tr>
<td>CSF immunology</td>
<td>Antibodies to myelin antigens present in CSF</td>
<td>Antibodies to myelin antigens are infrequent in CSF and do not constitute the antigen specificity of oligodendrocyte bands</td>
</tr>
</tbody>
</table>

Effect of immunotherapies

- **γ interferon**
  - Depends on route of administration and can either worsen or ameliorate EAE

- **β interferon**
  - Variable; can worsen EAE if given after immunization

- **Anti–TNF antibody**
  - Reverses EAE

- **Anti–VLA-4 antibody**
  - Reverses EAE

- **Anti–CD4 antibodies**
  - Cures EAE

EAE = experimental allergic encephalomyelitis; MS = multiple sclerosis; MBP = myelin basic protein; PLP = proteolipoprotein; MOG = myelin oligodendrocyte glycoprotein; CSF = cerebrospinal fluid.
Rituximab Efficiently Depletes Increased CD20-Expressing T Cells in Multiple Sclerosis Patients


In multiple sclerosis (MS), B cell-depleting therapy using monoclonal anti-CD20 Abs, including rituximab (RTX) and ocrelizumab, effectively reduces disease activity. Based on indirect evidence, it is generally believed that elimination of the Ag-presenting capabilities and Ag non-specific immune function of B cells underlie the therapeutic efficacy. However, a small subset of T lymphocytes (T cells) was shown to also express CD20, but controversy prevails surrounding the true existence of this T cell subpopulation. Using single-cell imaging flow cytometry and expression profiling of sorted lymphocyte subsets, we unequivocally demonstrate the existence of CD3⁺CD20⁺ T cells. We show that in MS patients, increased levels of CD3⁺CD20⁺ T cells are effectively depleted by RTX. The pathological relevance of this T cell subset in MS remains to be determined. However, given their potential proinflammatory function, depletion of CD20-expressing T cells may also contribute to the therapeutic effect of RTX and other mAbs targeting CD20. The Journal of Immunology, 2014, 193: 580-586.
Age-Associated B Cells
B Cell Subset Targeting in MS

Safety and tolerability of inebilizumab (MEDI-551), an anti-CD19 monoclonal antibody, in patients with relapsing forms of multiple sclerosis: Results from a phase 1 randomised, placebo-controlled, escalating intravenous and subcutaneous dose study

Mark A Agius, Gabriela Klodowska-Duda, Maciej Maciejowski, Andrzej Potemkowski, Jing Li, Kaushik Patra, Jacob Wesley, Soraya Madani, Gerard Barron, Eliezer Katz and Armando Flor
RESEARCH ARTICLE

Insufficient disease inhibition by intrathecal rituximab in progressive multiple sclerosis

Mika Komori¹, Yen Chih Lin¹, Irene Cortese², Andrew Blake¹, Joan Ohayon², Jamie Cherup¹, Dragan Maric³, Peter Kosa¹, Tianxia Wu⁴ & Bibiana Bielekova¹,⁵

¹Neuroimmunological Diseases Unit, National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, Maryland
²Neuroimmunology Clinic, NINDS, Bethesda, Maryland
³Flow Cytometry Core Facility, NINDS, Bethesda, Maryland
⁴Clinical Neuroscience Program, NINDS, Bethesda, Maryland
⁵NIH Center for Human Immunology (CHI), the National Institutes of Health (NIH), Bethesda, Maryland
B Cell Subsets

Atacicept in multiple sclerosis (ATAMS): a randomised, placebo-controlled, double-blind, phase 2 trial

Ludwig Kappos, Hans-Peter Hartung, Mark S Freedman, Alexey Boyko, Ernst Wilhelm Rodu, Daniel D Mikol, Marc Lamarine, Yann Hyvert, Ulrich Freudensprung, Thomas Plitz, Johan van Beek, for the ATAMS Study Group*

Summary

Background Depletion of B lymphocytes is associated with suppression of inflammatory activity in multiple sclerosis. We aimed to assess the safety and efficacy of atacicept, a recombinant fusion protein that suppresses B-cell function and antibody production.

Lancet Neurol 2014
Published Online
March 6, 2014
Atacicept in MS

Interpretation

By contrast with the positive results identified by our search, in our study anti-B-cell treatment with the recombinant protein atacicept, which targets more mature B cells than do anti-CD20 antibodies and reduces antibody production by B cells and plasma cells, resulted in disease exacerbation. This finding lends support to the idea that B cells have a dual function in both suppressing and stimulating autoimmune disease. This unforeseen adverse outcome shows that the effects of immune intervention can be difficult to predict in complex and only partly understood diseases such as multiple sclerosis. Our study emphasises the importance of thorough safety monitoring, including laboratory, imaging and, most importantly, clinical measures.
Summary

- B cells have pleiotropic immune functions
- B cells are involved in the pathogenesis of MS
- Suppressive and Pro-inflammatory properties of B cells are still being discovered/investigated
- Modeling B cell contributions to MS can be done using various EAE systems
- A reductionist approach may not be feasible for establishing the mechanism(s) of B cell involvement in MS pathogenesis
Remaining Questions

- Optimal B Cell Subsets to Target for Therapy
- Segregate B cell Functions for Therapy
- Ability to Target Ectopic Lymphoid Tissue
- Antigen-Selective Therapy
- Route of Administration
- Dose of B cell Depletion Therapy
Mechanisms of B Cell Participation in the Pathophysiology of MS
B Cells in Murine EAE

A) rMOG (rat) protein

B) hMOG (human) protein

C) rMOG_{35-55} and hMOG_{35-55}

D) WT mice with rMOG (w/human P42)

B cell-depletion therapy in MS: Background, clinical applications, and safety

John R. Rinker, II, MD
Birmingham VA Medical Center &
University of Alabama at Birmingham
August 29, 2018
PVA Summit, Dallas, TX
Disclosures

• Research support: Biogen Idec

• Off-label medication usage: rituximab, ofatumumab
Learning Objectives

1. Review the evidence and potential mechanisms associating B cells with the pathogenesis of multiple sclerosis.
2. Review the evidence supporting the use of B cell depletion therapy for multiple sclerosis.
3. Review the current practices and controversies in the use of B cell-depletion therapies for multiple sclerosis.
Overview of B cell-depletion in multiple sclerosis

• History of B cell therapeutics
• B cell-depletion in MS
• Comparison of B cell-depleting therapies
• Safety & Monitoring
• Comparison with other DMTs
Importance of B cells in MS pathogenesis

The road to B cell-targeted therapies

Clinical Studies

Quantitative Estimation of the Albumin and Gamma Globulin in Normal and Pathologic Cerebrospinal Fluid by Immunochemical Methods*

Elvin A. Kabat, Ph.D., Murray Glusman, M.D. and Vesta Knaub
New York, New York

1942: First descriptions of increased gamma globulins in CSF of patients with MS

1965: Studies in chickens established two lymphocyte lineages:
1. Bursa-derived B cells
2. Thymus-derived T cells


1975: Development of first monoclonal antibodies using hybridoma technique
The road to B cell targeted therapies

1980: Discovery of CD20 B cell surface antigen


1986: First Monoclonal Ab (OKT3) approved for transplant rejection

1997: Rituximab (anti-CD20) approved for treatment of non-Hodgkins lymphoma
Subsequent approval for CLL, treatment-refractory RA

Rituximab
Mechanisms of Action

ADCC
CD20
FcyRII, FcyRIII
Cell lysis
Complement activation (C1qC1rC1s)
MAC
Cell lysis

CDC
CD20

Apoptosis

ADCC = antibody-dependent cell mediated cytotoxicity.
CDC = complement-dependent cytotoxicity.

B cell targets in autoimmunity: Rheumatoid arthritis

**Rationale for B cell-depletion**

1. B cells found in synovium of RA patients
2. Antibodies targeting Fc domain of IgG perpetuate disease in RA
3. B cell antigen presentation and co-stimulation of pathogenic T cells
4. B cells contribute inflammatory cytokines

**Efficacy in rheumatoid arthritis**

1. Benefit of B cell depletion first demonstrated 1998
2. Eight controlled trials found superiority of RTX over placebo (adjunct to methotrexate)
3. 2006: FDA approval of rituximab for RA

B cell targets in autoimmunity: Off-label success

- Immune-mediated thrombocytopenia (including ITP)
- Autoimmune hemolytic anemia
- Wegener’s granulomatosis
- Systemic lupus erythematosus
- Angioedema
- Pemphigus
- Myasthenia gravis
- Neuromyelitis optica
- Multiple sclerosis
Rationale for B cell-directed therapy in MS

Activated autoreactive B cells

Plasma cells

Oligoclonal bands, \( \uparrow \) IgG synthesis
Questions Raised by This Review and Suggested Experimentation

The following are some questions raised by this report with suggested experiments to advance further our understanding of intra-BBB IgG synthesis as it relates to the etiopathogenesis of MS.

1. Is the site of immunoregulation of intra-BBB IgG synthesis within the BBB?
   Suggested experiments: (1) Determine cell mediators such as interleukin 1 and 2 and correlate with T subsets, macrophages, B cells, and NK cells in fresh autopsy material. (2) Determine IL1 and IL2 in blood/CSF and relate to intra-BBB IgG synthesis.

2. Can active plaques of MS synthesize intra-BBB IgG in vivo? Does this IgG have the same oligodendroglial pattern when compared with CSF IgG from the same patient?
   Suggested experiments: Culture fresh plaques and extract IgG synthesized; correlate in vitro synthesized IgG with histological activity and pre- and postmortem unique CSF oligodendroglial bands.

3. Will further studies of intra-BBB IgG synthesis be correlated with intra-BBB plasma cells intra-BBB, as proposed by Fbers et al.15

4. Will intra-BBB IgG synthesis be correlated with the size and activity of NMR lesions?

5. Will further systematic immunopharmacologic studies as proposed in this report disclose a treatment that will eradicate intra-BBB IgG synthesis?
   Suggested experiments: (1) Try repetitive cyclic treatment with ACTH and prednisone (burst of ACTH every four months followed by prednisone q.o.d.). (2) Try cyclosporine A with or without corticosteroids. (3) Try different types of interferon by different routes and different doses.

6. If prolonged or persistent eradication of intra-BBB IgG synthesis occurs, will a blood-CSF IgG isotope two compartment study, the benchmark for intra-BBB IgG synthesis, also demonstrate no synthesis?
   Suggested experiments: Use same design as we did to validate our formula.24

7. What is the specificity of intra-BBB IgG synthesis in MS?
   Suggested experiments: Apply ELISA technology to calculate IgG by per ml and utilize our intra-BBB IgG synthesis formula as we have done for SSPE.47

8. Can the detection of unique CSF oligodendroglial IgG be improved by performing isoelectrofocusing on agarose, followed by electrophoretic transfer to nitrocellulose paper, and immunoenzyme detection?

9. Can an improved technique mentioned in question 8 be used to screen for putative MS antigens?

10. Can virus be detected in MS brain using the technology of in situ hybridization?
    Suggested experiments: Do in situ hybridization with as many viral complementary probes as are available.32
2002: Rituximab add-on therapy for breakthrough relapsing multiple sclerosis

2004: A Study to Evaluate Rituximab in Adults With Relapsing Remitting Multiple Sclerosis (HERMES)

2004: Rituximab in patients with primary progressive multiple sclerosis (OLYMPUS)
Phase II, open-label, add-on to standard therapy (interferon or glatiramer acetate)

- 30 subjects with active MRIs despite platform therapy
- Rituximab given at dosing for B cell lymphoma (375 mg/m$^2$) x 4 doses
- CSF at baseline and week 24
- MSFC scores improved over 32 weeks
- EDSS improved in 7, stabilized in 21, worsened in 2 subjects

Phase 2, double-blind, 48-week placebo controlled trial

- Rituximab 1000 mg given on days 1 and 15
- Significant reduction in relapse rates to week 24

Lessons learned: Pharmacology

• Near-complete CD20 deletion by 2 weeks, sustained through 24 weeks, 30.7% of baseline by 48 weeks
• Naïve B cells recover faster than memory B cells
• Duration to therapeutic effect: apparent by 12 weeks
• Duration of effect (time to re-dosing): 3*-9 months

*Personal observation
Lessons learned: Mechanistic effects of B cell-depletion

Lessons learned: Mechanism of action

Hauser SL. Mult Scler 2015.
Comparison of B cell-depleting therapies
Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis


Opera I and II
- 1656 Subjects, 1:1 ocrelizumab: SQ Ifn-B1a
- Approximately 25% treatment-naïve
- Baseline EDSS approximately 2.8

Results
- ARR Ocrelizumab 0.16, Ifn-B1a 0.29
**A OPERA I Trial**

Interferon beta-1a (N=411) vs. Ocrelizumab (N=410)

<table>
<thead>
<tr>
<th>Week</th>
<th>Interferon beta-1a</th>
<th>Ocrelizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>48</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>96</td>
<td>0.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Mean no. through 96 wk, 0.29

P<0.001

**B OPERA II Trial**

Interferon beta-1a (N=418) vs. Ocrelizumab (N=417)

<table>
<thead>
<tr>
<th>Week</th>
<th>Interferon beta-1a</th>
<th>Ocrelizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>48</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>96</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Mean no. through 96 wk, 0.42

P<0.001

**No. of Patients**

- Interferon beta-1a: 372, 357, 335, 382, 377, 359
- Ocrelizumab: 372, 334, 311, 385, 373, 359
The pathogenesis of primary progressive multiple sclerosis: antibody-mediated attack and no repair?

Michael P. Pender

School of Medicine, Neuroimmunology Research Centre, The University of Queensland, Australia
Department of Neurology, Royal Brisbane and Women’s Hospital, Herston, Qld., Australia
Phase III randomized, double-blind, placebo controlled trial of 439 PPMS patients 2:1 rituximab
- 96 week trial
- Patients: 18-65 y/o, EDSS up to 6.5
- Primary endpoint: time to 12 week sustained EDSS progression

Double-blind, placebo controlled trial

732 patients, 2:1 ocrelizumab: placebo

Subjects received at least 5 doses (120 weeks) until approximately 253 events of disability progression (measured by EDSS, sustained over 12 weeks) occurred across the study cohort
# Ocrelizumab vs rituximab in PPMS

<table>
<thead>
<tr>
<th>Entry criteria: Age range</th>
<th>Rituximab</th>
<th>Ocrelizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (years)</td>
<td>No restrictions</td>
<td>For EDSS &gt;5, &lt;15 years; for EDSS &lt;=5, &lt;10 years</td>
</tr>
<tr>
<td>EDSS range</td>
<td>2-6.5 (pyramidal &gt;=2)</td>
<td>3-6.5 (pyramidal &gt;=2)</td>
</tr>
<tr>
<td>CSF</td>
<td>Required +OCB or ↑IgG index</td>
<td>Required +OCB or ↑IgG index</td>
</tr>
</tbody>
</table>

**Subject characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Rituximab</th>
<th>Ocrelizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at entry</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>9.1</td>
<td>6.4</td>
</tr>
<tr>
<td>EDSS (median)</td>
<td>5.0</td>
<td>4.5</td>
</tr>
<tr>
<td>% with Gd+ MRI lesions</td>
<td>24.5</td>
<td>26.1</td>
</tr>
</tbody>
</table>
Ofatumumab: fully human anti-CD20 Ab

• Human antibody (least possible immunogenicity)
• Slower dissociation rate than rituximab leading to improved CDC
• Phase 2 study of infused ofatumumab reported in 2014
• Phase 2 MIRROR study:
  1. Demonstrate efficacy of SQ administered ofatumumab
  2. Determine minimally effective dose of SQ-administered anti-CD20 Ab

>90% reduction in new T1Gd+ and T2 lesions after 4 weeks of therapy

Efficacy and Safety of Ofatumumab Compared to Placebo in Patients With Relapsing Multiple Sclerosis Followed by Extended Treatment With Open-label Ofatumumab (Phase II)

Efficacy and Safety of Ofatumumab Compared to Teriflunomide in Patients With Relapsing Multiple Sclerosis (ASCLEPIOS I) (Phase III)
Comparison of B cell-depleting therapies

<table>
<thead>
<tr>
<th></th>
<th>Rituximab</th>
<th>Ocrelizumab</th>
<th>Ofatumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>ADCC/CDC/apoptosis</td>
<td>ADCC&gt;CDC</td>
<td>CDC</td>
</tr>
<tr>
<td><strong>Delivery method</strong></td>
<td>IV</td>
<td>IV</td>
<td>SQ</td>
</tr>
<tr>
<td><strong>B cell depletion</strong></td>
<td>Complete</td>
<td>Complete</td>
<td>Incomplete</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Greatest</td>
<td>Low</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>Availability for clinical use</strong></td>
<td>Off-Label</td>
<td>FDA-approved</td>
<td>Investigational</td>
</tr>
</tbody>
</table>
Safety of B cell-depleting therapies

- **Acute**
  - Infusion reactions

- **Medium term (clinical trial duration)**
  - Infections
  - Neoplasms

- **Long-term**
  - Hypogammaglobulinemia
  - Infections/Prolonged immune suppression
  - PML
## Rituximab adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence (pooled from trials/registries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>25% (first infusion), then 13% &gt; 9% &gt; 3%</td>
</tr>
<tr>
<td>Serious infection</td>
<td>3.9/100 patient years (static over 9+ years)</td>
</tr>
<tr>
<td>Herpes zoster reactivation</td>
<td>9/1000 patient years</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0.06%</td>
</tr>
<tr>
<td>Hepatitis B infection/reactivation</td>
<td>0.03%</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>2.3/100,000 patient years</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Not increased over RA population</td>
</tr>
<tr>
<td>Hypogammaglobulinemia (&gt;9.5 years)</td>
<td>IgM (22.4%), IgG (3.5%),* IgA (1.1%)</td>
</tr>
</tbody>
</table>

*only Ig deficiency assoc w/ infection risk

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Mok CC. Drug Des Devel Ther 2014.
# Ocrelizumab adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence (pooled from trials registries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction (vs. placebo)</td>
<td>34-40 vs 10-26%</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td><strong>RA: OCR + MTX</strong></td>
<td>Serious infections greater than MTX alone</td>
</tr>
<tr>
<td>Upper respiratory infections</td>
<td>40-49 vs 33-43%</td>
</tr>
<tr>
<td>HSV</td>
<td>6 vs 4%</td>
</tr>
<tr>
<td>Skin infections</td>
<td>14 vs 11%</td>
</tr>
<tr>
<td>Herpes zoster reactivation</td>
<td>9/1000 patient years</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0.06%</td>
</tr>
<tr>
<td>Hepatitis B infection/reactivation</td>
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<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>2.3/100,000 patient years</td>
</tr>
<tr>
<td>Malignancy</td>
<td>6/781 in MS; Not increased in RA$^1$</td>
</tr>
</tbody>
</table>

Long-term B cell depletion: Immune reconstitution and hypogammaglobulinemia

Pharmacology
Half-life: Rituximab 18 d (RA dosing), Ocrelizumab (26 d)

Immune reconstitution
Median return of B cell counts to baseline or LLN is 72 weeks (range 27-175 weeks); at 2.5 years 90% have recovered

<table>
<thead>
<tr>
<th></th>
<th>Ocrelizumab RRMS (96 weeks)</th>
<th>Ocrelizumab PPMS (96 weeks)</th>
<th>Rituximab (24 weeks)</th>
<th>Rituximab (Long-term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>1.5%</td>
<td>1.1%</td>
<td>2.8%</td>
<td>5.5%</td>
</tr>
<tr>
<td>IgA</td>
<td>2.4%</td>
<td>0.5%</td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>IgM</td>
<td>16.5%</td>
<td>15.5%</td>
<td>10%</td>
<td>23.3%</td>
</tr>
</tbody>
</table>
Long-term B cell depletion: Progressive multifocal leukoencephalopathy

- **Class I (Greatest risk):** Natalizumab (~1:100-1:1000)
- **Class II (Real but low risk, >1:10,000):**
  - Fingolimod (~1:18,000)
  - Dimethyl fumarate (~1:50,000)
- **Class III (Theoretical or very low risk):**
  - Alemtuzumab
  - Teriflunomide
  - Rituximab (~1:30,000)
  - Ocrelizumab (5 “carry-over” cases out of >50,000 treated, 1 post fingolimod, 4 post natalizumab, as of 7/18/18)
- **Class IV (no PML risk):** Glatiramer acetate, beta-interferons

Berger JR. MSARD 2016.
Starting and maintaining anti-B cell therapy

**Startup Evaluations**
- Medical comorbidities and history of recurrent infections
- Hepatitis B (HBsAg, anti-HBc IgG) and C serologies
- Baseline immunoglobulins (low baseline IgG associated with increased infection risk on rituximab)
- Vaccination (pneumococcus, VZV) at least 4 weeks prior to starting therapy

**Maintenance Evaluations**
- B cell counts, serum immunoglobulins, blood counts and liver enzymes

Mok CC. Drug Des Devel Ther 2014.
Comparison to other MS DMTs: Cohort studies

What we don’t know

- What is the long-term efficacy of B cell depletion therapy?
- What is the long-term safety of B cell depletion?
- Are there advantages to early vs. late initiation of B cell depletion therapy?
- How to identify optimal responders to B cell depletion?
- How should B cell depletion be sequenced with other MS DMTs?
Conclusions

1. B cell depletion effectively reduces both inflammatory and degenerative aspects of multiple sclerosis
2. Effects of B cell depletion appear mediated primarily by B cell functions other than antibody synthesis and transition into plasma cells
3. Relative efficacy of rituximab, ocrelizumab, and ofatumumab remains undetermined; however, immunogenicity is reduced with increasingly human monoclonal antibodies
4. Safety over the short to medium term appears very good; long-term (years) safety is unknown
5. B cell depletion likely represents one of the more effective approaches to MS therapy based on limited observational data