

# Immune Reconstitution in MS: How Does This Impact Treatment Decisions? CME

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CME Released: 3/16/2018; Valid for credit through: 3/16/2019

### Target Audience

This activity is intended for neurologists, primary care physicians, and obstetricians and gynecologists.

### Goal

The goal of this activity is to define immune reconstitution and discuss the therapies that use this approach in the treatment of multiple sclerosis (MS).

### Learning Objectives

Upon completion of this activity, participants will:

- Have increased knowledge regarding the
  - New and emerging disease-modifying therapies (DMTs) for multiple sclerosis (MS) with evidence of immune reconstitution as a mechanism of action
  - Mechanisms of immune reconstitution as it relates to DMTs used for the treatment of MS
- Have greater competence related to
  - Identification of patients with MS who may benefit from treatment with DMTs with properties of immune reconstitution

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## Hardware/Software Requirements

To access activities, users will need:

- A computer with an Internet connection.
- Internet Explorer 8.x or higher, the latest versions of Firefox or Safari, or any other W3C standards compliant browser.
- Adobe Flash Player and/or an HTML5 capable browser may be required for video or audio playback.
- Occasionally other additional software may be required such as PowerPoint or Adobe Acrobat Reader.

## Disclosures

### *Moderator*

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Disclosure: Gavin Giovannoni, MBBCh, PhD, has disclosed the following relevant financial relationships:

Served as an advisor or consultant for: AbbVie Inc.; Bayer Schering Pharma; Biogen.; Canbex Therapeutics Ltd; Eisai Inc.; Elan Pharmaceuticals, Inc.; EMD Serono, Inc.; FivePrime Therapeutics; Genentech, Inc.; Genzyme Corporation; GlaxoSmithKline; GW Pharmaceuticals; Ironwood Pharmaceuticals, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc; Roche; sanofi-aventis; Synthon BV; Teva Pharmaceuticals USA; UCB Pharma, Inc.; Vertex Pharmaceuticals Incorporated

Dr Giovannoni does intend to discuss off-label uses of drugs, mechanical devices, biologics, or diagnostics approved by the FDA for use in the United States.

Dr Giovannoni does intend to discuss investigational drugs, mechanical devices, biologics, or diagnostics not approved by the FDA for use in the United States.

### *Scientific Director*

#### **Catherine Friederich Murray, BS**

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EDUCATION

## Immune Reconstitution in MS:

### *How Does This Impact Treatment Decisions?*

#### Moderator

**Gavin Giovannoni, MBBCh, PhD**

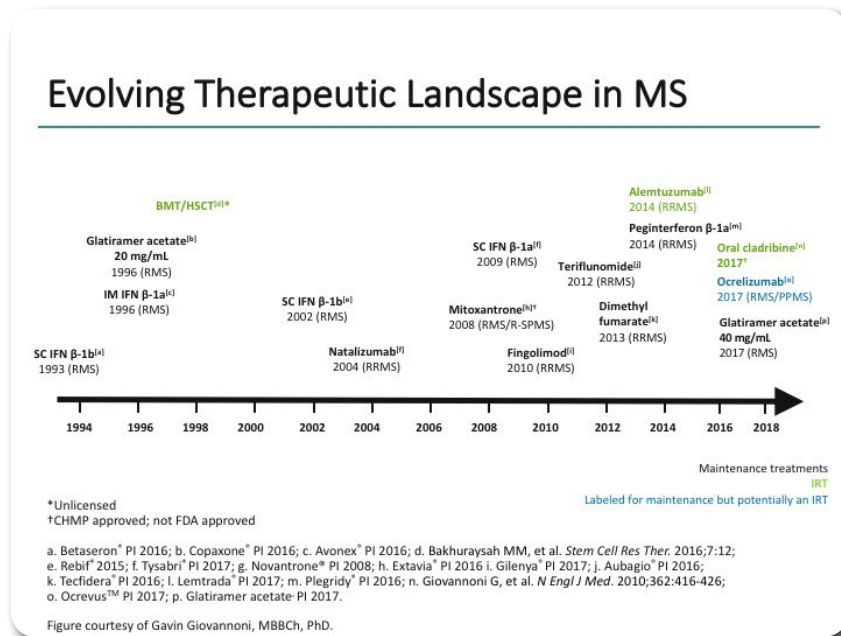
Professor and Chair of Neurology  
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Medicine and Dentistry  
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#### **Immune Reconstitution in MS: How Does This Impact Treatment Decisions?**

*This program will include a discussion of off-label treatment and investigational agents not approved by the FDA for use in the US, and data that were presented in abstract form. These data should be considered preliminary until published in a peer-reviewed journal.*

#### **Disclosure**

## Disease-modifying Therapies for MS

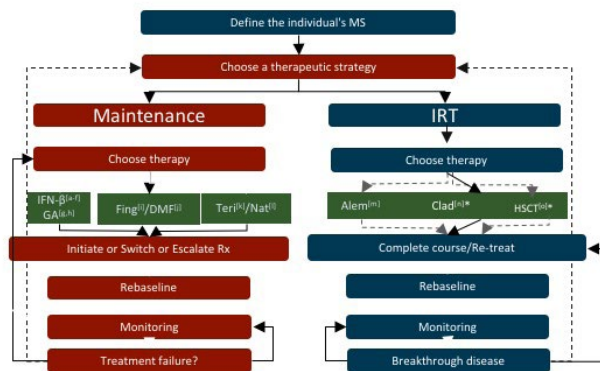


**Editor's note:** AbbVie and Biogen voluntarily withdrew daclizumab for the treatment of relapsing multiple sclerosis from the worldwide market on March 2, 2018.

### Evolving Therapeutic Landscape in MS<sup>[1-16]</sup>

The therapeutic landscape for multiple sclerosis (MS) is evolving. For the past 25 years we have had disease-modifying therapies (DMTs), but there has been an acceleration in the number of new treatments coming online. I have color-coded and divided these into treatments that are given continuously (ie, maintenance treatments) and those that we use intermittently (immune reconstitution therapies [IRTs]). The principle behind IRTs is that these drugs deplete the immune system and allow it to reconstitute itself. When the immune system comes back, it is normal in terms of immune function (ie, the immune system can respond to infections and survey the periphery for tumors). Ocrelizumab is an intermediate color because the anti-CD20 therapies, of which ocrelizumab is one, can potentially be used as IRT, but the current label for this is maintenance therapy given every 6 months.

## Barts-MS T2T-NEDA Algorithm



\*Cladribine and HSCT do not have FDA approval for the treatment of MS.  
a. Avonex<sup>®</sup> PI 2016; b. Betaseron<sup>®</sup> PI 2016; c. Extavia<sup>®</sup> PI 2016; d. Rebif<sup>®</sup> 2015; f. Plegridy<sup>®</sup> PI 2016; g. Copaxone<sup>®</sup> PI 2016;  
h. Glatiramer acetate PI 2017; i. Gilenya<sup>®</sup> PI 2017; j. Tecfidera<sup>®</sup> PI 2016; k. Aubagio<sup>®</sup> PI 2016; l. Tysabri<sup>®</sup> PI 2017; m. Lemtrada<sup>®</sup> PI 2017;  
n. Giovannoni G, et al. *N Engl J Med.* 2010;362:416-426; o. Bakhurst MM, et al. *Stem Cell Res Ther.* 2016;7:12.  
Figure courtesy of Gavin Giovannoni, MBBCh, PhD.

### Barts-MS T2T-NEDA Algorithm<sup>[1-16]</sup>

This is an algorithm that we have implemented in our center, at Barts in London, on how to use these 2 treatment options. On the left is the maintenance therapy, and on the right is the IRT. In the United Kingdom, we have 3 options. We have alemtuzumab; cladribine, which is an oral formulation; and, for a very small number of patients, hematopoietic stem cell transplantation (HSCT). On the left side is the maintenance curve, and those are all the other licensed DMTs.

There is a fundamental difference between IRT and maintenance therapies because, when we use maintenance treatments, we monitor patients on an annual basis clinically and with magnetic resonance imaging (MRI). When a patient is on maintenance therapy, has breakthrough activity, and the drug is working, that usually means a suboptimal or nonresponse; the strategy would be to escalate and switch DMTs. I say escalate because we tend not to go horizontally, we tend to go to a higher efficacy bracket. Whereas, on the IRT side, when you have reactivation of disease, that does not mean that the therapy has necessarily failed; usually it is an indication to give additional courses of the drug. I think that the difference between these 2 arms is that when we target no evident disease activity (NEDA) and we identify activity in our monitoring, the 2 arms are treated very differently.

## IRT vs Maintenance Therapy

### Defining IRT and Maintenance Therapy

- IRT is a short-course treatment that
  - Is given intermittently\*
  - Has the ability to
    - Induce long-term remission
    - In some cases, result in the possibility of a cure
- A maintenance therapy
  - Is given without interruption in dosing<sup>†</sup>
  - Has the ability to induce long-term remission
  - Cannot result in a cure

\*An IRT is not given continuously and additional courses of the therapy are only given if there is a recurrence of inflammatory activity, which, in MS, typically refers to clinical relapses, focal MRI activity (new T2 lesions and/or Gd+ lesions) or relapses and focal MRI activity.

<sup>†</sup>A maintenance therapy is given continuously; an indication of a suboptimal response is that, while on therapy, the patient has a recurrence of, or ongoing, inflammatory activity.

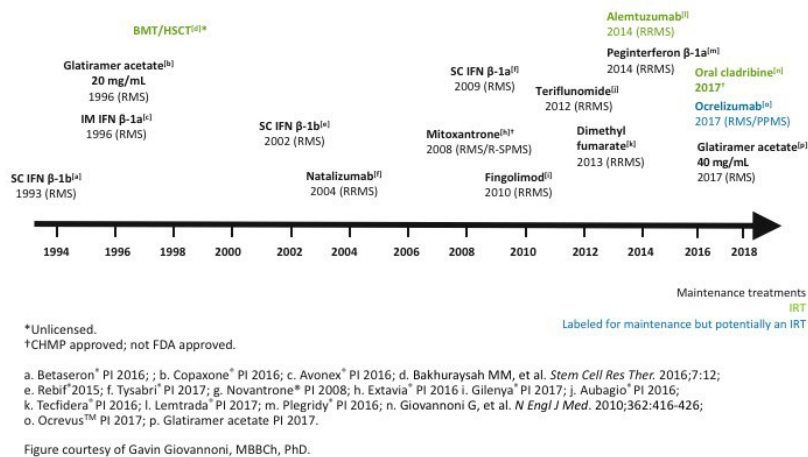
### Defining IRT and Maintenance Therapy

An IRT by definition is given as short courses, so it is intermittent and not given continuously. It has the ability to induce long-term remission and, in some cases, the possibility of a cure. I say that because there are cohorts of patients having been treated with IRTs, alemtuzumab, and HSCT, who have gone beyond 10 years, and their disease is quiescent; we cannot find any evidence of disease activity. I do not know if those patients' MS is cured because I have problems defining a cure in MS, but at least those people seem to be free of activity. What happens if they go 20, 25 years at some stage in the future? I think the MS community is going to start talking about a potential cure.

In comparison, a maintenance therapy is, by definition, given continuously without an interruption in dosing, and it has the ability to induce long-term remission. We all have patients who are on one of the maintenance therapies, and we see no activity or relapses and the MRI has quieted, but maintenance therapy cannot result in a cure because you are not treating the pathogenesis of the disease. You are blocking immune function, but, when you remove the drug, MS comes back. This is a fundamentally different type of treatment from the IRTs.



## Maintenance Therapies vs IRTs



### Maintenance Therapies vs IRTs<sup>[1-16]</sup>

Here we have the picture again just to remind you of the evolving landscape. I hope that framing the therapy of MS into 2 arms, maintenance-escalation vs IRT and how we use these treatments, will make this evolving therapeutic landscape a lot easier to implement clinically and how to deal with the individual drugs.

## Maintenance Therapies vs IRTs: Attributes

Maintenance Therapies	IRTs
<ul style="list-style-type: none"> <li>• Continuous treatment                             <ul style="list-style-type: none"> <li>- Adherence potential problem</li> </ul> </li> <li>• Low to very high efficacy</li> <li>• Reversible</li> <li>• Perceived to be lower risk                             <ul style="list-style-type: none"> <li>- Cumulative, or increased, risk with time</li> </ul> </li> <li>• Examples                             <ul style="list-style-type: none"> <li>- GA,<sup>[a,k]</sup> IFN-<math>\beta</math>,<sup>[e-l]</sup> teriflunomide,<sup>[g]</sup> dimethyl fumarate,<sup>[h]</sup> fingolimod,<sup>[f]</sup> natalizumab,<sup>[b]</sup> ocrelizumab<sup>[l]</sup></li> </ul> </li> <li>• Breakthrough disease                             <ul style="list-style-type: none"> <li>- Suboptimal or failure to respond</li> <li>- NEDA reliable metric for efficacy</li> </ul> </li> <li>• Rebound activity                             <ul style="list-style-type: none"> <li>- Highly likely</li> <li>- Can be life-threatening</li> </ul> </li> <li>• Pregnancy</li> <li>• No potential for a cure                             <ul style="list-style-type: none"> <li>- Rebound</li> <li>- SPMS and progressive brain atrophy</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Short-courses or pulsed therapy                             <ul style="list-style-type: none"> <li>- Adherence seldom a problem</li> </ul> </li> <li>• High to very high efficacy</li> <li>• Irreversible</li> <li>• Perceived to be higher risk                             <ul style="list-style-type: none"> <li>- Frontloading of risk or reduced risk with time</li> </ul> </li> <li>• Examples                             <ul style="list-style-type: none"> <li>- Nonselective: mitoxantrone,<sup>[c]</sup> alemtuzumab,<sup>[i]</sup> HSCT-BMT<sup>[o,p]</sup></li> <li>- Selective: cladribine<sup>[k]</sup></li> </ul> </li> <li>• Breakthrough disease                             <ul style="list-style-type: none"> <li>- Marker for retreatment</li> <li>- NEDA unreliable to assess efficacy</li> </ul> </li> <li>• Rebound activity                             <ul style="list-style-type: none"> <li>- Less likely</li> <li>- Unlikely to be life-threatening</li> </ul> </li> <li>• Pregnancy</li> <li>• Potentially "curative"?                             <ul style="list-style-type: none"> <li>- 15- to 20-year experiment</li> </ul> </li> </ul>

a. Copaxone<sup>®</sup> PI 2016; b. Glatiramer acetate PI 2017; c. Avonex<sup>®</sup> PI 2016; d. Betaseron<sup>®</sup> PI 2016; e. Extavia<sup>®</sup> PI 2016; f. Rebif<sup>®</sup> 2015 PI; g. Plegridy<sup>®</sup> PI 2016; h. Aubagio<sup>®</sup> PI 2016; i. Tecfidera<sup>®</sup> PI 2016; j. Gilenya<sup>®</sup> PI 2017; k. Tysabri<sup>®</sup> PI 2017; l. Ocrevus<sup>™</sup> PI 2017; m. Novantrone<sup>®</sup> PI 2008; n. Lemtrada<sup>®</sup> PI 2017; o. Bakhuraysah MM, et al. *Stem Cell Res Ther.* 2016;7:12; p. Giovannoni G, et al. *N Engl J Med.* 2010;362:416-426.  
<sup>†</sup>Not FDA approved for the treatment of MS.

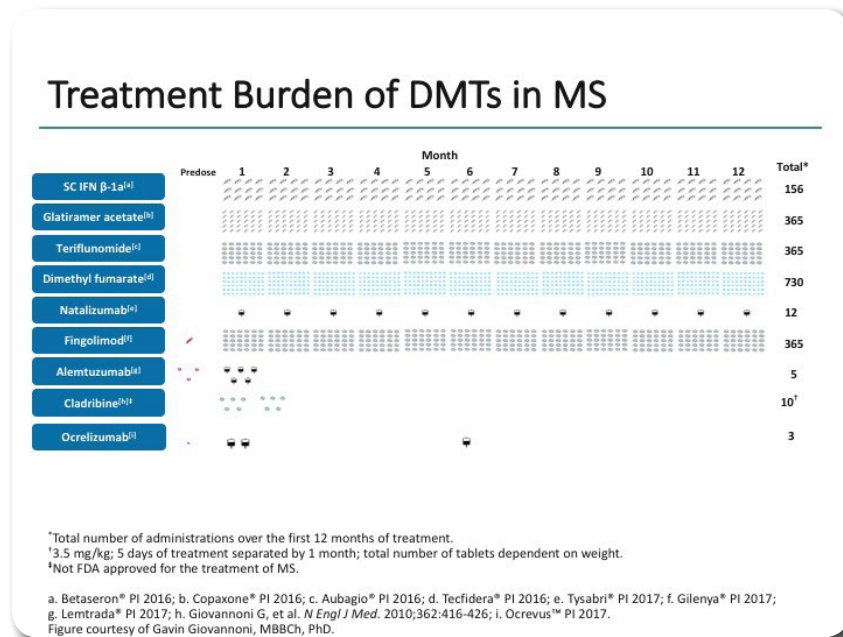
### Maintenance Therapies vs IRTs: Attributes<sup>[1-16]</sup>

This slide, with the 2 Tables, highlights the attributes of maintenance and IRTs. I would just like to point out some of the characteristics that differentiate these 2 treatment strategies. On the IRT side, it is irreversible. In other words, once you have given the drug, you cannot take it out of the system because it depletes the immune system and hopefully gets rid of all the autoreactive T cells and B cells. When the immune system reconstitutes, it is normal (ie, it can fight infections and can do tumor surveillance).

The maintenance therapies are on board all the time. If they are immunosuppressive, the risks accumulate with time, and so you see things like opportunistic infections emerging. The very favorable side of the IRTs is that the drugs are out of the system very quickly. Therefore, if the patient wanted to become pregnant, for example, the drug is not on board, so teratogenicity is not an issue. Vaccinations are not a problem if the immune system is reconstituted; whereas, for patients on a maintenance therapy, depending on which treatment they are on, pregnancy and vaccinations are contraindicated.

Also, maintenance drugs that block trafficking of lymphocytes into the central nervous system, such as natalizumab and fingolimod, increase the risk of rebound. We tend not to see rebound on IRTs. When disease activity reoccurs, it tends to come back more gently, and gives us an opportunity to identify and treat.

## Treatment and Monitoring Burden

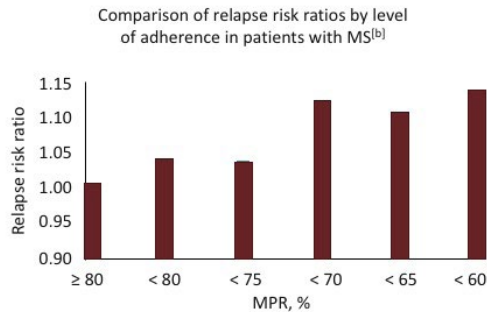


### Treatment Burden of DMTs in MS<sup>[1,2,6,9-12,14,15]</sup>

What is not captured on the previous slide is the treatment burden. You can see on this slide, when you look at the IRTs, alemtuzumab, cladribine, and HSCT, the treatment burden is up front. The actual treatment burden is very low compared with maintenance therapies.

As you can see, ocrelizumab, which is a maintenance treatment, actually looks like an IRT, with infusions only every 6 months. This is very important because treatment burden does have an impact on, for example, adherence.

## DMT Adherence in MS



Good adherence is important to optimize outcomes<sup>[a-d]</sup>

Psychological factors – forgetfulness and complacency – affect adherence<sup>[e]</sup>

a. Al-Sabbagh A, et al. *J Neurol*. 2008;255(suppl 2):s79; b. Steinberg SC, et al. *Clin Drug Invest*. 2010;30:89-100; c. Katsarava Z, et al. *BMC Neurol*. 2015;15:170; d. Kruk ME, et al. *Clin Ther*. 2006;28:1989-1995; e. Devonshire V, et al. *Eur J Neurol*. 2011;18:69-77.

### DMT Adherence in MS<sup>[17-21]</sup>

We know that adherence affects efficacy. In other words, if a patient is taking a daily tablet or injection, forgetfulness and side effects often result in poor adherence. With IRTs, you can guarantee that the patient has their therapies up front, and you do not have to worry about adherence. Things like forgetfulness, which is at the top of the list, do not occur with IRTs. There is one little proviso though -- disease monitoring.

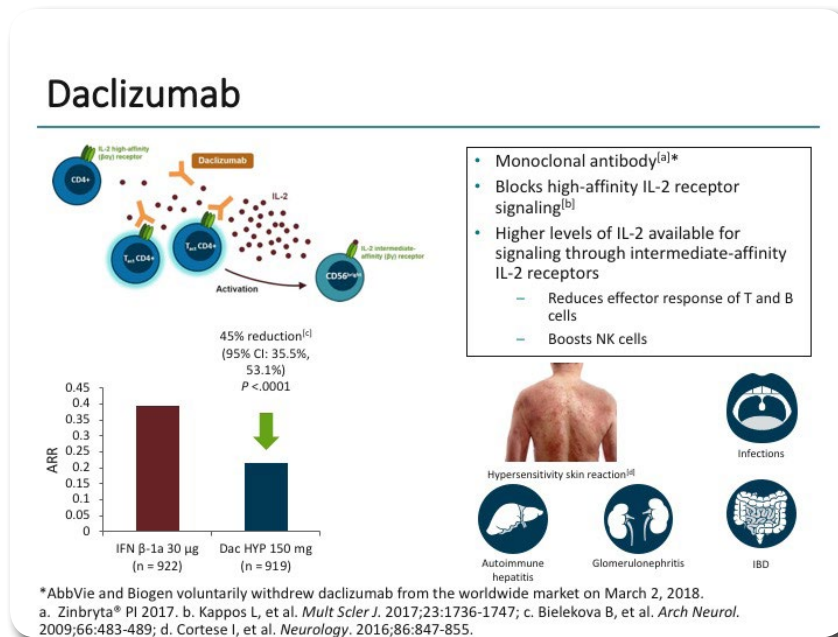
## Monitoring Burden With DMTs in MS

	Pre-Dose	First Dose	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
IFN β-1a <sup>[a]</sup>			BTx2		BTx2			BTx2						
Glatiramer acetate <sup>[b]</sup>			Renal function and cardiac function to be monitored in cases of renal impairment and preexisting cardiac disorder, respectively											
Teriflunomide <sup>[c]</sup>	BTx2	CV	BTx2	BTx2	BTx2	BTx2	BTx2	BTx2		BT		BT		BT
Dimethyl fumarate <sup>[d]</sup>	MRI, U, BTx3				BTx2, U			BTx3, U			BT			BTx3, U
Natalizumab <sup>[e]</sup>	BT, MRI, IS	HyperR						BT						BT, MRI
Fingolimod <sup>[f]</sup>	BTx2, CV	CV	BT		BTx2, O			BT			BT			BT
Alemtuzumab <sup>[g]</sup>	U, BTx3, TBS	IR	U, BTx2	U, BTx2	U, BTx3	U, BTx2	U, BTx2	U, BTx3	U, BTx2	U, BTx2	U, BTx3	U, BTx2	U, BTx2	U, BTx3
Cladribine <sup>[h]</sup>	TBS, HBVs, HCVs, BT		BT											
Ocrelizumab <sup>[i]</sup>	HBVs	IR, IS						BT						

\*Numbers indicate the number of blood tests.  
<sup>†</sup>Not FDA approved for the treatment of MS. Screening for latent infections prior to treatment in years 1 & 2.  
 a. Betaseron<sup>®</sup> PI 2016; b. Copaxone<sup>®</sup> PI 2016; c. Aubagio<sup>®</sup> PI 2016; d. Tecfidera<sup>®</sup> PI 2016; e. Tysabri<sup>®</sup> PI 2017; f. Gilenya<sup>®</sup> PI 2017; g. Lemtrada<sup>®</sup> PI 2017; h. Mavenclad<sup>™</sup> SmPc 2017; i. Ocrevus<sup>™</sup> PI 2017.  
 Figure courtesy of Gavin Giovannoni, MBBCh, PhD.

### Monitoring Burden With DMTs in MS<sup>[1,2,6,9-12,15,22]</sup>

With alemtuzumab, one of the complications is delayed secondary autoimmune complications, and we have to monitor patients on a monthly basis for at least 48 months after the last infusion. You are replacing a treatment burden with a monitoring burden with, for example, alemtuzumab. That is something you need to take into account when selecting patients for IRTs; not everybody is suitable. If you have a patient for whom you are worried about monitoring adherence, they should not be offered alemtuzumab.



### Daclizumab<sup>[23-26]</sup>

Let us go through some of the examples. This is daclizumab, a licensed monoclonal antibody that is the first in class, an interleukin (IL)-2 modulator. It binds to the high-affinity IL-2 receptor and, by so doing, allows IL-2 to move from the high-affinity receptor to the intermediate-affinity receptor. As part of that response, it reduces the effector response of T and B cells. It actually boosts natural killer cells. I think that is important because natural killer cells are part of our innate immune system, and their natural function is to fight infections. They are also tumor surveillance cells and regulate autoreactive T and B lymphocytes.

This drug is very interesting. It has not really been associated with immune suppression. We have not seen persistent lymphopenia with the drug, but we do find common infections, such as pharyngitis. Urinary tract infections can be more severe because daclizumab blunts the rapidity of the immune response.

The big issue with this drug, though, is autoreactive-type reactions, particularly in skin. About 2% of people have to stop the drug because of hypersensitivity skin reactions. There is also about a 2% incidence of transaminitis. Some patients have developed frank autoimmune hepatitis, and there have been a couple of deaths because of this. This drug also has to be monitored on a monthly basis with liver function tests.

## Immunosuppression

### Immunosuppression

- For a drug to be considered an immunosuppressant it should cause significant lymphopenia
- Immunosuppression may be associated with
  - Opportunistic infections
  - Secondary malignancies
  - Reduced antibody response to vaccines
- Immunosuppression can be categorized based on duration
  - Short-term or intermittent -- induction therapy
  - Long-term persistent -- maintenance therapy

Immunosuppression is a reduction of the activation or efficacy of the immune system

DMTs and Their Effect on the Immune System

Immunomodulatory	Immunosuppressant	Immunomodulatory with possible immunosuppressive effects
<ul style="list-style-type: none"> <li>• IFN-<math>\beta</math><sup>[a]</sup></li> <li>• Glatiramer acetate<sup>[h]</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Mitoxantrone<sup>[c]</sup></li> <li>• Natalizumab<sup>[d]</sup></li> <li>• Fingolimod<sup>[e]</sup></li> <li>• Dimethyl fumarate<sup>[f]</sup></li> <li>• Alemtuzumab<sup>[g]</sup></li> <li>• Cladribine<sup>[k]</sup>*</li> <li>• Ocrelizumab<sup>[i]</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Teriflunomide<sup>[j]</sup></li> <li>• Daclizumab<sup>[a]</sup>†</li> </ul>

\*Not FDA approved for the treatment of MS.  
 †As of March 2, 2018, daclizumab has been voluntarily withdrawn from the market worldwide.  
 a. Betaseron<sup>®</sup> PI 2016; b. Copaxone<sup>®</sup> PI 2016; c. Novantrone<sup>®</sup> PI 2008; d. Tysabri<sup>®</sup> PI 2017; e. Gilenya<sup>®</sup> PI 2017; f. Tecfidera<sup>®</sup> PI 2016; g. Lemtrada<sup>®</sup> PI 2017; h. Giovannoni G, et al. *N Engl J Med.* 2010;362:416-426; i. Ocrevus<sup>®</sup> PI 2017; j. Aubagio<sup>®</sup> PI 2016; k. Zinbryta<sup>®</sup> PI 2017.

### Immunosuppression<sup>[1,2,6,7,9-12,14,15,22,23]</sup>

This raises the issue of immune suppression. What is immune suppression? Regulators define it as any therapy that causes a significant lymphopenia, which is usually defined as being grade 2 or more -- <800 mm<sup>3</sup>. Associated opportunistic infections can occur, as can reduced antibody responses to vaccines, and these vaccines are usually not live; they are usually component or inactivated vaccines. Immune suppression can be associated with a secondary malignancy. These effects do not occur at once; rather, some of these risks emerge over time. For example, secondary malignancy may take years to emerge.

In this Table, I have highlighted DMTs that are immunosuppressive in red. The green refers to immunomodulatory therapies, the interferons and glatiramer acetate. I have put teriflunomide and daclizumab in orange because they are not labeled as being immunosuppressive, and the jury is out whether they will have an immunosuppressive profile in the future.

## Continuous vs Short-Term Immunosuppression

### Immunosuppressive Maintenance Therapies

- Examples: fingolimod,<sup>[a]</sup> natalizumab<sup>[b]</sup>
- Persistent immunosuppression
- Risks associated with immunosuppression increase over time (cumulative)
- Higher risk of
  - PML (complex pathogenesis)
  - Other opportunistic infections
  - Secondary malignancy
- Live vaccines contraindicated
- High-risk of exotic infections
  - Dengue
  - Zika
- Pregnancy not recommended
- Long-term burden of pharmacovigilance

### IRTs

- Examples: alemtuzumab,<sup>[c]</sup> cladribine<sup>[d]\*</sup>
- Short-term immunosuppression
- Risks associated with immunosuppression are front-loaded
- Lower risk of
  - PML
  - Opportunistic infections
  - Secondary malignancy
- After immune reconstitution occurs
  - Live vaccines are safe
  - Low risk of exotic infections
  - Pregnancy is safe
- Lower burden of pharmacovigilance

\*Not FDA approved for the treatment of MS.

a. Gilenya<sup>®</sup> PI 2017; b. Tysabri<sup>®</sup> PI 2017; c. Lemtrada<sup>®</sup> PI 2017; d. Giovannoni G, et al. *N Engl J Med.* 2010;362:416-426.

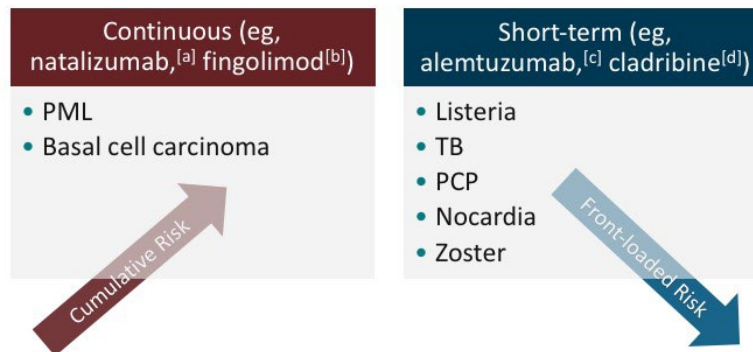
### Continuous vs Short-Term Immunosuppression<sup>[6,9,12,14]</sup>

When you look at immunosuppressants, there are 2 types. Maintenance treatments are continuous immunosuppressants. IRTs are short-term immunosuppressants; they cause immunosuppression for the period of time the drug causes the depletion of the immune system, and, once the immune system is reconstituted, the issue around immunosuppression disappears. The risk of adverse events related to immune suppression with IRTs are front-loaded; those that come with time, such as progressive multifocal leukoencephalopathy (PML), opportunistic infections, and secondary malignancy, are low. On the other hand, with continuous immunosuppression, these risks emerge with time.

With short-term immunosuppressive, live vaccines are potentially safe. We have given live vaccines to several of our patients who have had alemtuzumab. We just have to wait for the immune system to reconstitute before giving the live vaccines. Actually, with HSCT, which we use in a small number of patients, it is a mandatory part of our protocol to revaccinate patients with all their childhood vaccines after 18 months, and we have not seen any complications associated with that.

The other issue is exotic infections. For patients on continuous immunosuppression, you probably worry about them going to exotic places where they may be exposed to new viruses, whereas for patients receiving IRTs (ie, the short-term immunosuppressive side), once their immune system has come back, travel to exotic places is not really a risk.

## Immunosuppression Risks Over Time



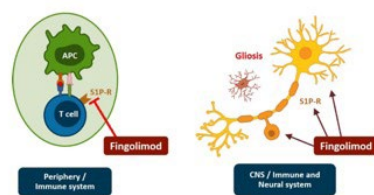
a. Tysabri<sup>®</sup> PI 2017; b. Gilenya<sup>®</sup> PI 2017; c. Lemtrada<sup>®</sup> PI 2017; d. Giovannoni G, et al. *N Engl J Med.* 2010;362:416-426.

### Immunosuppression Risks Over Time<sup>[6,9,12,14]</sup>

This Figure summarizes the trajectory of risk. With continuous therapies, risk accumulates with time; with short-term immunosuppression, the risks are front-loaded and drop with time.

## DMTs in MS

### Fingolimod



Gilenya<sup>®</sup> PI 2017.

- S1P modulator
  - Blocks S1P signaling
  - Traps lymphocytes in lymph nodes
- First-dose effects
- Vascular complications
- Opportunistic infections
- PML
- Secondary malignancies

### Fingolimod<sup>[9]</sup>

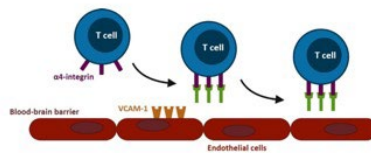
Fingolimod is a first in class sphingosine 1-phosphate (S1P) modulator. It blocks S1P signaling and, by doing so, traps lymphocytes in lymph nodes. The lymphocytes usually require the S1P gradient to migrate out of secondary lymphoid organs. It has all target effects because S1P biology is across multiple systems; it has a first-dose effect with bradycardia, potentially heart block. Vascular complications, such as posterior reversible encephalopathy syndrome and macular edema, may occur and require monitoring.

We are beginning to see an increasing number of opportunistic infections, such as pneumococcal meningitis, systemic cryptococcosis, Kaposi sarcoma, and histoplasmosis, emerging in patients taking fingolimod; PML and secondary malignancies may also occur. The risk of developing basal cell carcinoma is about 2.5 times background on fingolimod.

## Natalizumab



Figure courtesy of Gavin Giovannoni, MBBCh, PhD.



a. Barts MS website; b. Tysabri® PI 2017; c. Stüve O, et al. *Ann Neurol.* 2006;59:743-747.

- Selective adhesion molecule blocker<sup>[b]</sup>
- Infusion reactions
  - Anaphylactoid
  - Associated with antidrug antibodies
- Blocks CNS immune surveillance<sup>[c]</sup>
  - PML
  - CNS infections
  - Possible link with CNS lymphomas
- Rebound activity postwashout

### Natalizumab<sup>[6,27,28]</sup>

Natalizumab is again a first in class, a selective adhesion molecule inhibitor. It recognizes AL4, and by so doing stops trafficking of B and T lymphocytes into the central nervous system (CNS). Quite early on in the development of this drug, just after it was licensed and launched in the United States, we saw 3 cases of PML. We now know how to de-risk the PML; it is only really a risk in people who are JC virus seropositive. The risk is linked to duration of therapy, previous exposure to immunosuppression, and the index of antibody. There are ways of de-risking this as well; because it is a monoclonal antibody, we can wash it out using plasma exchange if a patient develops PML.

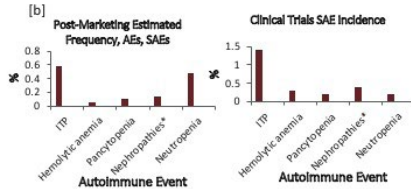
We are beginning to see other issues with natalizumab. One problem we have is not only PML, but also herpes encephalitis with very atypical manifestations. Clinicians using natalizumab need to think of other conditions. I think almost certainly CNS lymphoma is emerging as an adverse effect of this particular medication. There are too many reports in the literature. This is not a surprising finding if a patient develops a CNS lymphoma and does not have trafficking of the immune surveillance.

The other issue with natalizumab and fingolimod is rebound. It is not a good idea to leave people coming off natalizumab very long because of rebound.



## Alemtuzumab

- [a] • Daily blood samples from 15 patients who received 5-day alemtuzumab infusion cycle
- Leukocyte counts ↑
  - Granulocyte counts ↑
  - Lymphocyte counts ↓
  - CD3+, CD4+, CD8+, CD19+ ↓
  - NK cells ↓
- Nonselective leukocyte depletion<sup>[c]</sup>
    - Leukopenia (neutrophils and monocytes)
    - Prolonged lymphopenia
  - Opportunistic infections with immunosuppression
    - Bacterial
      - Listeriosis
      - Nocardia
      - TB
    - PCP
    - Viral
      - CMV
      - VZV
      - HPV
      - EBV
      - Molluscum



a. Thomas K, et al. *Neural Neuroimmunol Neuroinflamm*. 2016;3:e228; b. Selmaj K, et al. AAN 2017. Poster 338; c. Lemtrada® PI 2017.

### Alemtuzumab<sup>[12,29, 30]</sup>

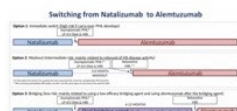
The first IRT licensed in Europe and the United States is alemtuzumab, a monoclonal antibody that recognizes CD52, which is expressed by leukocytes. This therapy not only depletes lymphocyte populations, but also takes out innate cells, such as monocytes. We see a particular adverse event profile due to this innate immune suppression. During the first few weeks after receiving alemtuzumab, patients have an increased risk of infection, including listeriosis, pneumocystis pneumonia, and other viruses, such as warts. While the patient has innate immunosuppression, you must be very vigilant for infections.

The listeria risk is not trivial. At the American Academy of Neurology meeting in 2017, the risk was put down at 0.26%. About 1 in 380 patients who receive alemtuzumab develop listeriosis, which is why it is critical to warn patients about preventing listeriosis. We also see cytomegalovirus (CMV) reactivation, which occurs in about 1 in 800, and there have been some serious liver toxicity cases linked to reactivation of CMV. Please be observant for those complications.

## Alemtuzumab Risks Identified in Clinical Trials

Identified Risk	Rate in alemtuzumab-treated patients	Notes
ITP	~1%-3% including 1 death <sup>1</sup>	<ul style="list-style-type: none"> <li>Onset generally occurred 14-36 mo after first exposure<sup>1d</sup></li> <li>Most cases responded to first-line medical therapy<sup>1d</sup></li> </ul>
Nephropathies	0.3% (anti-GBM n=2)	<ul style="list-style-type: none"> <li>Generally occurred within 39 mo after last administration<sup>1d</sup></li> <li>Responded to timely medical treatment and did not develop permanent kidney failure<sup>1d</sup></li> </ul>
Thyroid disorders (Hypo-/hyper-)	~39% <sup>a</sup> (serious, 1%)	<ul style="list-style-type: none"> <li>Onset occurred 6-61 mo after first alemtuzumab exposure; peaked in year 3 and declined thereafter<sup>1d</sup></li> <li>Most mild to moderate, most managed with conventional medical therapy; however, some patients required surgical intervention<sup>1d</sup></li> <li>Higher incidence in patients with history of thyroid disorders<sup>1d</sup></li> </ul>
IARs	>90% (serious, 1%-3%)	<ul style="list-style-type: none"> <li>Most occurred within 24 h of alemtuzumab administration<sup>1d</sup></li> <li>Most mild to moderate; rarely led to treatment discontinuation<sup>1d</sup></li> <li>May be caused by cytokine release following mAb-mediated cell lysis<sup>1d</sup></li> </ul>
Infections	~70% (serious, 2.7%)	<ul style="list-style-type: none"> <li>Incidence highest during first month after infusion; rate decreased over time</li> <li>Mostly mild to moderate<sup>1d</sup></li> <li>Generally of typical duration; resolved following conventional medical treatment<sup>1d</sup></li> </ul>

[e]



Reproduced from Pract. Neurol. Giovannoni G, 16, 389-393, copyright 2016 with permission from BMJ Publishing Group Ltd.

<sup>1</sup>Through 48 mo after first exposure. <sup>1d</sup>Before implementation of risk management program.

a. Havrdova E, et al. *Ther Adv Neurol Disord.* 2015;8:31-45; b. Wynn D, et al. ECTRIMS 2013. Abstract P597; c. Giovannoni G, et al. *Pract Neurol.* 2016;16:389-393; d. Willis MD, et al. *Mult Scler.* 2016;22:1215-1223.

Hemolytic anemia, cervical dysplasia,<sup>[d]</sup> MGUS,<sup>[d]</sup> orbitopathy, Goodpasture syndrome

### Alemtuzumab Risks Identified in Clinical Trials<sup>[31-34]</sup>

We can de-risk alemtuzumab. We can screen for infections before we start the drug. Because it causes cell lysis, an infusion reaction often occurs. Most patients develop infusion reactions, which can be quite severe. We pre-dose our patients with steroids and antihistamines to prevent that. When the immune system reconstitutes, a secondary autoimmunity may develop. The predominant one is thyroid disease; with 5-year follow-up, we are now seeing it in about 40% of patients.<sup>[35]</sup> Immune thrombocytopenia occurs in 2% to 3% of patients.<sup>[36]</sup> We also see renal disease, Goodpasture syndrome and membranous nephropathy, and that is a risk of about 1 in 800.<sup>[37]</sup> This is why we have to monthly monitor full blood counts and urine analysis to try and identify these autoimmune diseases before they become severe. They are treatable conditions.

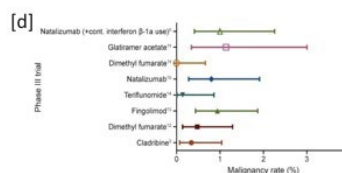
The spectrum is increasing. We are also seeing people with hemolytic anemias and immune neutropenias. We have seen a case of bullous pemphigoid plus 2 cases of acquired hemophilia. I think the spectrum of autoimmunity is going to increase with time post-alemtuzumab.

## Cladribine

- Approved in Europe but not the United States<sup>[a]</sup>
- Purine nucleoside analogue<sup>[b]</sup>
  - Designed to mimic ADA deficiency
  - Depletes T and B lymphocytes
  - Leaves other innate cells intact
- In phase 3 CLARITY trial, at 96 weeks, significantly reduced<sup>[b]</sup>
  - Relapse rates
  - Risk of disability progression
  - MRI measures of disease activity at 96 weeks
- AEs<sup>[c]</sup>
  - More mild/moderate than severe
  - VZV linked to grade 3/4 lymphopenia
  - TB

[c]

	Annualized relapse rate, %	Relative reduction vs placebo	P value vs placebo
Placebo (n = 437)	0.33		
Cladribine, 3.5 mg/kg (n = 433)	0.14	57.6	< .001
Cladribine, 5.25 mg/kg (n = 456)	0.15	54.5	< .001



Leist TP, Weissert R. *Clin Neuropharmacol* 2011;34:28-35 with permission of Wolters Kluwer.

a. Mavenclad™ [SmPc] 2017; b. Leist TP, et al. *Clin Neuropharmacol*. 2011;34:28-35; c. Giovannoni G, et al. *N Engl J Med*. 2010;362:416-426; d. Pakpoor J, et al. *Neurol Neuroimmunol Neuroinflamm*. 2015;2:e158.

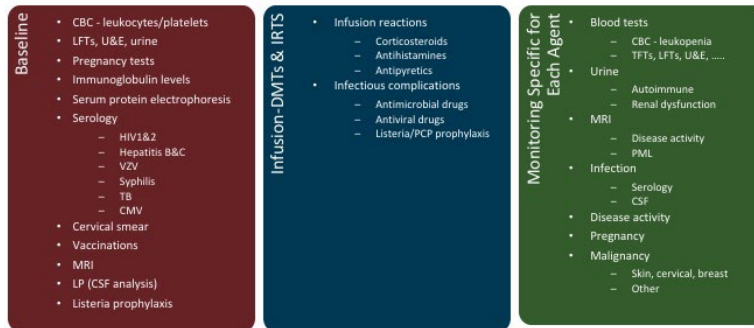
### Cladribine<sup>[14,22,35,36]</sup>

Cladribine is not licensed in the United States but is licensed in Europe. This is a very smart small molecule; it is a purine nucleoside analogue meant to mimic adenosine deaminase deficiency, which causes severe combined immune deficiency. The idea is to try to deplete T and B lymphocytes, similar to what children with adenosine deaminase deficiency have. Because of a quirk in the biology of the cells, lymphocytes are exquisitely sensitive to the effects of cladribine, particularly B lymphocytes, and it leaves other innate cells and other cells in the body relatively intact.

We saw in the 2-year study that it was a highly effective drug relative to placebo. What is interesting is that, in the extension trial, we observed that most people who went onto placebo remained disease-free. This is a typical IRT -- 2 cycles of therapy in year 1 and year 2 -- that gives up to 4 years of long-term remission. What we do beyond that will depend on generating more data.

The only real signal that emerged from a safety perspective was zoster, which was mainly linked to grade 3 and 4 lymphopenia. We monitor lymphocyte counts 2 and 4 months after the last dose of cladribine, and if patients develop grade 3 or 4 lymphopenia, we have the option of giving them antiviral agents. There was possibly a malignancy signal in the original data set, but we now know that that was a false scare driven by 0 malignancies in the placebo arm vs 4 in the treatment arm. You can see that when you compare the malignancy rate in the cladribine-treated arm, it was in the same ballpark as that of other DMTs. We think that, at least in the short to intermediate term, cladribine is not associated with malignancy. I would not like to guess what would happen long term. That is why we will find the answer to this question with our postmarketing and long-term surveillance programs.

## De-Risking Immunosuppression



### De-Risking Immunosuppression

This slide summarizes the way we de-risk immunosuppression in clinical practice. At baseline, you have to do routine blood work. In our center, we assess baseline immunoglobulin levels, primarily for patients receiving the anti-CD20 DMTs. We also do a serum protein electrophoresis because, if the patient has a monoclonal gammopathy, interferons are contraindicated because there is a risk of acquiring pulmonary capillary leak syndrome. We do a baseline infectious screen, and if people have any of these infections, we treat the infection before they begin DMT. If they are varicella zoster virus titer negative, we vaccinate them and wait 4 to 6 weeks before starting the immunosuppression. In patients who are women, we make sure they have had an up-to-date cervical smear, which we repeat every 3 years in the program. We also offer patients vaccines if they need vaccines.

During the infusions, we manage infusion reactions. If any infectious complications arise, we manage them with antimicrobial and antiviral drugs. We are now beginning to offer our patients the option of taking antibiotic prophylaxis (co-trimoxazole) to prevent listeria and pneumocystis. Monitoring requirements are dependent upon which DMT patients are on. Clinicians need to know each individual agent's requirements for monitoring.

## Vaccinations and Pregnancy

### Maintenance Therapies vs IRTs: Vaccines and Pregnancy

Maintenance Therapies	IRTs
<ul style="list-style-type: none"> <li>• Continuous treatment                             <ul style="list-style-type: none"> <li>– Adherence potential problem</li> </ul> </li> <li>• Low to very high efficacy</li> <li>• Reversible</li> <li>• Perceived to be lower risk                             <ul style="list-style-type: none"> <li>– Cumulative, or increased, risk with time</li> </ul> </li> <li>• Examples                             <ul style="list-style-type: none"> <li>– GA,<sup>a,k</sup> IFN-<math>\beta</math>,<sup>f-h</sup> teriflunomide,<sup>l</sup> dimethyl fumarate,<sup>i</sup> fingolimod,<sup>o</sup> natalizumab,<sup>k</sup> ocrelizumab<sup>l</sup></li> </ul> </li> <li>• Breakthrough disease                             <ul style="list-style-type: none"> <li>– Suboptimal or failure to respond</li> <li>– NEDA reliable metric for efficacy</li> </ul> </li> <li>• Rebound activity                             <ul style="list-style-type: none"> <li>– Highly likely</li> <li>– Can be life-threatening</li> </ul> </li> <li>• Pregnancy</li> <li>• No potential for a cure                             <ul style="list-style-type: none"> <li>– Rebound</li> <li>– SPMS and progressive brain atrophy</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Short-courses or pulsed therapy                             <ul style="list-style-type: none"> <li>– Adherence seldom a problem</li> </ul> </li> <li>• High to very high efficacy</li> <li>• Irreversible</li> <li>• Perceived to be higher risk                             <ul style="list-style-type: none"> <li>– Front-loading of risk or reduced risk with time</li> </ul> </li> <li>• Examples                             <ul style="list-style-type: none"> <li>– Nonselective: mitoxantrone,<sup>m</sup> alemtuzumab,<sup>n</sup> HSCT-BMT<sup>o,p</sup></li> <li>– Selective: cladribine<sup>q</sup></li> </ul> </li> <li>• Breakthrough disease                             <ul style="list-style-type: none"> <li>– Marker for retreatment</li> <li>– NEDA unreliable to assess efficacy</li> </ul> </li> <li>• Rebound activity                             <ul style="list-style-type: none"> <li>– Less likely</li> <li>– Unlikely to be life-threatening</li> </ul> </li> <li>• Pregnancy</li> <li>• Potentially "curative"?                             <ul style="list-style-type: none"> <li>– 15- to 20-year experiment</li> </ul> </li> </ul>

a. Copaxone® PI 2016; b. Glatiramer acetate PI 2017; c. Avonex® PI 2016; d. Betaseron® PI 2016; e. Extavia® PI 2016; f. Rebif® PI 2015; g. Plegridy™ PI 2016; h. Aubagio® PI 2016; i. Tecfidera® PI 2016; j. Gilenya® PI 2017; k. Tysabri® PI 2017; l. Ocrevus® PI 2017; m. Novantrone® PI 2008; n. Lemtrada® PI 2017; o. Baxuhuraysah MM, et al. *Stem Cell Res Ther.* 2016;7:12; p. Giovannoni G, et al. *N Engl J Med.* 2010;362:416-426.  
\*Not FDA approved for the treatment of MS.

### Maintenance Therapies vs IRTs: Vaccines and Pregnancy<sup>[1-16]</sup>

This slide, again, summarizes the 2 arms. I want to come back to this Table because the two things I am going to talk to you now are vaccinations and pregnancies, which I think are two important attributes that separate these arms.

### Case Study 1

- 42-year-old man
  - Married with 2 children
  - War correspondent with frequent travel to Afghanistan, Ukraine, Iraq, and Syria
- Initial symptoms, diagnosis, and treatment
  - Sensory symptoms in feet and Lhermitte sign
  - RRMS late 2014
  - Dimethyl fumarate
- 2 disabling attacks in 2015
  - Ataxia and leg weakness
  - Spinal cord lesion
  - Revised diagnosis: rapidly evolving severe MS
- Revised treatment options and rationale
  - Fingolimod: patient not keen about long-term immunosuppression
  - Natalizumab: contraindicated as found to be JCV-seropositive (index 1.86)
  - Interested in HSCT: not eligible under local guidelines
  - Alemtuzumab: concerns about monitoring and accessing urgent treatment in a war zone
- Final treatment decision
  - Jointly decided to treat with cladribine off-label (2 cycles given – Jan/Feb 2016 and 2017)



### Case Study 1

This patient is a journalist on one of the television stations in the United Kingdom. He was aged 42 years and married with 2 children when he developed MS. He frequently travels to war zones, including Afghanistan, Ukraine, Iraq, and Syria. His initial symptoms were sensory symptoms in his feet with Lhermitte phenomenon. He was put on dimethyl fumarate and had 2 relapses in 2015: 1 episode of ataxia, and then weakness in his leg with a mild drop foot when running.

Under our system, we could classify him as having rapidly evolving severe MS, which made him eligible for almost all our second-line therapies: fingolimod, natalizumab, and alemtuzumab. He did not want fingolimod because he was worried about immune suppression. He could not have natalizumab because of JC virus seropositivity. We could not refer him for HSCT because he was not eligible under our local guidelines, so we offered him alemtuzumab. I was personally very worried about alemtuzumab because of the monitoring requirements. If he developed immune thrombocytopenia or Goodpasture syndrome in Syria, would the healthcare system be able to look after him? We finally offered him parenteral cladribine; he has done very well on it. This case provides an example of how you go through a treatment algorithm and select an IRT that is suitable in terms of monitoring requirements for an individual patient.

## Vaccinations

- Fingolimod<sup>[a]</sup>: Avoid live attenuated vaccines during and 2 months after stopping treatment
- Natalizumab<sup>[b]</sup>: No data are available on the effects of vaccination in patients receiving natalizumab. No data are available on the secondary transmission of infection by live vaccines in patients receiving natalizumab
- Alemtuzumab<sup>[c]</sup>: Complete any necessary immunizations at least 6 weeks prior to treatment; determine whether patients have a history of varicella or have been vaccinated for VZV. If not, test the patient for antibodies to VZV and consider vaccination for those who are antibody-negative. Postpone treatment until 6 weeks after VZV vaccination; perform TB screening according to local guidelines
- Cladribine<sup>[d]</sup>\*: Treatment should not be initiated within 4 to 6 weeks after vaccination with live or attenuated live vaccines because of a risk of active vaccine infection. Vaccination with live or attenuated live vaccines should be avoided during and after treatment as long as the patient's WBCs are not within normal limits

\* Not FDA approved for the treatment of MS.  
a. Gilenya® PI 2017; Tysabri® PI 2017; Lemtrada® PI 2017; d. Mavenclad™ SmPc 2017.

### Vaccinations<sup>[6,9,12,22]</sup>

If a patient wants or needs to be vaccinated for work reasons, you do not want them on continuous immunosuppression. This is why alemtuzumab and cladribine are very appealing, because you can treat the MS, get the disease under control, and then wait for the immune system to reconstitute before vaccinating.

## Pregnancy

Fingolimod <sup>[a]</sup>	Inform patients that, based on animal studies, fingolimod may cause fetal harm. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Advise women of childbearing age of the need for effective contraception during fingolimod treatment and for 2 months after stopping fingolimod. Advise the patient that if she should nevertheless become pregnant, she should immediately inform her physician. Fingolimod should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A pregnancy registry has been established to collect information about the effect of GILENYA use during pregnancy.
IFN- $\beta$ <sup>[b-f]</sup>	Pregnancy: based on animal data, may cause fetal harm. Initiation of treatment is contraindicated during pregnancy. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Glatiramer acetate <sup>[g]</sup>	Administration of glatiramer acetate by subcutaneous injection to pregnant rats and rabbits resulted in no adverse events on offspring development. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, glatiramer acetate should be used during pregnancy only if clearly needed.

a. Betaseron<sup>®</sup> PI 2016; b. Avonex<sup>®</sup> PI 2016; c. Gilenya<sup>®</sup> PI 2017; d. Extavia<sup>®</sup> PI 2016; e. Rebif<sup>®</sup> PI 2015; f. Plegridy<sup>™</sup> PI 2016; g. Copaxone<sup>®</sup> PI 2016.

### Pregnancy<sup>[1-3,5,8,13]</sup>

I am not going to go through all these guidelines, but pregnancy is one of the main attributes of DMT that needs to be taken into account when considering therapies.

## Pregnancy (cont)

Cladribine <sup>[a]</sup>	Studies in animals have shown reproductive toxicity. Before initiation of treatment in year 1 and year 2, women of childbearing potential and males who could potentially father a child should be counseled regarding the potential for serious risk to the fetus and the need for effective contraception. Patients must take precautions to prevent pregnancy during cladribine treatment and for at least 6 months after the last dose. Cladribine is contraindicated in pregnant women.
Alemtuzumab <sup>[b]</sup>	There are no adequate and well-controlled studies in pregnant women. Alemtuzumab was embryolethal in pregnant huCD52 transgenic mice when administered during organogenesis. Autoantibodies may develop after administration of alemtuzumab. Placental transfer of antithyroid antibodies resulting in neonatal Graves' disease has been reported. Alemtuzumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

a. Not FDA approved for the treatment of MS. Mavenclad<sup>™</sup> SmPc 2017; b. Lemtrada<sup>®</sup> PI 2017.

### Pregnancy (cont)<sup>[12,22]</sup>

Again, because of the way IRTs work in the system for a very short period of time, they act within days to weeks, conception can happen safely once the immune system reconstitutes. In Europe, we have to wait at least 4 months after alemtuzumab and 6 months after oral cladribine.

## Pregnancy (cont)

Teriflunomide <sup>[a]</sup>	AUBAGIO is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Teratogenicity and embryolethality occurred in animals administered teriflunomide. Exclude pregnancy prior to initiating therapy. Advise use of effective contraception in females of reproductive potential during treatment and during an accelerated drug elimination procedure. Stop teriflunomide and use an accelerated drug elimination procedure if the patient becomes pregnant. Boxed warning.
Dimethyl fumarate <sup>[b]</sup>	There are no adequate and well-controlled studies in pregnant women. In animals, adverse events on offspring survival, growth, sexual maturation, and neurobehavioral function were observed when dimethyl fumarate was administered during pregnancy and lactation at clinically relevant doses. Dimethyl fumarate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Natalizumab <sup>[c]</sup>	Based on animal data, may cause fetal harm. There are no adequate and well-controlled studies in pregnant women. Natalizumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Ocrelizumab <sup>[d]</sup>	Based on animal data, may cause fetal harm. There are no adequate data on the developmental risk associated with use of ocrelizumab in pregnant women. There are no data on B-cell levels in human neonates following maternal exposure to ocrelizumab. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy.

a. Aubagio® PI 2016; b. Tecfidera® PI 2016; c. Tysabri® PI 2017; d. Ocrevus™ PI 2017.

### Pregnancy (cont)<sup>[6,10,11,15]</sup>

I would not recommend HSCT to a young woman who wants to extend her family. At least in the United Kingdom, we use 4-hydroxycyclophosphamide for ablation, which is very toxic to the ovaries; therefore, about 40% to 50% of women who have HSCT are rendered infertile. I would not include HSCT as a safe IRT for patients who are considering pregnancy in the future.

## An MS Cure?

### Defining an MS Cure?

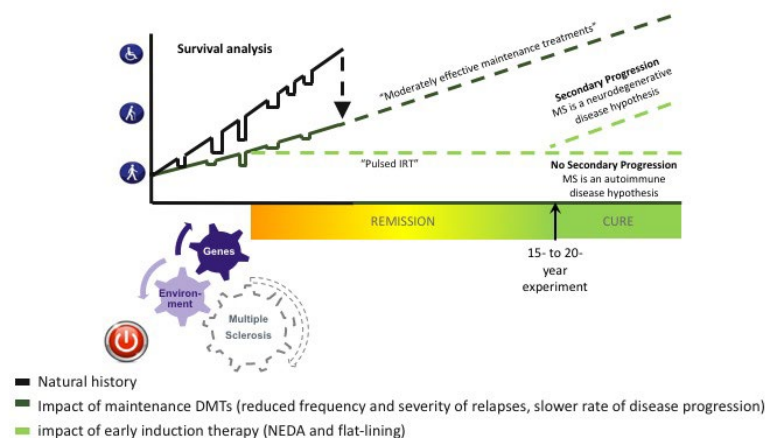


Figure courtesy of Gavin Giovannoni, MBBCh, PhD.

### Defining an MS Cure?

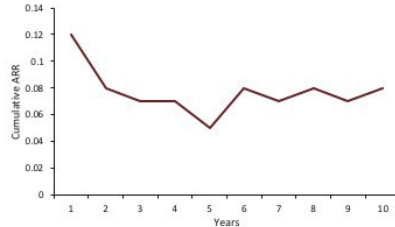
What about a cure? This is what the IRTs do. Is there any evidence that patients go into long-term remission? This is what we have done: we have taken people relatively early in their disease, we have given them an IRT, and they are now going for a long period without symptoms. Are they cured?



## 10-Year Durable Efficacy of Alemtuzumab CAMMS223

- Patients
  - 60 enrolled in extension study
  - 57 followed for  $\geq 10$  y
- EDSS scores from baseline to year 10
  - Stable: 59.3%
  - Improved: 18.5%

Courses of alemtuzumab, 12 mg, no.	Patients, n (%)
2	20 (33)
3	26 (43.3)
4	7 (11.7)
5	6 (10)

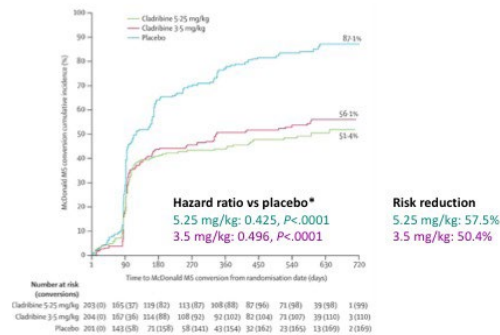


Coles AJ, et al. *Neurology*. 2016;86 (suppl 16). Poster P3.053.

### 10-Year Durable Efficacy of Alemtuzumab<sup>[37]</sup>

This slide shows the 10-year follow-up of the phase 2 trial of alemtuzumab vs interferon  $\beta$ -1a, subcutaneously. Most patients who continued in the extension study are stable, with flatlining of the Expanded Disability Status Scale (ie, no increase in disability). This cohort is selective; about half of the patients have dropped out; however, I think what we have to focus on is the proportion of patients who received alemtuzumab and are in long-term remission.

## CIS Conversion to MS With Cladribine



Patients enrolled in ORACLE-MS were treatment-naïve with an FCDE at high risk of converting to MS.

Reprinted from *Lancet Neurol*, 13, Leist TP et al., Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial, 257-267, Copyright 2013, with permission from Elsevier

\*Cox proportional hazards model controlling for the randomization stratification factor (region).

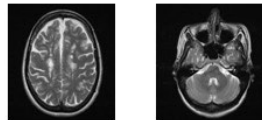
### CIS Conversion to MS With Cladribine<sup>[38]</sup>

ORACLE is the study of oral cladribine in patients with clinically isolated syndrome (CIS). Most people with CIS convert to MS within the first 3 to 6 months. In this study, only half of the patients converted to McDonald-positive MS on cladribine, whereas more than 80% in the placebo arm converted to MS.

Would it not be wonderful to see a significant proportion of these patients go 5 to 10 years without converting? I think this experiment is the most interesting experiment of all using an IRT very early, as early as we can in the course of MS, right after patients' first presentation, to see if we can put them into long-term remission.

## Case Study 2

- 48-year-old woman
  - Married with 2 children
  - Employed as a counselor
- History
  - 1996 -- Probable first symptoms with mild transient sensory symptoms in legs
  - 2001 -- Diagnosed with MS after an episode of weakness in right hand
  - 2003 -- R-optic neuritis
  - 2004 -- Weakness in legs with bladder involvement
- Clinical trial participation
  - 2005-2007 -- CLARITY study (active treatment)
  - 2008-2010 -- CLARITY EXTENSION (placebo)
- Decade of stability without additional treatment
  - 2005-2015 -- NEDA, EDSS 3.0 (stable), walking unrestricted
- Relapse in 2015
  - Symptoms: numbness and pain in R side of face
  - MRI: new T2 lesion in brainstem
  - Treatment
    - Refused platform DMTs
    - 2 cycles of parenteral cladribine

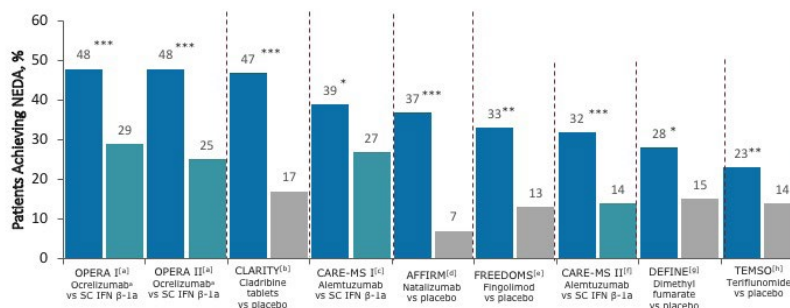


Figures courtesy of Gavin Giovannoni, MBBCh, PhD.

### Case Study 2

This participant in the pivotal CLARITY phase 3 trial had quite active disease; she was not put on a DMT and was referred for the trial in 2005. She was randomly assigned to active therapy with the licensed dose of cladribine (ie, 3.5 mg/kg) and had treatment only in the first 2 years with tablets given 4 or 5 days in week 1 of month 1, repeated again in month 2, with the cycle repeated in year 2. She entered the extension trial and had no further treatment. Ten years after her first course of treatment, she returned to the clinic, presenting with numbness and pain in the right side of her face; she had a new T2 lesion in the brain stem. At that stage, licensed oral cladribine was not available, so we offered her all of the DMTs that were available (ie, the interferons, injectables, dimethyl fumarate, teriflunomide, and alemtuzumab). She turned them all down. We offered her parenteral cladribine; after undergoing 2 cycles, she has been doing well ever since.

## NEDA Rates in Phase 3 Trials



\* $P < .05$ , \*\* $P < .001$ , \*\*\* $P < .0001$  study drug vs comparator.

NEDA defined as no relapses, no 3-month CDP, and no new T1 Gd+ lesions, and no new enlarging or enlarged T2 lesions on cranial MRI (except CLARITY, CARE-MS I, and CARE-MS II: based on no 6-month CDP).

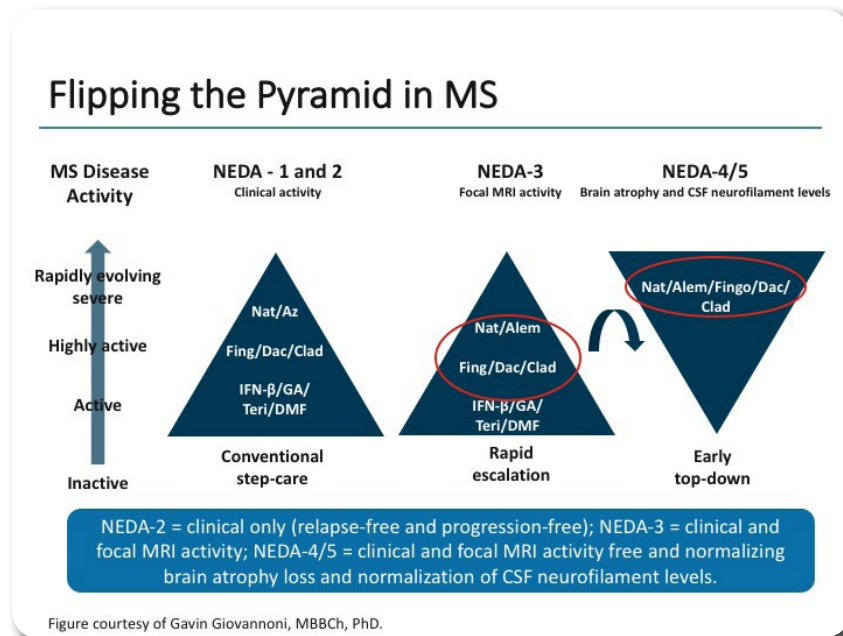
a. Traboulsee A, et al. *Neurology*. 2016;86(suppl). Abstract PLO2.004; b. Giovannoni G, et al. *Lancet Neurol*. 2011;10:329-337; c. Cohen JA, et al. *Lancet*. 2012;380:1819-1828; d. Havrdova E, et al. *Lancet Neurol*. 2009;8:254-260; e. Bevan CJ, et al. *JAMA Neurol*. 2014;71:269-270; f. Coles AJ, et al. *Lancet*. 2012;380:1829-1839; g. Giovannoni G, et al. *Neurology*. 2012;75(suppl 1). Abstract PDS.005; h. Freedman MS. *Ther Adv Chronic Dis*. 2013;4:192-205.

Figure courtesy of Gavin Giovannoni, MBBCh, PhD.

### NEDA Rates in Phase 3 Trials<sup>(39-46)</sup>

This graph highlights that, when you start looking at IRTs, they bat in the top of the range for disease efficacy. This is using NEDA rates based on the baseline MRI scan in phase 3 trials. You can see that alemtuzumab and oral cladribine are very effective in terms of NEDA rates.

## Personalizing Treatment in MS Based on New Approaches



### Flipping the Pyramid in MS

In our center now, we do not use the conventional stepped care approach. We either offer our patients rapid escalation or, if they are eligible, would flip the pyramid and give them the most effective therapies first line. I think that is where the MS field is going. We are moving away from this slow passive approach to a much more active, aggressive approach for managing the disease. There are very good data, not only from clinical trials, but also from real-life data sets, such as MSBase, showing that rapid escalation and the top-down approach are much more effective on average than the conventional stepped care approach. Practicing neurologists need to seriously think about how to manage MS going forward, in terms of optimizing disease management.

## A New Classification of DMTs for RMS

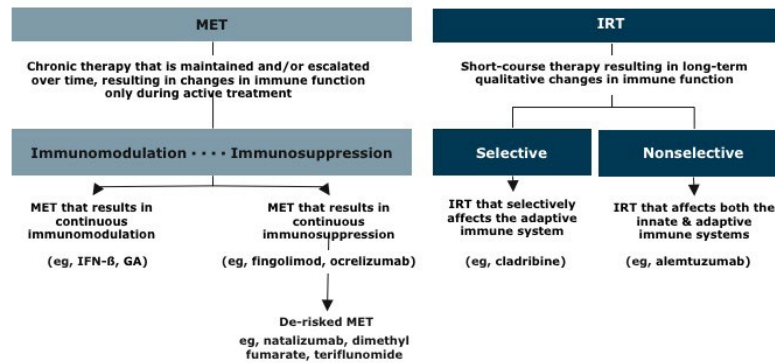
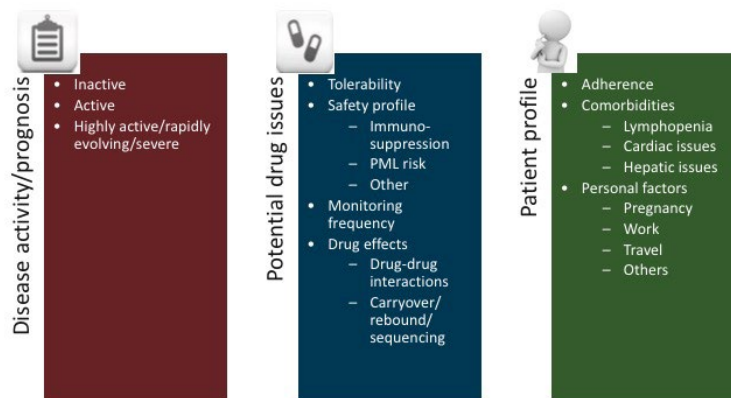


Figure courtesy of Gavin Giovannoni, MBBCh, PhD.

### A New Classification of DMTs for RMS

I would like to propose a new classification system to try to put this into some kind of pigeonholing to help you understand these treatments. On the left, we have the maintenance escalation treatments, which I like to divide into immunomodulatory, interferon and glatiramer acetate, vs immunosuppressive. Whereas, on the immune reconstitution arm, we split these into the nonselective, those that cause adaptive and innate immune suppression and wipe out the immune system (alemtuzumab and HSCT) vs the more selective one, cladribine. As I have already pointed out, cladribine is pretty selective for T and B, mainly B lymphocytes, and it leaves the innate cells intact, which is why you have a completely different profile with cladribine. The other aspect that I did not highlight earlier is that cladribine does not lyse cells; it reduces the lymphocyte counts gradually over weeks to months, so we do not see a cell lysis syndrome with cladribine, which is another positive aspect of that drug.

## Personalizing Therapy



Wingerchuk DM, et al. *BMJ*. 2016;354:i3518.

### Personalizing Therapy<sup>[47]</sup>

Despite that classification system, it is not only the benefits or the efficacy of the drugs that need to be taken into account when deciding which DMT to use. I would urge you to think about the individual in front of you and try and individualize that treatment decision based on the attributes of that patient.

## Conclusion

### Conclusions

- Changing therapeutic landscape; more complex -- more choices
- DMTs are either maintenance or IRTs
  - IRTs (selective or nonselective)
- DMTs are immunomodulatory or immunosuppressive
  - Long-term/maintenance or short-term/induction
- Risks of MS vs benefits of treatment vs risks of treatment
- De-risking treatments
  - Baseline screening
  - Monitoring
  - Timely switching
  - Shift from maintenance (cumulative) to induction (front-loaded) risk
- DMT-specific knowledge
- Databases (pharmacovigilance monitoring, pregnancy, registries)
- Education

### Conclusions

In conclusion, I have given you a very rapid tour of how the therapeutic landscape is becoming much more complex and hope that simplifying the options into a classification system of maintenance vs IRT helps, as does considering whether a treatment is immunomodulatory vs immunosuppressive. On the immunosuppressive side, DMTs can be separated into those that cause long-term vs short-term immunosuppression. I have also provided information on how we de-risk these treatments, manage them in clinical practice, and monitor patients. I would like to stress that you still need to have specific knowledge about each DMT. Hopefully, with pharmacovigilance, pregnancy, and other databases, we will have a much better idea of how to use these therapies relative to each other going forward.

### Thank You

*This transcript has been edited for style and clarity.*

## Abbreviations

ADA = adenosine deaminase	IM = intramuscular
AE = adverse event	IR = infusion reaction
Alem = alemtuzumab	IRT = immune reconstitution therapy
ARR = annualized relapse rate	IS = immunosuppression
BMT = bone marrow transplantation	JCV = JC virus
BT = blood test	LFT = liver function test
CBC = complete blood cell count	LP = lumbar puncture
CDP = confirmed disability progression	mAb = monoclonal antibody
CHMP = Committee for Medicinal Products for Human Use	MET = maintenance-escalation therapy
CIS = clinically isolated syndrome	MGUS = monoclonal gammopathy of undetermined significance
Clad = cladribine	MPR = medication possession ratio
CMV = cytomegalovirus	MRI = magnetic resonance imaging
CNS = central nervous system	MS = multiple sclerosis
CSF = cerebrospinal fluid	NAB = neutralizing antibody
CV = cardiovascular	Nat = natalizumab
Dac = daclizumab	NEDA = no evident disease activity
DMF = dimethyl fumarate	O = ophthalmology
DMT = disease-modifying therapy	PCP = pneumocystis pneumonia
EBV = Epstein-Barr virus	PML = progressive multifocal leukoencephalopathy
ECG = electrocardiogram	PPMS = primary progressive multiple sclerosis
EDSS = Expanded Disability Status Scale	R-SPMS = relapsing secondary progressive multiple sclerosis
ELISpot = Enzyme-Linked ImmunoSPOT	RMS = remitting multiple sclerosis
FCDE = first clinical demyelinating event	RRMS = relapsing-remitting multiple sclerosis
FDA = US Food and Drug Administration	Rx = treatment
Fing = fingolimod	S1P = sphingosine 1-phosphate
GA = glatiramer acetate	S1P-R = S1P receptor
GBM = glomerular basement membrane	SAE = serious adverse event
Gd = gadolinium	SC = subcutaneous
HBVs = Hepatitis B virus screening	SPMS = secondary progressive multiple sclerosis
HIV = human immunodeficiency virus	T2T = treat to target
HPV = human papillomavirus	TB = tuberculosis
HSCT = hematopoietic stem cell transplantation	TBs = tuberculosis screening
HYP = high-yield process	Teri = teriflunomide
HyperR = hypersensitivity reaction	TFT = thyroid function test
IAR = infusion-associated reaction	U = urinalysis
IBD = inflammatory bowel disease	U&E = urea and electrolytes
IFN = interferon	VZV = varicella-zoster virus
IL = interleukin	WBC = white blood cell

## Related Links

### *Highlights From the 2017 Annual European MS Meeting*

<https://www.medscape.org/viewarticle/887946>

### *MS Highlights From the 2017 Annual Neurology Meeting*

<https://www.medscape.org/viewarticle/881721>

### *Clinical Advances in Multiple Sclerosis*

<https://www.medscape.org/sites/advances/ms>

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