Disease modifying agents for patients with multiple sclerosis: Adherence, compliance, and efficacy

Olaf Stüve, M.D., Ph.D.

Neurology Section
VA North Texas Health Care System
Medical Service, Dallas

Department of Neurology & Neurotherapeutics
University of Texas
Southwestern Medical Center at Dallas
Disclosures

- Dr. Stüve serves on the editorial boards of JAMA Neurology, Multiple Sclerosis Journal, Therapeutic Advances in Neurological Disorders
- Dr. Stüve has received grant support from Teva Pharmaceuticals and Opexa Therapeutics
- Dr. Stüve has served on data monitoring committees for TG Therapeutics, Pfizer and Sanofi-Aventis without monetary compensation
- Dr. Stüve served on an advisory board for Sanofi Genzyme and Genentech, and he advised Navigant Consulting
- Dr. Stüve represented Novartis at the European Medicines Agency (EMA)
- Dr. Stüve is funded by a Merit grant from the US Department of Veterans Affairs
- PESG and PVA staff have no interest to disclose.

- This continuing education activity is managed and accredited by Professional Education Services Group in cooperation with PVA. PESG, PVA, and all accrediting organization do not support or endorse any product or service mentioned in this activity.
Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. To understand the biological rationale for using first generation DMTs in patients with relapsing forms of MS
2. To learn about the MOA of these agents
3. To comprehend the data on efficacy and safety of GA and IFNβ preparations
CE/CME Credit

If you would like to receive continuing education credit for this activity, please visit:

http://PVA.cds.pesgce.com
Multiple Sclerosis

- Inflammatory disease of the CNS that destroys myelin, oligodendrocytes and axons
- Affects more than 2.5 million individuals in North America and Europe
- Major cause of non-traumatic neurologic disability in young adults
Four Types of MS

- Relapsing-Remitting
- Primary-Progressive
- Secondary-Progressive
- Progressive-Relapsing

Clinically isolated syndrome (CIS)

1996
MS clinical description
Subtypes

- Relapsing-remitting disease (RRMS)
  - With full recovery from relapses
  - With sequelae/residual deficit after incomplete recovery

2013
MS disease modifiers
Phenotypes

- Clinically isolated syndrome (CIS)
  - Not active*
  - Active* **

- Relapsing-remitting disease (RRMS)
  - Not active*
  - Active*

Immunopathogenesis of MS
Is the primary effect of MS risk alleles in CNS or leukocytes?

Threshold of significance, accounting for the number of cell types and tissues tested.

All other tissue (skin, muscle, GI tract, endocrine tissue, ...)

Hematologic malignancies & immune tissue

Peripheral blood immune cells

CNS regions-cortical and subcortical

Jager et al.
Interferon beta
In Memoriam: Jean Lindenmann (1924-2015)

A Circuitous Interfering Power in Neurology

Cliff Stone, MD, PhD

Sometimes, the intended consequences of scientific discovery are not the ones that ultimately have the greatest impact on humanity. This is certainly the case of the interferons, which were discovered jointly by Jean Lindenmann and Alick Isaacs in an attempt to elucidate the role of interferons in host innate immune responses against viral infections.

Dr. Lindenmann, a Swiss virologist who passed away on January 15, 2015, in Zürich, Switzerland, was an outstanding scientist whose contributions to the interferon field were groundbreaking. He joined Dr. Isaacs in the mid-1950s as a postdoctoral fellow at the National Institute for Medical Research in Mill Hill in London, England. The purpose of his research was to study the nature of “viral interference.” When he commenced his work it was already established that incubation of a tissue or tissue culture with host-inactivated virus could prevent the replication of a virus that was subsequently added. Drs. Lindenmann and Isaacs subsequently demonstrated that fluid conditioned for 24 hours with chick choetro-allantoic membranes exposed to inactivated virus could transfer this “interfering power” to fresh membranes, indicating that additional “interfering activity” had been generated. Dr. Lindenmann then showed that a certain time lapse was required to obtain interference, suggesting that a new protein had to be generated to achieve this. Furthermore, dilution experiments indicated a linear relationship between the concentration of interferon and its antiviral potency. The seminal article reporting the discovery of interferons was published in 1957, which ultimately proved to be a family of proteins with a very high specific activity and a broad spectrum of biological effects.

Dr. Lindenmann returned to Zürich but did not pursue the purification and structural analysis of interferon. He was convinced that this task would be more or less rapidly accomplished by biochemists. In retrospect, this decision may appear misguided. Thousands of man-years later, in 1966, Ernest Kieff remarked that “the best way to describe the progress in purification and characterization of the interferon proteins is that it has just begun.” At that time, the multiplicity of interferon species and the low levels of production proved to be an almost unsurmountable barrier. Rather than purifying interferon, Dr. Lindenmann explored its mechanism of action and identified a dominant autosomal gene, which he called Mx (now called Mx1), that mediated interferon-induced resistance against influenza and some other viruses.

The Mx promoter is a powerful tool to direct controlled expression of a downstream gene and is now widely used in inducible gene expression in experimental mice. After 1980, research in the interferon field progressed rapidly as recombinant DNA technology clarified the relationship between the many interferon species and allowed the production of pure interferon on the kilogram scale. Most importantly, the generation of interferons on an industrial scale led to legitimate clinical applications. In 1987, Hillel Panitch, MD, and colleagues conducted a clinical trial with interferon gamma in patients with relapsing-remitting multiple sclerosis (MS). At that time, many MS experts considered MS to be a viral, postiral, or paraviral disorder, which made interferon gamma a plausible intervention. Unexpectedly, a disproportionate number of patients displayed disease exacerbations, and bioassays detected an increase in circulating HLA-DR-positive monocytes in peripheral blood of recipients. These observations strongly suggested that MS disease exacerbations are immune mediated and not the consequence of viral illness.

In contrast, interferon beta preparations have been approved and used for the treatment of MS for more than 20 years. The biological beneficial effects of interferon beta in MS, which include the reduction of disease attacks and brain lesions on magnetic resonance imaging, are pleiotropic and still incompletely understood. The recent approval of pegylated interferon beta-1a will likely ensure that they remain a mainstay of MS therapy for decades to come. Thus, Dr. Lindenmann's discovery not only opened up a new area of basic research, but also led to practical medical benefits.

Those who knew Dr. Lindenmann describe him as a gifted communicator who time and again delighted ly Veteran and colleagues alike with his philosophical and historical discourses on scientific topics. Modest and unassuming, he kept out of the limelight toward which many another with his accomplishments would have striven.
Intrathecal Interferon Reduces Exacerbations of Multiple Sclerosis

Abstract. Ten patients with multiple sclerosis who were treated with human fibroblast interferon (IFN-B) for 6 months showed a significant reduction in their exacerbation rates compared with their rates before treatment (P < .01). The IFN-B was administered intrathecally by serial lumbar punctures. There was no significant change in the exacerbation rates of ten multiple sclerosis control patients before and during the period of observation. The IFN-B recipients have now been on the study a mean of 1.5 years, the controls, 1.2 years. The clinical condition of five of the IFN-B recipients and one of the control patients has improved, whereas the condition of five of the controls and one of the IFN-B recipients has deteriorated (P < .036). These findings warrant cautious optimism about the efficacy of intrathecal IFN-B in altering the course of multiple sclerosis and support concepts of a viral or immune etiology of the disease.

Table 1. Effects of intrathecally administered IFN-B on patients with MS.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Type of disease*</th>
<th>Duration of disease before study (years)</th>
<th>Exacerbations before study</th>
<th>Years on study</th>
<th>Exacerbations on study</th>
<th>Match†</th>
<th>Exacerbation rate on study</th>
<th>Clinical assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>F</td>
<td>ER-R</td>
<td>1</td>
<td>4</td>
<td>1.5</td>
<td>6.0</td>
<td>0</td>
<td>No (less)</td>
<td>Better</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>F</td>
<td>ER-P</td>
<td>6.2</td>
<td>14</td>
<td>2.3</td>
<td>3.6</td>
<td>0</td>
<td>No (less)</td>
<td>Better</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>F</td>
<td>ER-P</td>
<td>9.1</td>
<td>26</td>
<td>2.9</td>
<td>4.6</td>
<td>1</td>
<td>No (less)</td>
<td>Unchanged</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>F</td>
<td>ER-P</td>
<td>8.1</td>
<td>10</td>
<td>1.5</td>
<td>1.9</td>
<td>0</td>
<td>No (less)</td>
<td>Better</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>F</td>
<td>ER-R</td>
<td>6.3</td>
<td>21</td>
<td>3.3</td>
<td>5.3</td>
<td>3</td>
<td>No (less)</td>
<td>Worse</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>M</td>
<td>S-R</td>
<td>10.2</td>
<td>6</td>
<td>1.6</td>
<td>1.0</td>
<td>0</td>
<td>No (less)</td>
<td>Better</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>F</td>
<td>ER-R</td>
<td>2.5</td>
<td>4</td>
<td>1.6</td>
<td>2.1</td>
<td>0</td>
<td>No (less)</td>
<td>Better</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>F</td>
<td>S-R</td>
<td>7.9</td>
<td>5</td>
<td>0.9</td>
<td>1.1</td>
<td>0</td>
<td>No (less)</td>
<td>Unchanged</td>
</tr>
<tr>
<td>9</td>
<td>39</td>
<td>M</td>
<td>S-R</td>
<td>19.4</td>
<td>8</td>
<td>0.4</td>
<td>0.6</td>
<td>0</td>
<td>Yes</td>
<td>Unchanged</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>F</td>
<td>S-R</td>
<td>10.5</td>
<td>8</td>
<td>0.8</td>
<td>1.1</td>
<td>0</td>
<td>No (less)</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

| Controls |     |     |                  |                                        |                           |               |                       |        |                          |                   |
| 1        | 15          | F   | ER-P            | 3.2                                    | 4                         | 1.3           | 1.5                   | 3      | No (more)                | Worse             |
| 2        | 26          | F   | ER-R            | 2.8                                    | 3                         | 1.1           | 1.3                   | 1      | Yes                      | 0.9               |
| 3        | 39          | F   | S-R             | 5.5                                    | 3                         | 0.7           | 0.8                   | 1      | Yes                      | Better            |
| 4        | 39          | F   | ER-P            | 4.5                                    | 3                         | 0.9           | 1.0                   | 2      | No (more)                | Unchanged         |
| 5        | 39          | M   | S-R             | 20.5                                   | 4                         | 0.2           | 0.2                   | 0      | Yes                      | Unchanged         |
| 6        | 31          | F   | ER-R            | 10.5                                   | 5                         | 0.5           | 0.6                   | 0      | Yes                      | 1.7               |
| 7        | 34          | M   | S-R             | 14.5                                   | 5                         | 0.3           | 0.4                   | 2      | No (more)                | Unchanged         |
| 8        | 26          | F   | S-R             | 6.5                                    | 5                         | 0.8           | 1.0                   | 0      | No (less)                | Worse             |
| 9        | 39          | F   | S-R             | 9.8                                    | 3                         | 0.3           | 0.4                   | 1      | No (more)                | 0.9               |
| 10       | 38          | F   | S-R             | 7.7                                    | 6                         | 0.8           | 0.9                   | 0      | Yes                      | Unchanged         |

*Type of disease when entering study: ER-R, exacerbating-relapsing with residual; ER-P, exacerbating, progressive; S-R, stable with residual. †Determined by multiplying the exacerbation rate before the study by the number of years on the study. Determined by comparing the expected exacerbation rate with the actual number of exacerbations on the study: "No (less)" indicates disagreement, actual number less than expected; "No (more)" indicates disagreement, actual number more than expected; "Yes" indicates agreement.
How intrathecal IFN-B might have had a beneficial effect in these patients is unknown; the mechanisms of interferon’s actions are complex and incompletely understood. Interferon is a mediator of T-lymphocyte suppression; the treatment may have stabilised the fluctuations in suppressor T-cell activity known to occur during the course of MS, which have been postulated to be an integral part of the exacerbation/remission cycle.\textsuperscript{8,27,31} Alternatively, IFN-B may have changed the viral trigger for repeated exacerbations through clearance of a persistent CNS viral infection, possibly by inducing HLA-marker expression on the surface of infected cells, thus exposing them to the immune system.\textsuperscript{3}

Mean exacerbation rates (exacerbations/year) before and during the study in 34 recipients and 35 controls with MS.
Treatment of multiple sclerosis with gamma interferon: Exacerbations associated with activation of the immune system

Hillel S. Panitch, MD; Robert L. Hirsch, PhD; John Schindler, PhD; and Kenneth P. Johnson

Gamma or immune IFN has many of the antiviral and immunoregulatory properties of other interferons; in addition, it can activate macrophages and induce class II histocompatibility antigens on monocytes, endothelial cells, and astrocytes. These are properties that could stimulate an autoimmune process.

Figure 1. Increase in exacerbation rate during treatment with gamma interferon compared with pretreatment and follow-up periods.

Figure 2. M3+/HLA-DR+ cells (activated monocytes) expressed as percent of M3+ cells in peripheral blood for each dosage group (top) and for all patients combined (bottom). The combined values (means ± SE) were significantly increased at days 7 and 21 (p < 0.05) and day 14 (p < 0.01).

MMP-9 is elevated in serum of MS patients

Interferon β-1b Decreases the Migration of T Lymphocytes In Vitro: Effects on Matrix Metalloproteinase-9

Olaf Stüve, MD,* Nora P. Dooley, MSc,* Joon H. Uhm, MD,* Jack P. Antel, MD,* Gordon S. Francis, MD,* Gary Williams, PhD,† and Voon Wee Yong, PhD*

---

Interferon Beta-1b Inhibits Gelatinase Secretion and In Vitro Migration of Human T Cells: A Possible Mechanism for Treatment Efficacy in Multiple Sclerosis

David Leppert, MD,*† Emmanuelle Waubant, MD,‡ Martin R. Bürk, BSc,* Jorge R. Oksenberg, PhD,‡ and Stephen L. Hauser, MD‡
Serum MMP-9 and TIMP-1 levels are related to MRI activity in relapsing multiple sclerosis

E. Waubant, MD; D.E. Goodkin, MD; L. Gee, MPH; P. Bacchetti, PhD; R. Sloan; T. Stewart, RN; P.-B. Andersson, MBChB, DPhil; G. Stabler; and K. Miller, DPhil

IFNβ - Potential Mechanisms of Action

• Acts in periphery (does not cross BBB)
• Has antiviral effect
• IFNγ antagonistic
• Blocks T cell activation
• Induces an anti-proliferative effects
• Induces apoptosis of autoreactive T cells
• Induces cytokine shifts

Glatiramer acetate
COP 1 is synthesized by the random polymerization of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine in the ratio of 6.0:1.9:4.7:1.0 (molecular weight, 14,000 to 23,000). It was one of a series of polypeptides prepared to simulate myelin basic protein, a natural component of the myelin sheath.\textsuperscript{1-3}

Myelin basic protein in Freund’s complete adjuvant induces experimental allergic encephalomyelitis, an animal model of multiple sclerosis. In saline, it suppresses the response in challenged animals.\textsuperscript{4,5} Some of the polypeptides simulating myelin basic protein, particularly Cop 1, proved incapable of inducing experimental allergic encephalomyelitis, yet suppressed the disease in rabbits, guinea pigs, mice, and nonhuman primates.\textsuperscript{1,6-9} Studies in mice suggest that it acts through the production of antigen-specific suppressor T cells.\textsuperscript{10,11} Cop 1 is also nontoxic during short-term and longer-term (three to six months) administration in mice, rabbits, and dogs (Meshorer A: personal communication).

\textit{Bornstein et al. NEJM. 1987.}
Abstract

A synthetic polypeptide, copolymer I (COP I), composed of alanine, glutamic acid, lysine, and tyrosine, has been demonstrated to be nonencephalitogenic and nontoxic in laboratory animals, yet it is capable of suppressing experimental allergic encephalomyelitis. A preliminary open trial examined the ability of COP I to alter the course of disease in 12 patients with chronic progressive and 4 with exacerbating-remitting multiple sclerosis (MS). After therapy for as long as two years or more, no undesirable side reaction was noted in any patient. Three patients with chronic progressive MS and 2 with exacerbating-remitting disease are better. These results, which may represent simply a placebo effect or may be a significant response, are now being examined in randomized, placebo-controlled, double-blind pilot trials.

A PILOT TRIAL OF COP 1 IN EXACERBATING–REMITTING MULTIPLE SCLEROSIS


The 12 batches from the Weizmann Institute had a suppression rate ranging from 10 to 80 percent (average, 33.5 percent); the rate for 14 batches produced by Bio-Yeda ranged from 10 to 75 percent (average, 40.6 percent).

Table 1. Base-Line Characteristics of the Study Population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment Group</th>
<th>Placebo</th>
<th>COP 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Cop 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>randomized</td>
<td>included in analysis</td>
<td></td>
</tr>
<tr>
<td>No. entered</td>
<td>25</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Average age (yr)</td>
<td>31.0</td>
<td>31.1</td>
<td>30.0</td>
</tr>
<tr>
<td>Average duration of disease (yr)</td>
<td>6.1</td>
<td>6.4</td>
<td>4.9</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Race/ethnic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>25</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Black/Hispanic</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Disability score (Kurtzke Scale)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>11</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>3–4</td>
<td>7</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>5–6</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Average disability score</td>
<td>3.2</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Prior exacerbation rate</td>
<td>3.9</td>
<td>3.9</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Figure 1. Exacerbations Occurring during the Two Years of the Trial.

Bornstein et al. NEJM. 1987.
Glatiramer acetate: Potential mechanisms of action

- Blocks autoimmune T cells
- Induces anergy
- Induces bystander suppression
- Upregulates neuronal preservation
- Induction of regulatory T<sub>H</sub>2 and T<sub>H</sub>3 cells that penetrate CNS
- Enhanced expression of BDNF, IL-10, TGF-β
- Sustained augmentation of BDNF, NT-3, NT-4 in the brain
- Augmentation of processes of neurogenesis: cell proliferation, migration, differentiation

Pivotal clinical trials
Interferon beta-1b is effective in relapsing-remitting multiple sclerosis.

I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial

The IFNB Multiple Sclerosis Study Group*

NEUROLOGY 1993;43:655-661

Figure 2. Kaplan-Meier analysis showing the probability of remaining exacerbation-free in the first 2 years of the study.
Interferon beta-1b is effective in relapsing-remitting multiple sclerosis.

II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial

D.W. Paty, MD; D.K.B. Li, MD; the UBC MS/MRI Study Group; and the IFNB Multiple Sclerosis Study Group

Table 5. Active lesion rate

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Statistic</th>
<th>Placebo</th>
<th>IFNB 1.6 MIU</th>
<th>IFNB 8 MIU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active lesions per year</td>
<td>Median</td>
<td>3.0</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>4.9</td>
<td>1.8</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td>1.3</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Overall:</td>
<td></td>
<td></td>
<td>p = 0.0234</td>
<td></td>
</tr>
<tr>
<td>Placebo vs 8 MIU:</td>
<td></td>
<td>p = 0.0089</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo vs 1.6 MIU:</td>
<td></td>
<td>p = 0.0412</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6 vs 8 MIU:</td>
<td></td>
<td>p = 0.5070</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multiple Sclerosis Centers of Excellence

Interferon beta-1b (Betaseron®, Extavia®)

Interferon beta-1b (Betaseron®, Extavia®) treats relapsing forms of MS. Studies show that it can slow the accumulation of physical disability and reduces frequency of exacerbations when used regularly over long periods of time. It does not improve existing MS symptoms and it is not used to treat acute MS attacks. Interferon beta-1b is an injectable medication and is usually prescribed at a dose of 250 mg administered subcutaneously (just under the skin) every other day. Auto-injectors, prefilled easy-to-use syringes, are available. Before starting medication a complete blood count (CBC) with differential and liver function tests should be completed. Ongoing lab tests will monitor for common adverse reactions of change in blood cell counts. The common side effects include injection-site reactions, redness around injection site, general weakness, flu-like symptoms (fever, chills, muscle aches, tiredness and/or sweating) headache and/or pain. Individuals who have questions about Interferon beta-1b (Betaseron®, Extavia®) should contact their healthcare provider.

For more information.

Betaseron (https://www.betaseron.com/) (website for patients and professionals)
Extavia (http://www.extavia.com/) (website for patients and professionals)
Intramuscular Interferon Beta-1a for Disease Progression in Relapsing Multiple Sclerosis

Lawrence D. Jacobs, MD,* Diane L. Cookfair, PhD,† Richard A. Rudick, MD,‡ Robert M. Herndon, MD,§ John R. Richert, MD,¶ Andres M. Salazar, MD,**, Jill S. Fischer, PhD,† Donald E. Goodkin, MD,†† Carl V. Granger, MD,‡‡ Jack H. Simon, MD, PhD,§§ John J. Alam, MD,¶¶ David M. Barroszak, MD,** Dennis N. Bourdette, MD,*** Jonathan Bratman, MD,** Carol M. Brownscheidle, PhD,* Michael E. Coats, MD,** Stanley L. Cohan, MD,¶ David S. Dougherty, MD,**, Revere P. Kinkel, MD,‡ Michele K. Mass, MD,§ Frederick E. Munschauer, III, MD,* Roger L. Priore, ScD,† Patrick M. Pullicino, MD, PhD,* Barbara J. Scherokman, MD,†† Bianca Weinstock-Guttman, MD,‡ Ruth H. Whitham, MD,** and The Multiple Sclerosis Collaborative Research Group (MSCRG)

<table>
<thead>
<tr>
<th>Table 5. Frequency of Exacerbations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exacerbations for Patients with at Least 104 Weeks On-Study</td>
</tr>
<tr>
<td></td>
<td>Placebo (N = 87)</td>
</tr>
<tr>
<td></td>
<td>Number (%)</td>
</tr>
<tr>
<td>No. of exacerbations*</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23 (26)</td>
</tr>
<tr>
<td>1</td>
<td>26 (30)</td>
</tr>
<tr>
<td>2</td>
<td>10 (11)</td>
</tr>
<tr>
<td>3</td>
<td>12 (14)</td>
</tr>
<tr>
<td>≥4</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Annual exacerbation rates (per patient-year)</td>
<td></td>
</tr>
<tr>
<td>All patients§</td>
<td>0.82</td>
</tr>
<tr>
<td>104-week patient subset*</td>
<td>0.90</td>
</tr>
</tbody>
</table>

*Calculated using the first 104 weeks of data for patients accrued early enough to complete ≥104 weeks of follow-up.

§Calculated using all patients, all data, all-time on-study.

¶Mann-Whitney rank sum test.

**Likelihood ratio test.

# Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis

**PRISMS** (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) Study Group*

<table>
<thead>
<tr>
<th>Relapses per patient</th>
<th>Placebo (n=187)</th>
<th>Interferon β-1a 22 µg (n=189)</th>
<th>Interferon β-1a 44 µg (n=184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>2.56</td>
<td>1.82*</td>
<td>1.73*</td>
</tr>
<tr>
<td>% reduction vs placebo</td>
<td>--</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>% reduction vs placebo (95% CI) by GLM log link</td>
<td>--</td>
<td>27 (14–39)</td>
<td>33 (21–44)</td>
</tr>
<tr>
<td>% relapse-free over 1 year</td>
<td>22</td>
<td>37*</td>
<td>45*</td>
</tr>
<tr>
<td>% relapse-free over 2 years</td>
<td>16</td>
<td>27†</td>
<td>32*</td>
</tr>
<tr>
<td>% with 1–2 relapses</td>
<td>39</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>% with ≥3 relapses</td>
<td>45</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Odds ratio, none vs any relapses (95% CI)</td>
<td>1.00</td>
<td>2.01 (1.21–3.35)†</td>
<td>2.57 (1.56–4.25)*</td>
</tr>
</tbody>
</table>

**Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study**

Peter A Calabresi, Remo C Kieser, Douglas L Arnold, Laurell Balcer, Alexey Boyko, Jean Pelletier, Shifang Liu, Ying Zhu, Ali Sedighzadeh, Serena Hung, Aaron Dukin, for the ADVANCE Study Investigators

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n=500)</th>
<th>Peginterferon beta-1a 125 µg every 2 weeks group (n=512)</th>
<th>Peginterferon beta-1a 125 µg every 4 weeks group (n=500)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annualised relapse rate at 48 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualised relapse rate (95% CI)*</td>
<td>0.378 (0.328-0.428)</td>
<td>0.256 (0.206-0.318)</td>
<td>0.288 (0.234-0.355)</td>
</tr>
<tr>
<td>Rate ratio (vs placebo; 95% CI)</td>
<td>-</td>
<td>0.644 (0.500-0.831)</td>
<td>0.725 (0.565-0.930)</td>
</tr>
<tr>
<td>p value (vs placebo)</td>
<td>-</td>
<td>0.0007</td>
<td>0.0114</td>
</tr>
<tr>
<td><strong>Proportion of patients with a relapse at 48 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>142</td>
<td>90</td>
<td>105</td>
</tr>
<tr>
<td>Estimated proportion relapsed (SE)</td>
<td>0.291 (0.0206)</td>
<td>0.187 (0.0178)</td>
<td>0.232 (0.0191)</td>
</tr>
<tr>
<td>Hazard ratio vs placebo (95% CI)**</td>
<td>-</td>
<td>0.619 (0.47-0.80)</td>
<td>0.74 (0.57-0.95)</td>
</tr>
<tr>
<td>p value (vs placebo)**</td>
<td>-</td>
<td>0.0003</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Disability progression at 48 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>50</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Estimated proportion with disability progression (SE)</td>
<td>0.105 (0.0142)</td>
<td>0.068 (0.0119)</td>
<td>0.068 (0.0119)</td>
</tr>
<tr>
<td>Hazard ratio vs placebo (95% CI)**</td>
<td>-</td>
<td>0.62 (0.40-0.97)</td>
<td>0.62 (0.40-0.97)</td>
</tr>
<tr>
<td>p value (vs placebo)**</td>
<td>-</td>
<td>0.0383</td>
<td>0.0380</td>
</tr>
<tr>
<td><strong>New or newly enlarging T2-weighted hyperintense lesions at 48 weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients evaluated</td>
<td>476</td>
<td>457</td>
<td>462</td>
</tr>
<tr>
<td>Adjusted mean number of lesions (95% CI)**</td>
<td>10.9 (9.6-12.5)</td>
<td>3.6 (3.1-4.2)</td>
<td>7.9 (6.9-9.0)</td>
</tr>
<tr>
<td>Lesion volume ratio (95% CI)**</td>
<td>-</td>
<td>0.33 (0.27-0.40)</td>
<td>0.72 (0.60-0.87)</td>
</tr>
<tr>
<td>p value (vs placebo)**</td>
<td>-</td>
<td>&lt;0.0001</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**EDSS**:Expanded Disability Status Scale. Peginterferon-beta-1a interferon. *Based on negative binomial regression; adjusted for baseline EDSS (<4 vs ≥4), baseline relapse rate, and age (<40 vs ≥40). †Based on Cox proportional hazards model, adjusted for baseline EDSS (<4 vs ≥4), age (<40 vs ≥40), baseline relapse rate, and baseline gadolinium-enhancing lesions (presence vs absence). ‡Defined as ≤1.0 point increase on the EDSS from a baseline EDSS ≥1.0 sustained for 12 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS ≥1.0 sustained for 12 weeks. §Based on Cox proportional hazards model, adjusted for baseline EDSS at age (<40 vs ≥40) years. ||Intention-to-treat population with ≥1 post-baseline lesion on MRI scan. ‖Data after patients switched to alternative multiple sclerosis drugs were deemed missing; all missing data were imputed on the basis of previous visit data assuming a constant rate of lesion development. 18 participants in the placebo group, 2 in the every 4 weeks group, and 18 in the every 4 weeks group had imputed data. *Based on negative binomial regression analysis, adjusted for region and baseline T2 lesion number.

Table 2: Primary and secondary clinical and MRI results

---

Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years

KP Johnson*,1, BR Brooks2, CC Ford3, A Goodman4, J Guarnaccia5, RP Lisak6, LW Myers7, HS Panitch1, A Pruitt6, JW Rose8, N Kachuck9, JS Wolinsky*10 and the Copolymer 1 Multiple Sclerosis Study Group†

*Department of Neurology, University of Maryland, Baltimore, Maryland, USA; †Department of Neurology, University of Wisconsin, Madison, Wisconsin, USA; ‡Department of Neurology, University of New Mexico, Albuquerque, New Mexico, USA; §Department of Neurology, University of Rochester, Rochester, New York, USA; ¶Department of Neurology, Yale University, New Haven, Connecticut, USA; ‡Department of Neurology, Wayne State University, Detroit, Michigan, USA; ‡Department of Neurology, University of California, Los Angeles, California, USA; §Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania, USA; ¶Department of Neurology, University of Utah and the Veterans Administration Medical Center, Salt Lake City, Utah, USA; ‡Department of Neurology, University of Southern California, Los Angeles, California, USA; ¶Department of Neurology, University of Texas, Houston, Texas, USA

Table 3  Reduction from baseline in annual relapse rate

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Entered open-label study</th>
<th>Annual relapse rate at randomization (mean ± s.d.)</th>
<th>Annual relapse rate during the double-blind phase</th>
<th>P-value (Paired t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Yes (n=101)</td>
<td>1.49±0.65</td>
<td>0.61±0.68</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>No (n=24)</td>
<td>1.33±0.55</td>
<td>1.05±0.94</td>
<td>NS</td>
</tr>
<tr>
<td>Group B</td>
<td>Yes (n=107)</td>
<td>1.45±0.56</td>
<td>0.81±0.88</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>No (n=19)</td>
<td>1.55±0.62</td>
<td>1.47±1.14</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS=not significant.
United States open-label glatiramer acetate extension trial for relapsing multiple sclerosis: MRI and clinical correlates

Jerry S Wolinsky*,1, Ponnada A Narayana2, Kenneth P Johnson3 and the Copolymer 1 Multiple Sclerosis Study Group and the MRI Analysis Center4

1Department of Neurology, The University of Texas-Houston, Health Science Center, Houston, Texas, USA; 2Department of Radiology, The University of Texas-Houston, Health Science Center, Houston, Texas, USA; 3Department of Neurology, The University of Maryland-Baltimore, Maryland, USA

European/Canadian Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Effects of Glatiramer Acetate on Magnetic Resonance Imaging–Measured Disease Activity and Burden in Patients with Relapsing Multiple Sclerosis

Giancarlo Comi, MD,1 Massimo Filippi, MD,2 Jerry S. Wolinsky, MD,3 and the European/Canadian Glatiramer Acetate Study Group

Glatiramer acetate (Glatopa)

Glatopa™ (glatiramer acetate) 20mg/mL is a subcutaneous injection indicated for the treatment of patients with relapsing-forms of multiple sclerosis. It is considered therapeutically equivalent to the brand name medication called Copaxone. Similar to Copaxone, there is an immediate post-injection reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria), generally transient and self-limiting. Some patients may experience chest pain, which is short-term. Proper injection technique and rotating injection sites can avoid/minimize lipoatrophy and skin necrosis. Glatopa can modify immune response.

For more information:

Glatopa (http://glatopa.com/) (website for patients and providers)
Three Times Weekly Glatiramer Acetate in Relapsing–Remitting Multiple Sclerosis

Omar Khan, MD,1 Peter Rieckmann, MD,2 Alexey Boyko, MD,3 Krzysztof Selmaj, MD,4 and Robert Zivadinov, MD, PhD,5 for the GALA Study Group

Objective: To assess the efficacy and safety of glatiramer acetate (GA) 40 mg administered 3× weekly (tw) compared with placebo in patients with relapsing–remitting multiple sclerosis (RRMS).

Methods: This randomized, double-blind study was conducted in 142 sites in 17 countries. Patients with RRMS with at least 1 documented relapse in the 12 months before screening, or at least 2 documented relapses in the 24 months before screening, and an Expanded Disability Status Scale score ≤ 5.5, were randomized 2:1 to receive either subcutaneous (sc) GA 40 mg tw (1ml) or placebo for 12 months.

Results: Of 1,524 patients screened, 1,404 were randomized to receive GA 40 mg sc tw (n = 943) or placebo (n = 461). Ninety-three percent and 91% of patients in the placebo and GA groups, respectively, completed the 12-month study. GA 40 mg tw was associated with a 34.0% reduction in risk of confirmed relapses compared with placebo (mean annualized relapse rate = 0.331 vs 0.505; p < 0.0001). Patients who received GA 40 mg tw experienced highly significant reduction (p < 0.0001) in the cumulative number of gadolinium-enhancing T1 (44.8%) and new or newly enlarging T2 lesions (34.7%) at months 6 and 12. GA 40 mg tw was safe and well tolerated. The most common adverse events in the GA group were injection site reactions (35.5% with GA vs 5.0% with placebo).

Interpretation: GA 40 mg sc tw is a safe and effective regimen for the treatment of RRMS, providing the convenience of fewer sc injections per week.

**TABLE 2. Annualized Relapse Rate/Severe Relapse Rate, Time to First Relapse, and Proportion of Relapse-Free Subjects**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Analysis Estimate (95% CI)</th>
<th>GA 40mg tw, n = 943</th>
<th>Placebo, n = 461</th>
<th>RR, GA vs placebo</th>
<th>p</th>
<th>RRR, GA vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualized relapse rate</td>
<td>0.331 (0.280–0.392)</td>
<td>0.505 (0.418–0.609)</td>
<td>0.656 (0.539–0.799)</td>
<td>&lt;0.0001</td>
<td>34.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Exploratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualized severe relapse rate</td>
<td>0.301 (0.252–0.359)</td>
<td>0.466 (0.383–0.568)</td>
<td>0.644 (0.526–0.790)</td>
<td>&lt;0.0001</td>
<td>35.4%</td>
<td></td>
</tr>
<tr>
<td>Time to first relapse, days</td>
<td>393</td>
<td>377</td>
<td>0.606 (0.493–0.744)</td>
<td>&lt;0.0001</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Relapse-free patients, %</td>
<td>77.0</td>
<td>65.5</td>
<td>1.928 (1.491–2.494)</td>
<td>&lt;0.0001</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*Hazard ratio.

bOdds ratio.

CI = confidence interval; GA = glatiramer acetate; NA = not applicable; RR = risk ratio; RRR = relative risk reduction; tw = 3× weekly.
Dose comparison trials
Randomized, comparative study of interferon β-1a treatment regimens in MS

The EVIDENCE Trial

H. Panitch, MD; D.S. Goodin, MD; G. Francis, MD; P. Chang, PhD; P.K. Coyle, MD; P. O'Connor, MD; E. Monaghan, PhD; D. Li, MD; and B. Weinshenker, MD, for the EVIDENCE (EVidence of Interferon Dose-response: European North American Comparative Efficacy) Study Group and the University of British Columbia MS/MRI Research Group*
EVIDENCE trial

Adapted with permission from Panitch et al. Neurology. 2002.
Articles

Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN)

Luca Durelli, Elisabetta Verdun, Pierangelo Barbero, Mauro Bergui, Elisabetta Versino, Angelo Ghezzi, Enrico Montanari, Mauro Zaffaroni, and the Independent Comparison of Interferon (INCOMIN) Trial Study Group*
INCOMIN study

Adapted with permission from Durelli et al. Lancet. 2002.
Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing–remitting MS

J.A. Cohen, MD; M. Rovaris, MD; A.D. Goodman, MD; D. Ladkani, PhD; D. Wynn, MD; and M. Filippi, MD; for the 9006 Study Group

NEUROLOGY 2007;68:939–944

Figure 2. Gadolinium-enhancing (GdE) lesion number at each visit.
IFNβ - GA comparison trials
250 µg or 500 µg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study

Paul O’Connor*, Massimo Filippi*, Barry Arnason, Giancarlo Comi, Stuart Cook, Douglas Goodin, Hans-Peter Hartung, Douglas Jeffery, Ludwig Kappos, Francis Boateng, Vitali Filippov, Maria Grath, Volker Knappertz, Christian Kraus, Rupert Sandbrink, Christoph Pohl†, Timon Bogumil†, for the BEYOND Study Group†.

Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial

Daniel D Mikol, Frederik Barkhof, Peter Chang, Patricia K Coyle, Douglas R Jeffery, Steven R Schwid, Bettina Stubinski, Bernard M J Uitdehaag, on behalf of the REGARD study group*
Treatment optimization studies
Randomized Study Combining Interferon and Glatiramer Acetate in Multiple Sclerosis

Fred D. Lublin, MD,1 Stacey S. Cofield, PhD,2 Gary R. Cutter, PhD,2
Robin Conwit, MD,3 Ponnada A. Narayana, PhD,4 Flavia Nelson, MD,5
Amber R. Salter, MPH,2 Tarah Gustafson, RN,1 and Jerry S. Wolinsky, MD,5
for the CombiRx Investigators

Objective: A double-blind, randomized, controlled study was undertaken to determine whether combined use of interferon β-1a (IFN) 30μg intramuscularly weekly and glatiramer acetate (GA) 20mg daily is more efficacious than either agent alone in relapsing–remitting multiple sclerosis.

Methods: A total of 1,008 participants were randomized and followed until the last participant enrolled completed 3 years. The primary endpoint was reduction in annualized relapse rate utilizing a strict definition of relapse. Secondary outcomes included time to confirmed disability, Multiple Sclerosis Functional Composite (MSFC) score, and magnetic resonance imaging (MRI) metrics.

Results: Combination IFN + GA was not superior to the better of the single agents (GA) in risk of relapse. Both the combination therapy and GA were significantly better than IFN in reducing the risk of relapse. The combination was not better than either agent alone in lessening confirmed Expanded Disability Status Scale progression or change in MSFC over 36 months. The combination was superior to either agent alone in reducing new lesion activity and accumulation of total lesion volumes. In a post hoc analysis, combination therapy resulted in a higher proportion of participants attaining disease activity-free status (DAFS) compared to either single arm, driven by the MRI results.

Interpretation: Combining the 2 most commonly prescribed therapies for multiple sclerosis did not produce a significant clinical benefit over 3 years. An effect was seen on some MRI metrics. In a test of comparative efficacy, GA was superior to IFN in reducing the risk of exacerbation. The extension phase for CombiRx will address whether the observed differences in MRI and DAFS findings predict later clinical differences.

ANN NEUROL 2013;73:327-340
TABLE 3. Exacerbation Summary and Relapse Risk Comparisons by Exacerbation Type and Treatment Group

<table>
<thead>
<tr>
<th>Relapse Information by Type</th>
<th>IFN + GA, n = 499</th>
<th>IFN, n = 250</th>
<th>GA, n = 259</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDEs</td>
<td>150</td>
<td>97</td>
<td>70</td>
</tr>
<tr>
<td>NPDEs</td>
<td>135</td>
<td>96</td>
<td>78</td>
</tr>
<tr>
<td>PDEs + NPDEs</td>
<td>285</td>
<td>193</td>
<td>148</td>
</tr>
<tr>
<td>Total person-years</td>
<td>1,218.9</td>
<td>604.4</td>
<td>650.7</td>
</tr>
<tr>
<td>No. (%) participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>relapse free</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDEs</td>
<td>384 (77.0)</td>
<td>185 (74.0)</td>
<td>206 (79.5)</td>
</tr>
<tr>
<td>PDEs + NPDEs</td>
<td>305 (61.1)</td>
<td>139 (55.6)</td>
<td>166 (64.1)</td>
</tr>
</tbody>
</table>

**Group Comparisons**

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>p^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>[95% CI]</td>
<td></td>
</tr>
<tr>
<td><strong>PDE treatment group</strong></td>
<td></td>
</tr>
<tr>
<td>IFN + GA vs GA</td>
<td>1.10</td>
</tr>
<tr>
<td>IFN vs GA</td>
<td>1.43</td>
</tr>
<tr>
<td><strong>PDE + NPDE treatment groups</strong></td>
<td></td>
</tr>
<tr>
<td>IFN + GA vs GA</td>
<td>1.01</td>
</tr>
<tr>
<td>IFN vs GA</td>
<td>1.36</td>
</tr>
</tbody>
</table>

^aAge-adjusted, Cox proportional hazards model with Anderson–Gill modification.
^bStatistically significant.
CI = confidence interval; GA = glatiramer acetate; IFN = interferon β-1a; NPDE = non-protocol-defined exacerbation; PDE = protocol-defined exacerbation.
**TABLE 5. MRI Results at Month 36**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IFN + GA</th>
<th>IFN</th>
<th>GA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with month 36 MRI</td>
<td>388</td>
<td>187</td>
<td>215</td>
</tr>
<tr>
<td>Change in Z4, mean (SD)$^a$</td>
<td>$-0.02$ ($1.30$)</td>
<td>$0.05$ ($1.27$)</td>
<td>$0.10$ ($2.09$)</td>
</tr>
<tr>
<td>T2 volume at month 36, ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume mean (SD)</td>
<td>$8.99$ ($10.92$)</td>
<td>$9.42$ ($10.16$)</td>
<td>$10.93$ ($12.39$)</td>
</tr>
<tr>
<td>Volume median [range]</td>
<td>$4.66$ [0.1 to 67.1]</td>
<td>$5.88$ [0.2 to 63.0]</td>
<td>$6.54$ [0.2 to 80.0]</td>
</tr>
<tr>
<td>Change from baseline in the T2-hyperintense lesion volume component, ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)$^b$</td>
<td>$-1.38$ ($5.38$)</td>
<td>$-0.25$ ($4.18$)</td>
<td>$0.01$ ($4.81$)</td>
</tr>
<tr>
<td>Median [range]</td>
<td>$-0.87$ [-29.1 to 50.4]</td>
<td>$-0.20$ [-17.7 to 16.7]</td>
<td>$0.06$ [-19.6 to 19.1]</td>
</tr>
<tr>
<td>Change from baseline in normalized CSF, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change (SD)</td>
<td>$0.60$ ($1.34$)</td>
<td>$0.51$ ($1.22$)</td>
<td>$0.57$ ($1.14$)</td>
</tr>
<tr>
<td>% change</td>
<td>$2.91$ ($6.32$)</td>
<td>$2.46$ ($5.70$)</td>
<td>$2.78$ ($5.30$)</td>
</tr>
<tr>
<td>Change from baseline in normal-appearing gray matter, ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change (SD)</td>
<td>$-2.60$ ($27.98$)</td>
<td>$-2.99$ ($23.55$)</td>
<td>$-5.16$ ($23.66$)</td>
</tr>
<tr>
<td>% change</td>
<td>$-0.33$ ($4.79$)</td>
<td>$-0.36$ ($3.92$)</td>
<td>$-0.77$ ($3.93$)</td>
</tr>
<tr>
<td>Change from baseline in normal-appearing white matter, ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change (SD)</td>
<td>$-1.73$ ($22.63$)</td>
<td>$-0.71$ ($17.01$)</td>
<td>$-1.72$ ($15.66$)</td>
</tr>
<tr>
<td>% change</td>
<td>$-0.41$ ($5.61$)</td>
<td>$-0.12$ ($3.59$)</td>
<td>$-0.37$ ($3.48$)</td>
</tr>
</tbody>
</table>

$^a$No. for Z4: IFN + GA = 381, IFN = 185, GA = 211.

$^b$IFN + GA vs IFN, $p = 0.008$; IFN vs GA, $p = 0.48$, adjusted for baseline T2-hyperintense lesion volume component and age.

Potential side effects - safety
IFNβ: Long-term considerations

- Flu-like syndrome (fever, chills, fatigue)
- Injection-site reaction, necrosis
- Depression
- Liver function abnormalities (transaminases)
- Bone marrow suppression
- NAbs
- Possibly hypothyroidism and thyroid autoimmunity\(^1\), unconfirmed\(^2,3\)

\(^1\)Caraccio et al. J Clin Endocrinol Metab. 2005.
\(^3\)Menge et al. Neurology. 2009.
IFNβ: Flu-like symptoms

• Begin 3 hours to 6 hours after injection
• May last up to 24 hours
• Management
  – Injection at night
  – NSAIDs or acetaminophen as co-medications
  – Dose titration

IFN$\beta$: Laboratory testing & monitoring

- Baseline complete blood count and differential
- Liver function test
- Thyroid-stimulating hormone test
- Monitor laboratory test values at regular intervals after initiation of therapy
- (Consider dose adjustment or discontinuation of treatment if abnormalities persist)

IFNβ: Neutralizing antibodies

NAbs present in

- 45% of patients receiving IFNβ-1b in 2-year trial¹
- 5% of patients receiving IM IFNβ-1a for at least 1 year²
- 24% of patients receiving SC IFNβ-1a in 2-year trial³

Recommendations from AAN: IFNβ neutralizing antibodies

1. IFNβ treatment is associated with NAb production

2. NAb presence, especially in persistently high titers, may be associated with a reduction in the radiographic and clinical efficacy of IFNβ treatment

Recommendations from AAN: IFNβ neutralizing antibodies

3. NAb prevalence may be affected by IFNβ
   - Formulation
   - Dose
   - Administration route
   - Frequency

4. IM IFNb-1a less immunogenic than SC IFNb-1a and IFNb-1b but persistence is difficult to determine

5. Insufficient information on NAb testing to provide specific recommendations
   - When to test
   - Which test to use
   - How many tests are necessary
   - Which cut-off titer to apply

IFNβ: Skin care management

Skin necrosis

– Discontinue SC injections: Medical intervention if necessary
– Not infected: Sterile covering with antibiotic ointment
– Infected: Surgical intervention and broad-spectrum antibiotics
Glatiramer acetate: Laboratory testing & monitoring

None

Glatiramer acetate: Injection-site reactions

Mild-to-moderate skin reactions
  – Continue therapy
  – Apply a warm compress after injection
  – Allow drug to reach room temperature
  – Use NSAIDs

Glatiramer acetate: Injection-site reactions

Lipoatrophy occurs infrequently in patients treated with glatiramer acetate

- Characterized by loss of subcutaneous fat in previously inflamed tissue
- Results in areas of skin depression
- Prevention requires adequate injection-site rotation

Glatiramer acetate: Other potential side effects

- Post-injection reactions
  - Flushing
  - Chest pain
  - Palpitations
  - Anxiety
  - Dyspnea
  - Urticaria

- Temporal relation to injections
- These side effects are usually self-limited and occur unpredictably

# Disease-modifying therapies: Pregnancy categories

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Risk Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatiramer acetate</td>
<td>B</td>
<td>Safe in animals; no human data</td>
</tr>
<tr>
<td>IFNβ-1b</td>
<td>C</td>
<td>AEs in animals; no human data</td>
</tr>
<tr>
<td>SC IFNβ-1a</td>
<td>C</td>
<td>AEs in animals; no human data</td>
</tr>
<tr>
<td>IM IFNβ-1a</td>
<td>C</td>
<td>AEs in animals; no human data</td>
</tr>
</tbody>
</table>

Compliance

- A recent retrospective cohort study used pharmacy claims from Medco Health Solutions, Inc., of patients who initiated DMTs between October 2010 and February 2011.
- Compliance was measured via proportion of days covered (PDC) and medication possession ratio (MPR) for 12 months post-index.
- Discontinuation was defined as a ≥ 60 day gap of index DMT supply.
- Cox proportional hazard models compared time to discontinuation between cohorts.

\(^1\text{Agashivala et al. BMC Neurology. 2013.}\)
New MS drugs as first line - Yes

- Of 1,891 MS patients:
  - 13.1% initiated fingolimod
  - 10.7% interferon beta-1b
  - 20.0% intramuscular interferon beta-1a
  - 18.8% subcutaneous interferon beta-1a
  - 37.4% glatiramer acetate
- Patients initiating fingolimod had highest average PDC and MPR in both experienced and naïve DMT users
- The proportion of patients discontinuing index DMT within 12 months was significantly lower for the fingolimod cohort
- Adjusted results found that patients receiving self-injected DMTs discontinued significantly sooner than fingolimod users

\(^1\text{Agashivala et al. BMC Neurology. 2013.}\)
Conclusions

- MS in an inflammatory disorder of the CNS
- IFNβ and GA have pleiotropic anti-inflammatory properties
- The mechanisms of action of IFNβ and GA remain incompletely understood
Conclusions

• IFNβ and GA have been approved for approximately 20 years for the treatment of relapsing-remitting MS
• Both mediations are now also approved for patients with CIS
• IFNβ and GA are considered to be equally effective in reducing clinical relapses and MRI outcome
Conclusions

• IFNβ and GA are considered safe
• Laboratory monitoring is recommended for IFNβ
• GA requires no laboratory monitoring
• Side effects are typically mild-to-moderate
The End
Disease modifying agents for patients with multiple sclerosis: Adherence, compliance, and efficacy

Stacey L. Clardy, MD PhD
Neurologist, Salt Lake City VA
Assistant Professor of Neurology, University of Utah
Director, Autoimmune Neurology Fellowship
Disclosures

Presenter has the following interest to disclose:
- Site investigator for the Alexion clinical trial for Eculizumab in Relapsing NMO patients
- Consulting for The Davick Group, L.E.K. consulting, and Trinity Partners
- Research Funding from the Western Institute for Biomedical Research

PESG and PVA staff have no interest to disclose.

This continuing education activity is managed and accredited by Professional Education Services Group in cooperation with PVA. PESG, PVA, and all accrediting organization do not support or endorse any product or service mentioned in this activity.
Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Discuss newer and emerging therapies in MS
2. Discuss rationale for therapeutic approach based on immune-mediated mechanisms
3. Consider factor affecting therapy choice in patients
CE/CME Credit

If you would like to receive continuing education credit for this activity, please visit:

http://PVA.cds.pesgce.com
Current MS Treatments

1993 - First FDA approved therapy for MS

- Betaseron (Interferon B 1b)
- Avonex (Interferon B 1a)
- Copaxone (Glatiramir Acetate)
- Glatopa (glatiramer acetate generic)
- Novantrone (Mitoxantrone)
- Rebif (Interferon B 1a)
- Extavia (Interferon B 1b)
- Plegridy (Peginterferon beta-1a)
- Zinbryta (Daclizumab)

Oral therapies

- Gilenya (Fingolimod)
- Aubagio (Teriflunomide)
- Tecfidera (Dimethyl Fumarate)

Infusions

- Novantrone (Mitoxantrone)
- Tysabri (Natalizumab)
- Lemtrada (Alemtuzumab)
### Immunologic Mechanisms of Action for MS Therapies
Reveal Important Components of Pathogenesis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism(s) of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA</td>
<td>Block Antigen Presentation</td>
</tr>
<tr>
<td></td>
<td>Bystander Suppression</td>
</tr>
<tr>
<td></td>
<td>Regulation of Immune Response by CD8 T cells</td>
</tr>
<tr>
<td>IFN</td>
<td>Induces anti-inflammatory cytokines</td>
</tr>
<tr>
<td></td>
<td>Inhibits synthesis of MMPs (Matrix metallo proteinases)</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Traps autoreactive T cells in Lymph Nodes</td>
</tr>
<tr>
<td>Estriol</td>
<td>Shifts immune response to Th2</td>
</tr>
<tr>
<td>Plasma Exchange</td>
<td>Reduces circulating Immunoglobulins &amp; Complement</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Blocks CNS infiltration</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Increases NK cell function (Blocks T cell activation)</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Sustained reduction of T cells</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Sustained reduction of B cells</td>
</tr>
</tbody>
</table>
MS mechanism = Drug Targets

- CNS damage in MS is believed to result from an immune-mediated process.
- Includes components of:
  - Innate immune system (macrophages, natural killer cells)
  - Adaptive immune system (CD4+ lymphocytes, CD8+ lymphocytes and B lymphocytes in the peripheral lymph tissues).
- In MS, bias toward a Th1 and Th17 environment with T regulatory dysfunction that allows for inflammation
MS mechanism = Drug Targets

- B cells function as antigen presenting cells and produce antibodies and pro-inflammatory cytokines that can result in downstream damage to myelin and oligodendrocytes
- Importance of B cells in MS immunopathogenesis is supported by the consistent finding of oligoclonal immunoglobulins in the CSF
FOCUS:
ORAL AGENTS FOR TREATING MULTIPLE SCLEROSIS

- Fingolimod (Gilenya)
- Teriflunomide (Aubagio)
- Dimethyl Fumarate/BG-12 (Tecfidera)
Fingolimod/Gilenya: Mechanism of Action

- Developed from fungus used in Chinese medicine
- Sphingosine 1 Phosphate receptor modulator
- S1P receptor becomes internalized on lymphocytes
- Sequesters activated lymphocytes in lymph tissue
- Number of circulating lymphocytes is decreased (70-80%); it is reversible
- S1P receptors in many places
  - Several “me too” medications under study with greater S1P receptor specificity
Fingolimod/Gilenya: Side Effects

- Increased AV block, symptomatic bradycardia (effect is self limited due to receptor desensitization)
- **Contraindications:** Concomitant use of QT prolonging drugs, class I/II antiarrhythmic
- QTc > 500 ms
- MI, unstable angina, stroke, TIA, CHF requiring hospitalization, class II/IV heart failure, Mobitz type II 2nd degree or 3rd degree AV block or SSS unless patient has pacemaker
Fingolimod/Gilenya: Side Effects

- Macula edema (0.4%)
- LFT abnormality
- Hypertension
- Possible risk of HSV, VZV infections (2 Herpes related deaths in clinical trials only with higher dose which is not used and in conjunction with corticosteroid use)
- PFT abnormality
- Pregnancy category C (takes 2 months to be out of system)
Fingolimod/Gilenya: Monitoring

- CBC, LFTs, baseline ophthalmologic evaluation, well known h/o chickenpox or Ab testing for exposure or VZV immunization. If negative or low titer, vaccinate prior.
- First dose monitoring: EKG before, QTc > 500 ms, exclusion.
- **Monitor for 6 hours in clinic for symptomatic bradycardia**
- EKG after 6 hours of monitoring. If QTc increased, admit for observation overnight
- **Ophthalmologic eval at 3-4 months for r/o macula edema**
- PFTs if symptomatic or at risk
- Follow BPs, LFTs, CBC (will likely be decreased)
- If patient stops treatment after 14 days, will require remonitoring
Teriflunomide/Aubagio: Mechanism of Action

- Inhibitor of dihydroorotate-dehydrogenase (DHODH), a key mitochondrial enzyme involved in pyrimidine synthesis in rapidly proliferating cells.

- **Reduces activity of proliferating T-lymphocytes and B-lymphocytes**, diminishing overall inflammatory response.

- Cytostatic rather than cytotoxic, acting on rapidly dividing cells

- Other effects: inhibition of protein tyrosine-kinases, alteration of cytokine production, modulation of expression of cell surface molecules
Teriflunomide/Aubagio: Side Effects

- GI: Nausea, diarrhea
- Hair thinning/decreased hair density
- Elevated ALT levels
- Small reductions in neutrophil and lymphocyte counts
- Small increase in BP
- No serious opportunistic infections
Teriflunomide/Aubagio: Pregnancy

- Existing experience with leflunomide used in RA for > 14 yrs.
- **Pregnancy category X** (based on leflunomide’s known teratogenicity in animals)
- If become pregnant: cholestyramine or activated charcoal-based washout (65 pregnancies in trials o.k.)
- **Males: are cautioned not to father a child** while on teriflunomide.
Dimethyl Fumarate/Tecfidera: Mechanism of Action

- Exhibits potential neuroprotective effect in experimental models of neurodegeneration and oxidative stress, mediated through activation of the Nrf2 pathway which plays a key role in helping cells defend against oxidative stress (unclear if this is responsible for treatment effect)

- Immunomodulatory effects may include shifting dendritic cell differentiation and inhibiting proinflammatory pathways.
Dimethyl Fumarate/Tecfidera: Side Effects

- **Skin**: **Flushing** mostly, some pruritus and erythema
- **Gastrointestinal**: Diarrhea, nausea, vomiting, abdominal pain (27% treated first 3 months, 17% placebo)
- Slight decrease in mean peripheral WBC and lymphocyte counts; no increased risk of infection or opportunistic infection in phase III trials
  - Persistent lymphopenia in subset of patients
- 20 years experience with Fumaderm in Europe
Dimethyl Fumarate/Tecfidera

- Attractive option for first-line treatment, breakthrough disease activity, intolerance to other therapies, possibly natalizumab-treated patients with positive JC virus serology
- Should be used as monotherapy
- Pregnancy Category C
FOCUS:
AN OLDER INFUSION
FOR TREATING MULTIPLE SCLEROSIS

• Mitoxantrone (Novantrone)
Mitoxantrone (Novantrone)

- 12mg/m2 IV every three months; maximum cumulative dose: 140mg/m2
- Indication: worsening relapsing-remitting, progressive-relapsing, secondary progressive MS
- Pregnancy Cat: D
Mitoxantrone (Novantrone)

- Disrupts DNA synthesis and repair; inhibits B cell, T cell, and macrophage proliferation; impairs antigen presentation, as well as secretion of interferon gamma, TNFα and IL-2.
- Severe local tissue damage if extravasation - cardiotoxicity - acute myelogenous leukemia - myelosuppression (infection)
- **Boxed Warning** cardiotoxicity and secondary leukemia (monitoring required long-term)
FOCUS:
MONOCLONALS FOR TREATING MULTIPLE SCLEROSIS

- Tysabri (Natalizumab)
- Lemtrada (Alemtuzumab)
- Zinbryta (Daclizumab)

In Progress:
- Ocrelizumab
- Ofatumumab
Natalizumab/Tysabri

- 300mg IV every 28 days
- Indication: relapsing forms of MS
- Pregnancy Cat: C

- Mechanism of action in MS has not been fully defined. It has been shown to block α4integrin on lymphocytes, thus reducing trafficking of lymphocytes into the CNS
Natalizumab/Tysabri

- Progressive multifocal leukoencephalopathy (PML)
- Hepatotoxicity
- Herpes encephalitis and meningitis caused by herpes simplex and varicella zoster viruses
- Hypersensitivities
- Immunosuppression/infections
- **Boxed Warning** Because of the risk of PML, natalizumab is available only through a restricted distribution program called the TOUCH® Prescribing Program.
Daclizumab/Zinbryta

- Humanized monoclonal antibody
- NOT an INFUSION – SC!
- Alpha subunit (CD25) of IL-2 receptor
  - Activated T-cells upregulate CD25 expression

- Anti-CD25 antibodies:
  - Decrease T-cell activation and proliferation
  - Lead to expansion of regulatory NK (CD56) cells

Daclizumab: Adverse Effects

- Serious adverse events in 15% of patients in daclizumab group vs. 10% in interferon beta-1a group.
- Infections more common in daclizumab group than in interferon beta-1a group (in 65% vs. 57% of patients, including serious infection in 4% vs. 2%)
- Cutaneous events such as rash or eczema (in 37% vs. 19%, including serious events in 2% vs. <1%)
- Elevations in liver aminotransferase levels that were more than 5 times the upper limit of the normal range (in 6% vs. 3%).
Daclizumab: Prescribing

• In clinical trials, 1 patient died due to autoimmune hepatitis.
• Liver injury, including autoimmune hepatitis, can occur at any time during treatment, with cases reported up to 4 months after the last dose
  ▫ Contraindicated in patients with pre-existing hepatic disease or hepatic impairment
• Transaminase levels and total bilirubin monthly and before the next dose
• Follow transaminase levels and total bilirubin monthly for 6 months after the last dose
Daclizumab/Zinbryta

- Serious immune-mediated conditions were observed in 5% of patients (lymphadenopathy, skin reactions and non-infectious colitis)
- Must prescribe through “Zinbryta REMS program”
- Available in 150mg subcutaneous dosing
Alemtuzumab/Lemtrada

- Indications: relapsing forms of MS – generally patients who have had an inadequate response >2 MS therapies
- 12mg/day IV on 5 consecutive days, followed 12 months later by 12mg/day on 3 consecutive days
- Pregnancy Cat: C
Alemtuzumab/Lemtrada

- Mechanism of action is presumed to involve binding to CD52, a cell surface antigen present on T and B lymphocytes, and on natural killer cells, monocytes and macrophages.
- Results in antibody-dependent cellular cytolysis and complement-mediated lysis.
FOCUS:
INFUSIONS - IN TRIALS AND OFF LABEL FOR TREATING MULTIPLE SCLEROSIS

In Progress:
• Ocrelizumab
• Ofatumumab

Off Label:
• Rituximab
Ocrelizumab & Ofatumumab

“B-cell therapies” – Recombinant antibodies to CD20 B-cells

Theory of B-cell therapy

- B cells originate from hematopoietic stem cells in bone marrow
- Immature B cells migrate to lymphoid tissues; most continue development into mature follicular B cells.
- B-cell receptor complex of mature B cell binds foreign antigen, and cell becomes activated and differentiates into an antibody-secreting plasma cell.
- B cell monoclonals (anti-CD-20) thus used to treat diseases characterized by overactive, dysfunctional, or excessive B cells.
Ocrelizumab

- 90% humanized monoclonal IgG – anti-CD20

Ofatumumab

- Fully humanized anti-CD20 monoclonal IgG
Rituximab

- Chimeric (mouse/human) anti CD-20

- Success of Rituximab led to development of the other anti CD-20s.

- Approval for MS not being sought, but has been used off-label in treatment of MS
Summary

- 14 medications FDA-approved to treat MS:
  - 8 different mechanisms of action
  - Different route and frequency of administration
  - Different side effect and risk profiles
- None of the medications are curative
- Efficacy varies for any given individual at different points in time.
Summary

- Treatment with any disease-modifying medication should be started as soon as possible, and continued indefinitely.

- Ability to take a disease-modifying medication over a long period of time is essential to effectiveness.

- Variety of medications -- with varied dosing and route of administration -- affords many options for patients.

- If not able to adhere to a treatment regime for one reason or another, access to other options is essential.
Thank you!

Stacey.Clardy@va.gov
Supplementary slides

(presenter only)
Vitamin D and MS Relapse

Higher D level = reduced hazard of relapse

Vitamin D Suggestions

- AAP
  - 400 IU/day for babies and children
- IOM report (Nov. 2010)
  - Recommended intake 800 IU/day
  - Safe maximum intake 4,000 IU/day
  - Above 10,000 IU/day is unsafe for long term use.
- “Best” dose in MS is unknown
Vitamin D Suggestions for MS

- Use Vit D3 (cholecalciferol)
- Check levels when convenient
  - < 30 ng/ml, supplement
- Dose – 4,000 or 5,000 IU/day
- Follow-up – Check another level after a few months
  - Make sure at least 40 ng/ml, preferably higher, max 100 ng/ml
Daclizumab

Daclizumab SELECT trial

Daclizumab SELECT Findings

• The annualized relapse rate was lower for patients given daclizumab
  ▫ 150 mg (0.21, 95% CI 0.16–0.29; 54% reduction, 95% CI 33–68%; p<0.0001),
  ▫ 300 mg (0.23, 0.17–0.31, 50% reduction, 28–65%; p=0.00015)
  ▫ placebo (0.46, 0.37–0.57).

• More patients were relapse free in the daclizumab 150 mg (81%) and 300 mg (80%) groups than in the placebo group (64%; p<0.001 in 150, p=0.003 in 300)
**Figure 3:** Change in number of new or enlarged gadolinium contrast-enhancing lesions
Cumulative number of new or enlarged gadolinium contrast-enhancing lesions by visit. Bars = standard error. *p < 0.05 versus interferon beta and placebo.
Daclizumab CHOICE findings

- The adjusted mean number of new or enlarged gadolinium contrast-enhancing lesions:
  - 4.75 in the interferon beta and placebo group
  - 1.32 in the interferon beta and high-dose daclizumab (difference 72%, 95% CI 34% to 88%; p=0.004)
  - 3.58 in the interferon beta and low-dose daclizumab group (25%, −76% to 68%; p=0.51)
Daclizumab DECIDE phase III

- 1841 patients
  - Daclizumab 150mg subq every 4 weeks
  - Interferon beta-1a 30ug once weekly

- Primary end point: annual relapse rate
Daclizumab DECIDE findings

- Annualized relapse rate: lower with daclizumab than interferon beta-1a (0.22 vs. 0.39; 45% decrease, $P<0.001$)
- New or enlarged lesions on MRI over a period of 96 weeks: lower with daclizumab than interferon beta-1a (4.3 vs. 9.4; 54% lower, $P<0.001$)
Daclizumab

**Time to First Relapse**

- Hazard ratio for relapse: 0.59 (95% CI, 0.50–0.69) 
P<0.001

- Estimated percent of patients who were relapse free at 144 wk:
  - Interferon beta-1a, 51%
  - Daclizumab HYP, 67%
Ocrelizumab phase II

**Figure 1: Study design and treatment protocol**

Randomisation stratified by geographical region.

Ocrelizumab phase II

Figure 3: Gadolinium-enhancing lesions by week in each study group

Ocrelizumab phase II

- At week 24, the number of enhancing lesions was
  - 89% lower (95% CI 68–97; p<0.0001) in the 600 mg ocrelizumab group than in the placebo group
  - 96% lower (89–99; p<0.0001) in the 2000 mg group.

Ocrelizumab - Opera I and II (Phase 3)

**Groups**
- ocrelizumab 600mg via intravenous infusion every 24 weeks
- subcutaneous IFNβ-1a 44μg three-times weekly over 96 weeks.

**Measurements**
- Brain MRI endpoints included the total number of T1 gadolinium-enhancing lesions, new/enlarging T2 hyperintense lesions, and new T1 hypointense lesions at weeks 24, 48, and 96, and change in whole brain volume from baseline and week 24 to week 96.

Ocrelizumab - Opera I and II (Phase 3)

- Ocrelizumab reduced enhancing lesions by 94% in OPERA I and 95% in OPERA II (both p<0.0001)

- New/enlarging lesions reduced by 77% in OPERA I and 83% in OPERA II (both p<0.0001)

- New T1 hypointense lesions by 57% in OPERA I and 64% in OPERA II (both p<0.0001)

- Brain volume loss from baseline to week 96 by 23% (p<0.0001) and 23.8% (p=0.0001) and from week 24 to week 96 by 22.7% (p=0.0042) and 14.9%(p=0.0900)

NEDA in Opera I and II

- At 96 weeks, 47.9% and 47.5% of ocrelizumab-treated patients vs 29.2% and 25.1% of IFNβ-1a-treated patients achieved NEDA in OPERA I (64% increase; p<0.0001) and OPERA II (89% increase; p<0.001)

- 80.4% and 78.9% of ocrelizumab-treated patients vs 66.7% and 64.5% of IFNβ-1a-treated were without relapses

- 92.4% and 89.4% of ocrelizumab-treated patients vs 87.8% and 84.9% of IFNβ-1a-treated were without CDP

Ofatumumab Phase II

- 2 infusions (100 mg, 300 mg, or 700 mg) or placebo 2 weeks apart.
- At week 24, patients received alternate treatment.