Medscape EDUCATION

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

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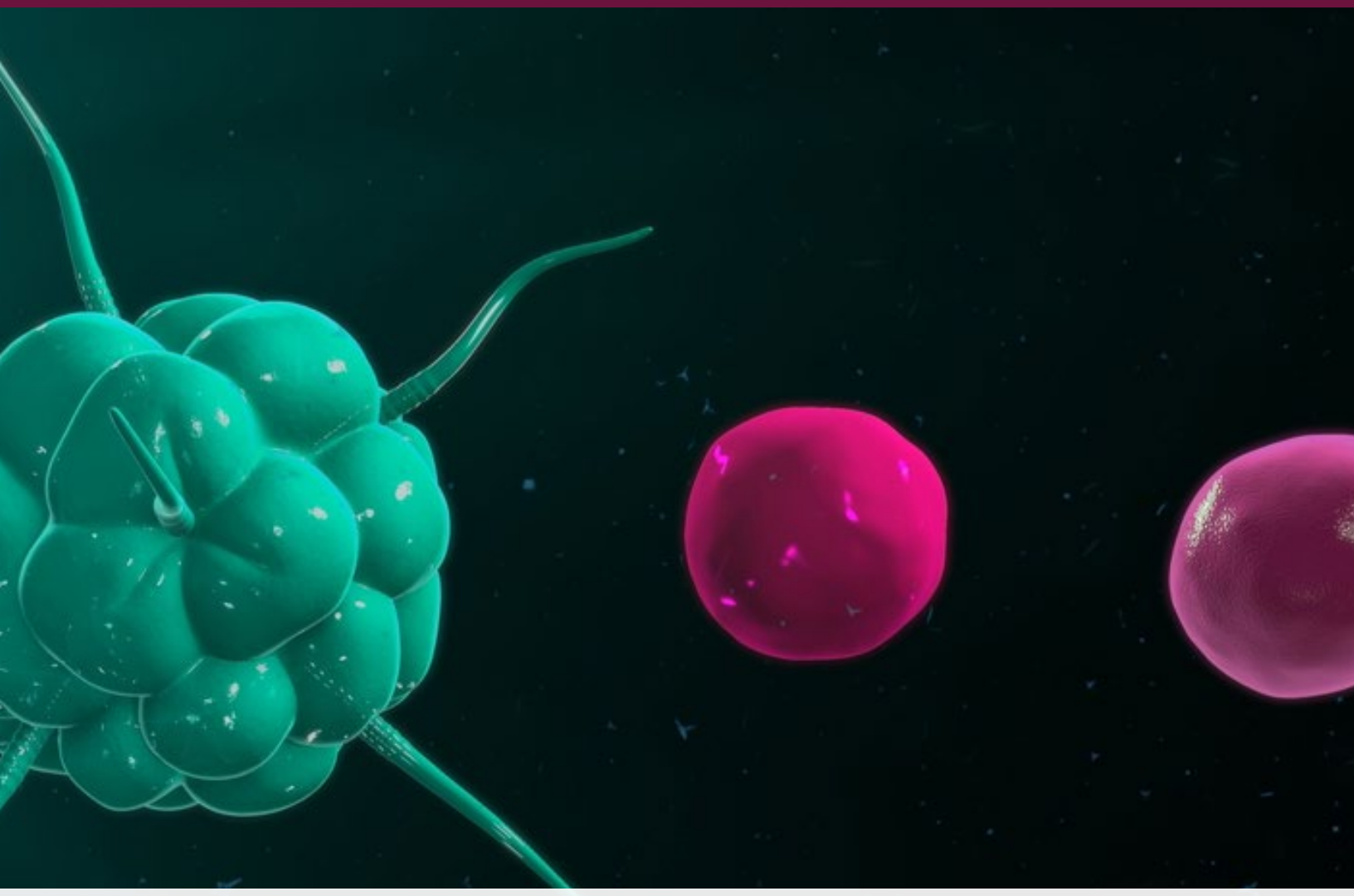

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CME Released: 3/16/2018; Valid for credit through: 3/16/2019

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

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Associate Scientific Director, Medscape, LLC

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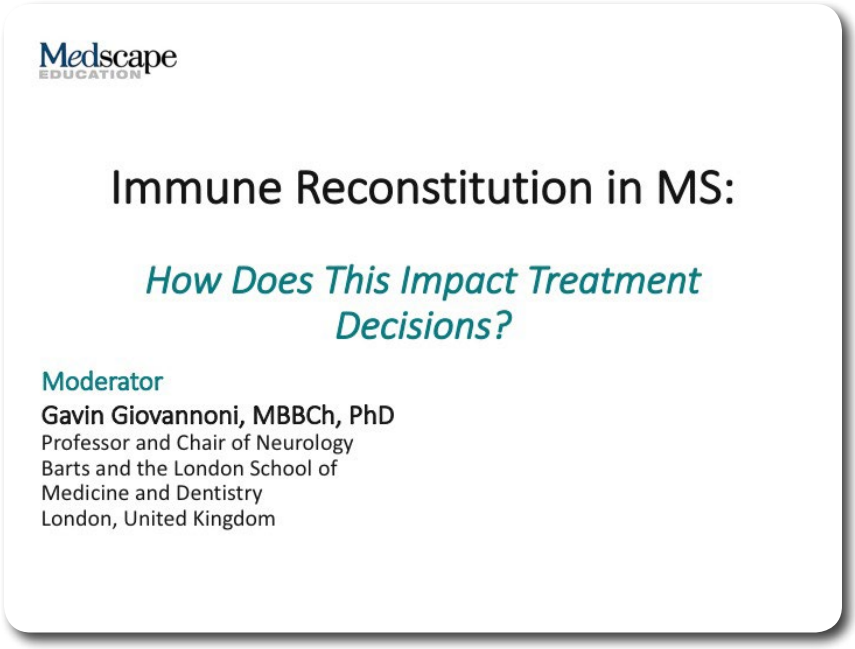
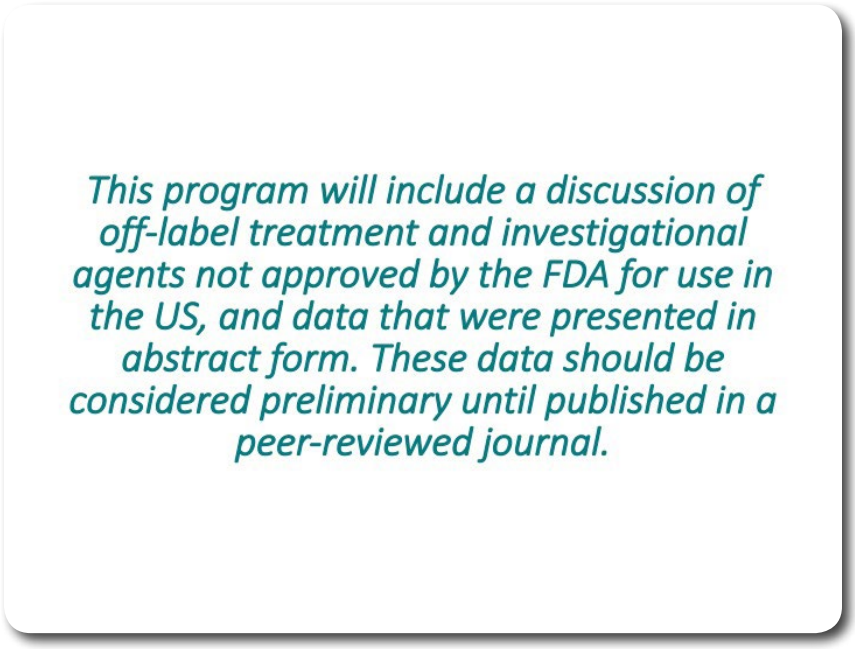
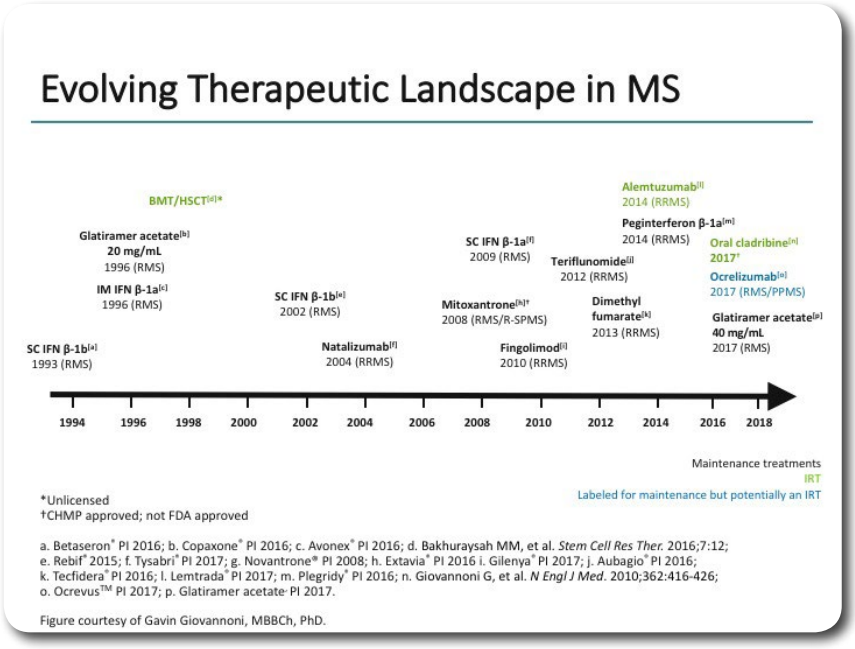


Immune Reconstitution in MS: How Does This Impact Treatment Decisions?



Disclosure

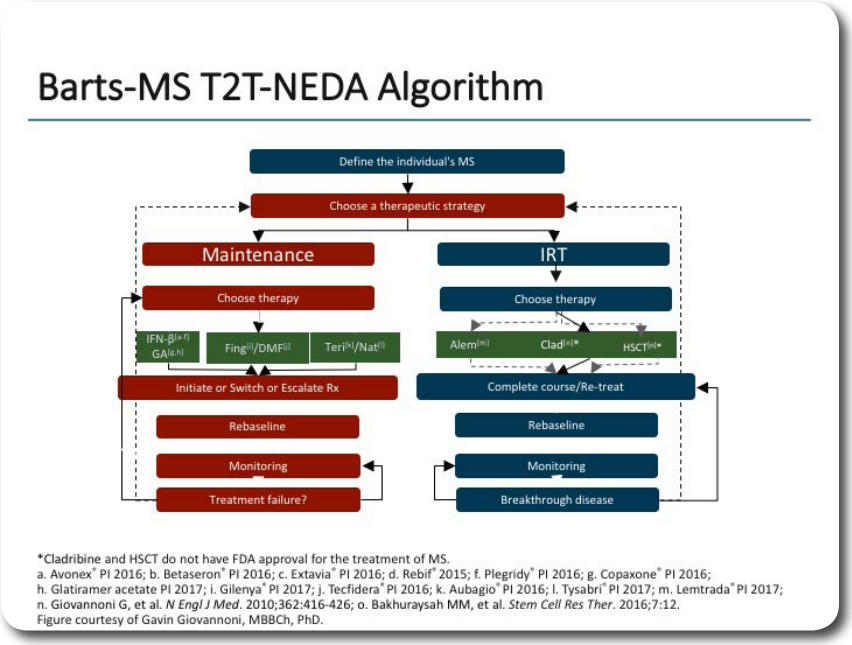
Disease-modifying Therapies for MS



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[1-16]

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.

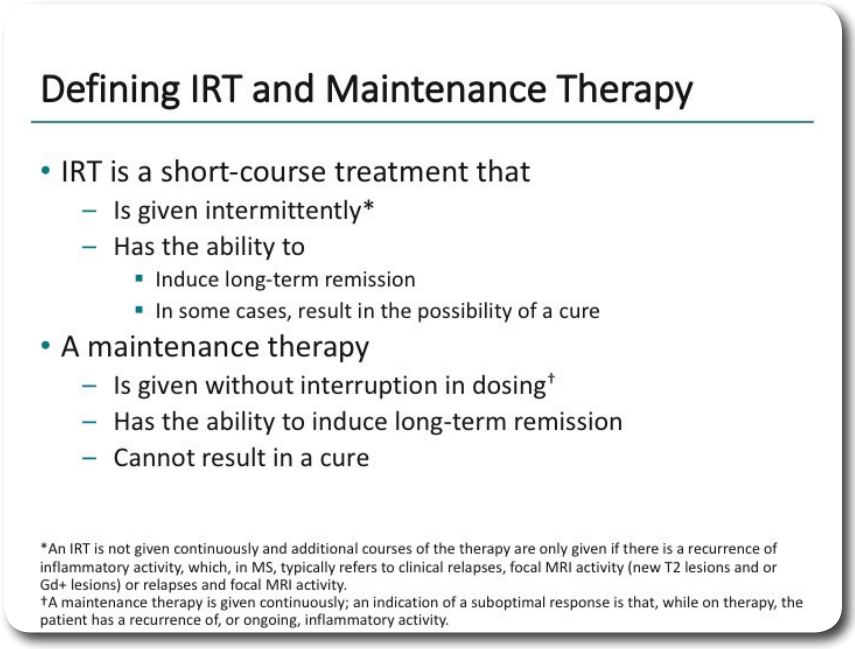


Barts-MS T2T-NEDA Algorithm[1-16]

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.

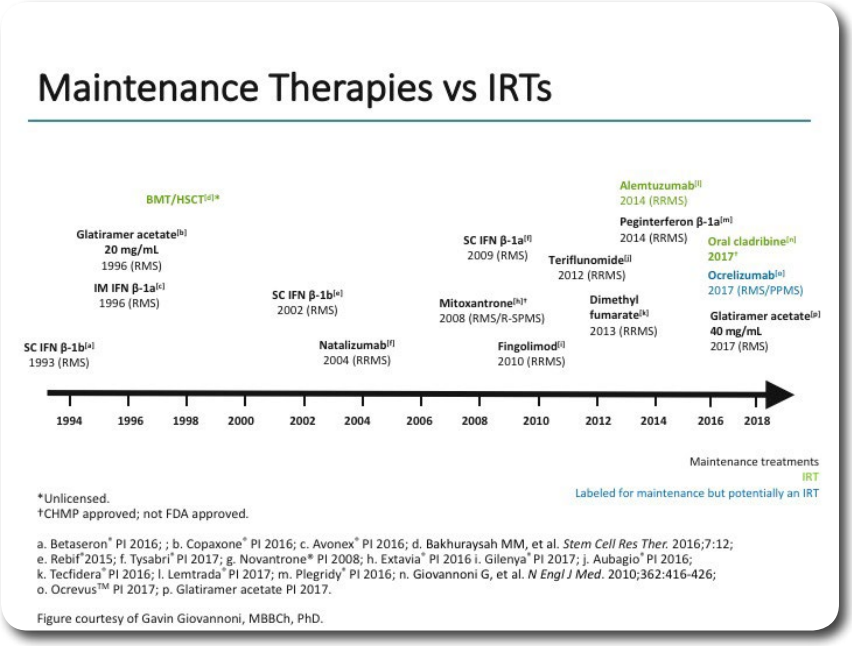
IRT vs Maintenance Therapy



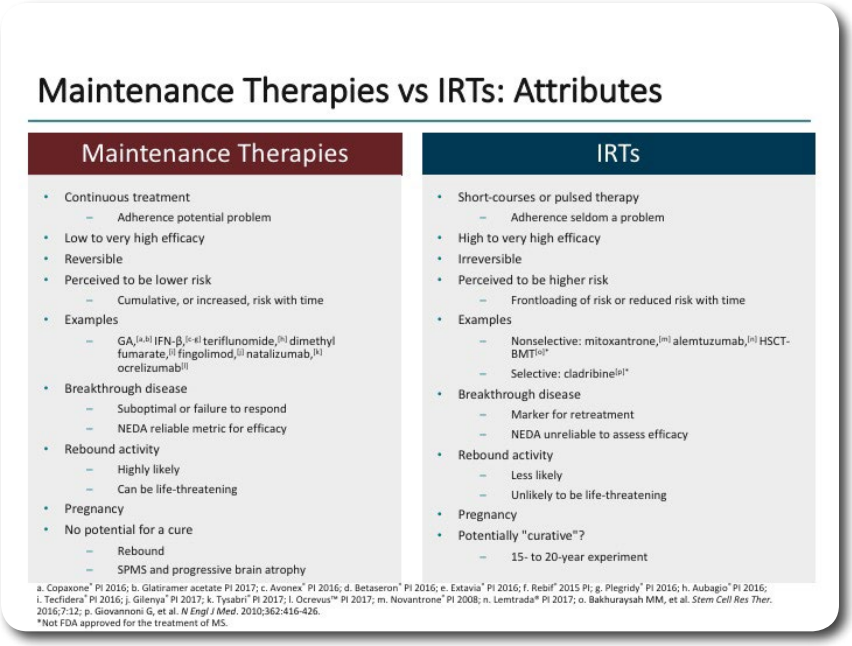
Defining IRT and Maintenance Therapy

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[1-16]
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.

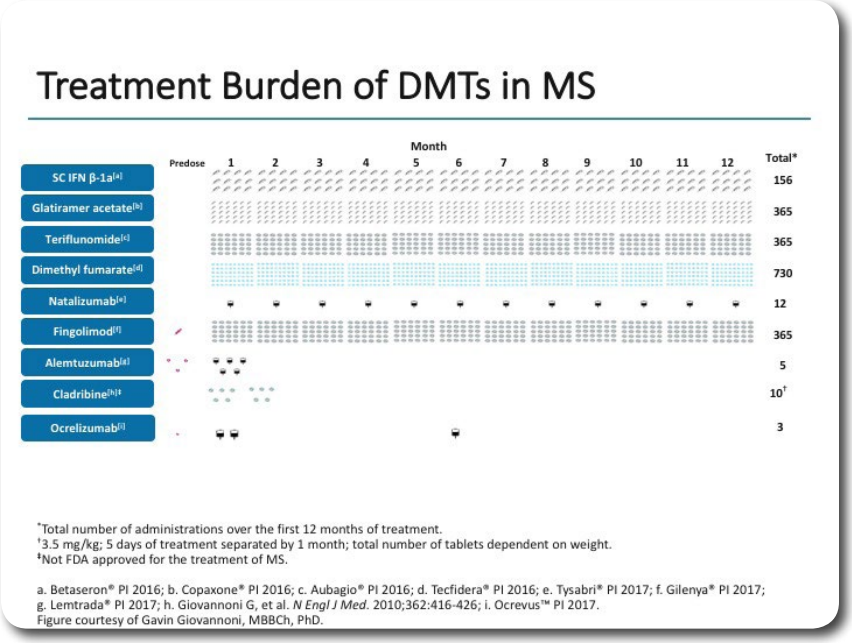


Maintenance Therapies vs IRTs: Attributes[1-16]
This slide, with the 2 Tables, highlights the attributes of maintenance and IRTs. I would just like to point out some of the characteristics that differentiate these 2 treatment strategies. On the IRT side, it is irreversible. In other words, once you have 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.

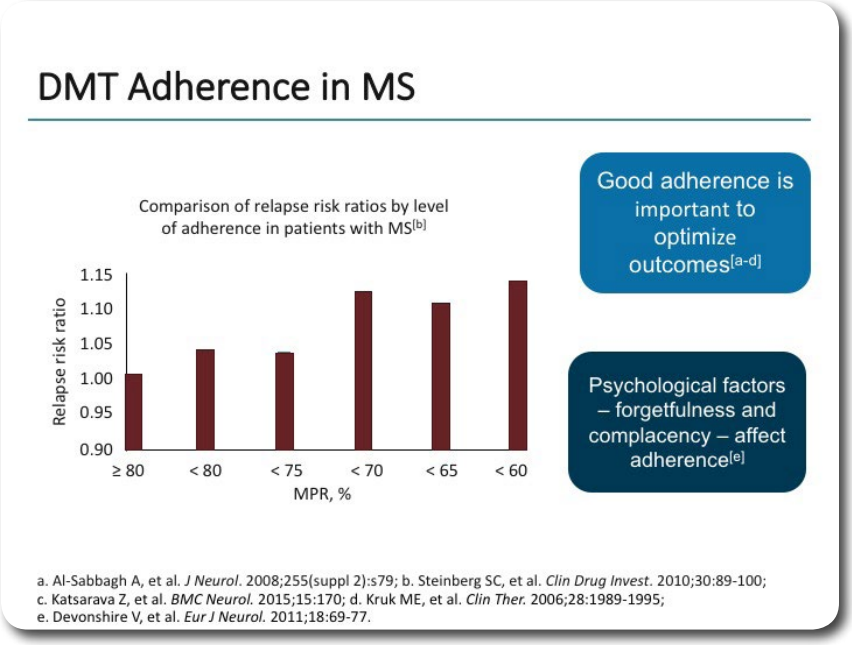
Also, maintenance drugs that block trafficking of lymphocytes into the central nervous system, such as natalizumab and fingolimod, increase the risk of rebound. We tend not to see rebound on IRTs. When disease activity reoccurs, it tends to come back more gently, and gives us an opportunity to identify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

Treatment and Monitoring Burden



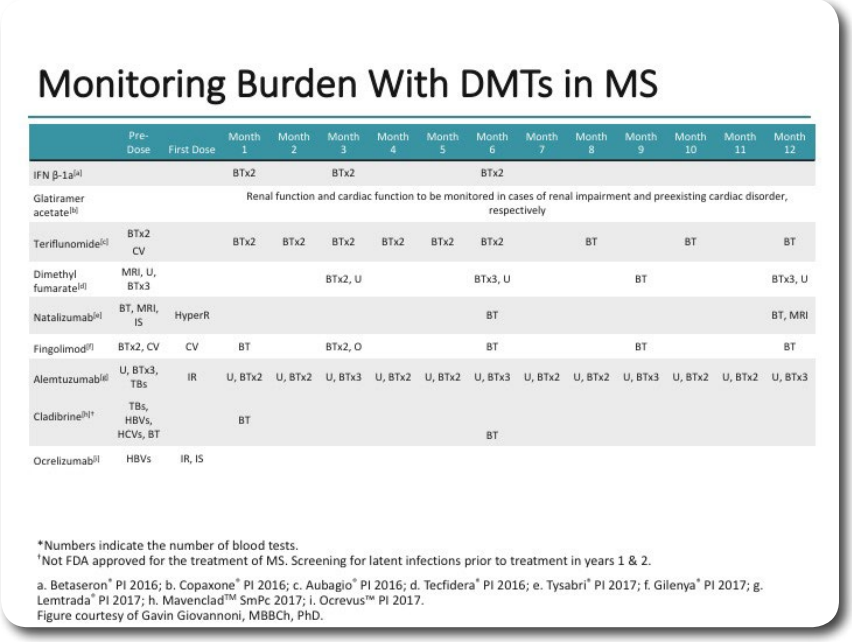
Treatment Burden of DMTs in MS[1,2,6,9-12,14,15]
What is not captured on the previous slide is the treatment burden. You can see on this slide, when you look at the IRTs, alemtuzumab, cladribine, and HSCT, the treatment burden is up front. The actual treatment burden is very low compared with maintenance 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.



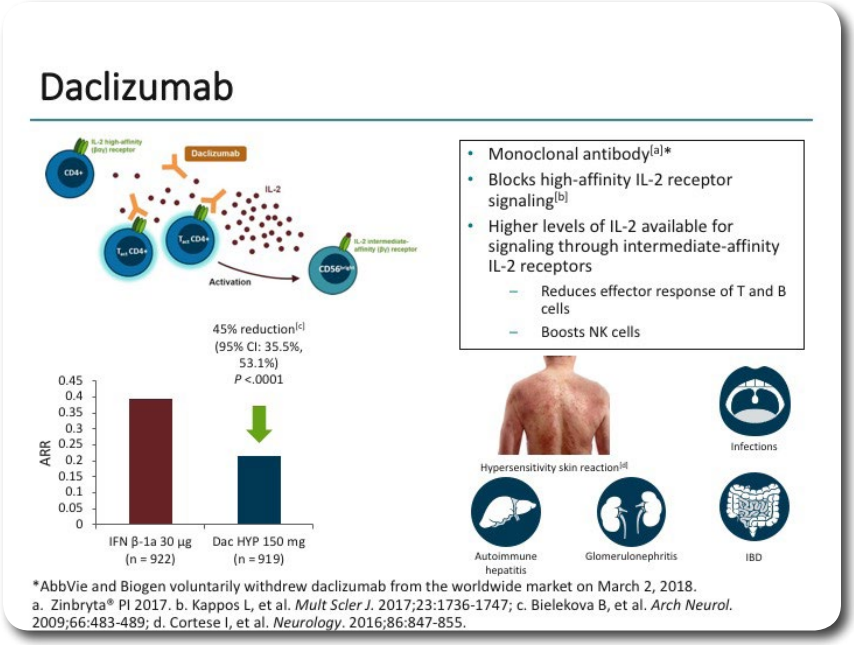
DMT Adherence in MS[17-21]

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[1,2,6,9-12,15,22]

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.



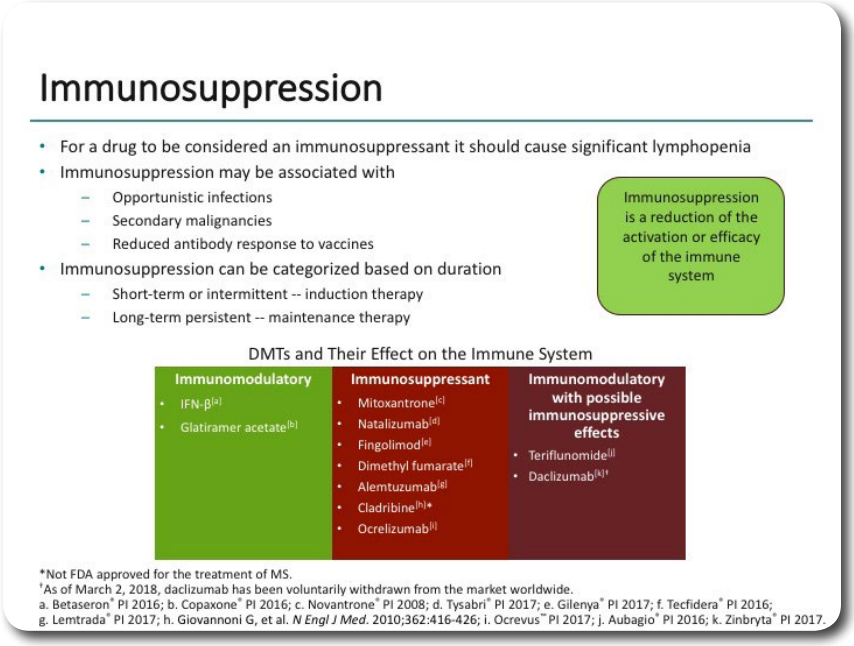
Daclizumab[23-26]

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.

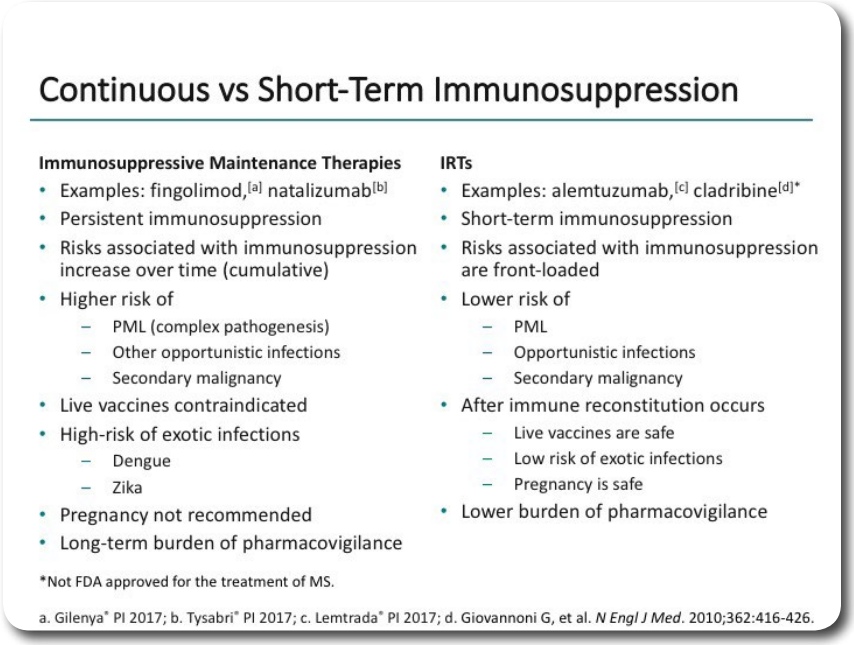
The big issue with this drug, though, is autoreactive-type reactions, particularly in skin. About 2% of people have to stop the drug because of hypersensitivity skin reactions. There is also about a 2% incidence of transaminitis. Some patients have developed frank autoimmune hepatitis, and there have 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[1,2,6,7,9-12,14,15,22,23]
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^3. 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.

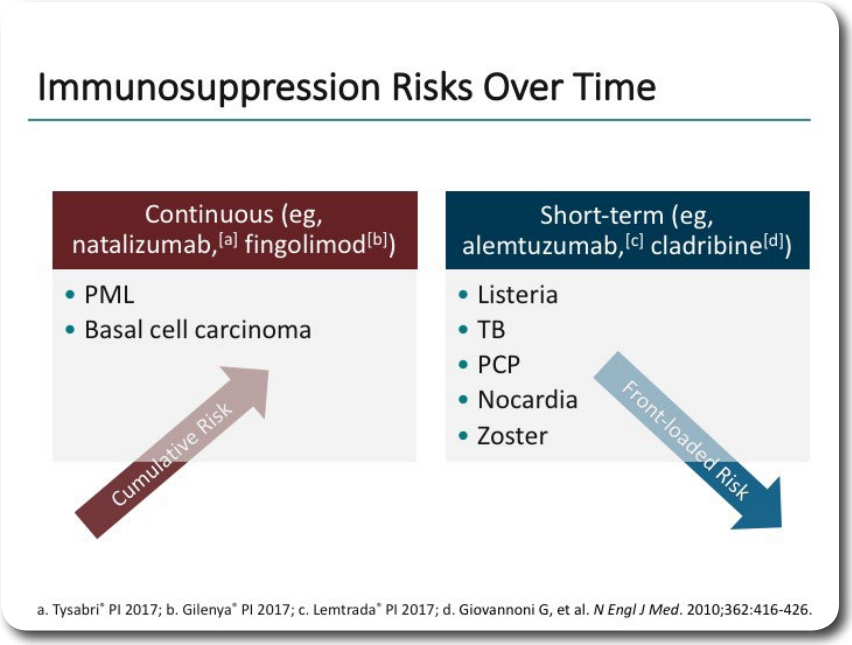
In this Table, I have highlighted DMTs that are immunosuppressive in red. The green refers to immunomodulatory therapies, the interferons and glatiramer acetate. I have put teriflunomide and daclizumab in orange because they are not labeled as being immunosuppressive, and the jury is out whether they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



Continuous vs Short-Term Immunosuppression[6,9,12,14]
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.

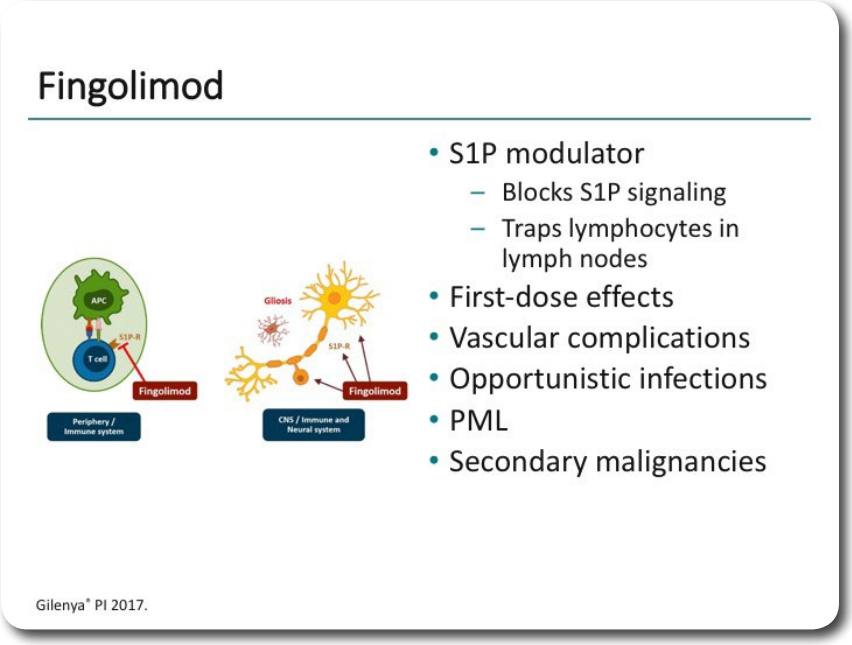
With short-term immunosuppressive, live vaccines are potentially safe. We have given live vaccines to several of our patients who have had alemtuzumab. We just have to wait for the immune system to reconstitute before giving the live vaccines. Actually, with HSCT, which we use in a small number of patients, 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.



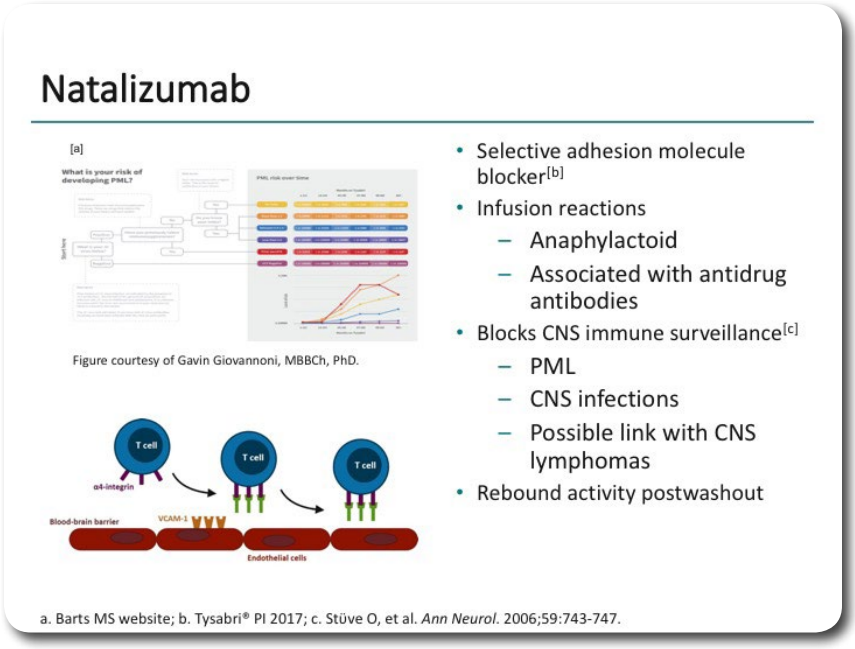
Immunosuppression Risks Over Time[6,9,12,14]
This Figure summarizes the trajectory of risk. With continuous therapies, risk accumulates with time; with short-term immunosuppression, the risks are front-loaded and drop with time.

DMTs in MS



Fingolimod[9]
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.

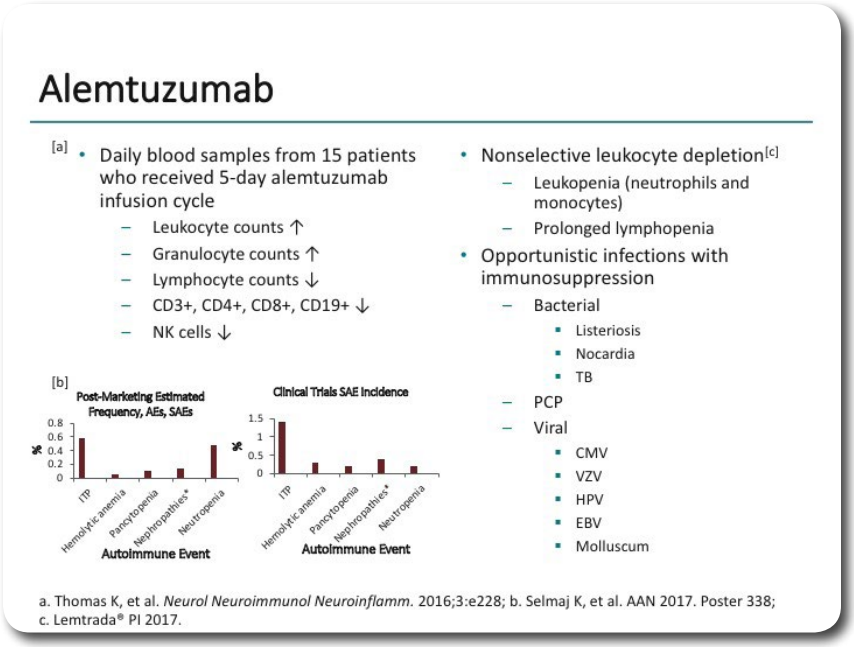


Natalizumab[6,27,28]

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.

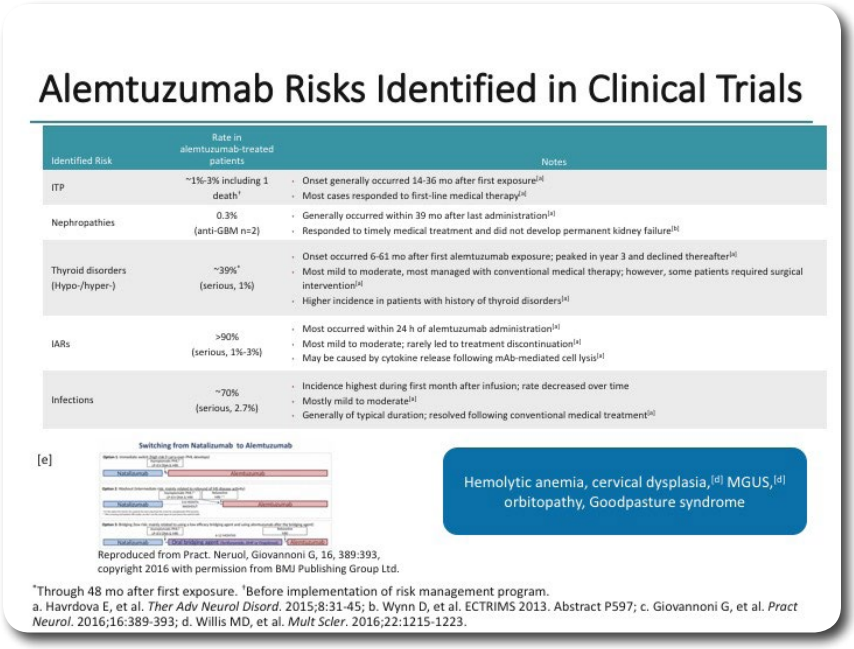
The other issue with natalizumab and fingolimod is rebound. It is not a good idea to leave people coming off natalizumab very long because of rebound.



Alemtuzumab[12,29,30]

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[31-34]

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 predose 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.[35] Immune thrombocytopenia occurs in 2% to 3% of patients.[36] We also see renal disease, Goodpasture syndrome and membranous nephropathy, and that is a risk of about 1 in 800.[37] 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.

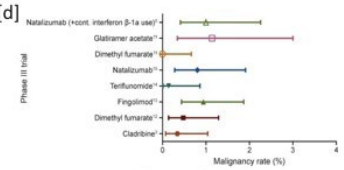
Cladribine

- Approved in Europe but not the United States[a]
- Purine nucleoside analogue[b]
  - 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[b]
  - Relapse rates
  - Risk of disability progression
  - MRI measures of disease activity at 96 weeks
- AEs[c]
  - 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

[d]



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

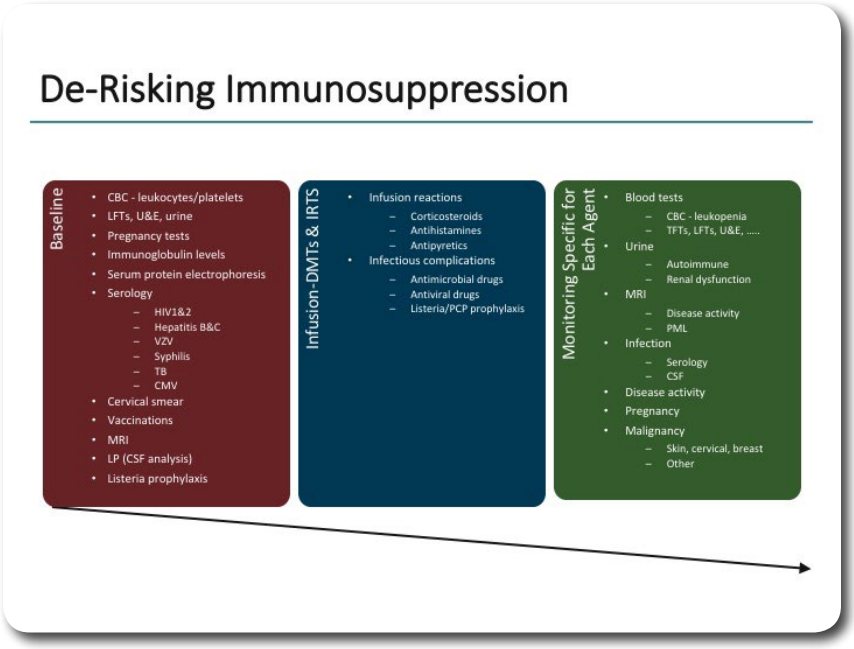
a. Mavenclad™ [SmPc] 2017; b. Leist TP, et al. *Clin Neuropharmacol*. 2011;34:28-35; c. Giovannoni G, et al. *N Engl J Med*. 2010;362:416-426; d. Pakpoor J, et al. *Neurol Neuroimmunol Neuroinflamm*. 2015;2:e158.

Cladribine[14,22,35,36]

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.

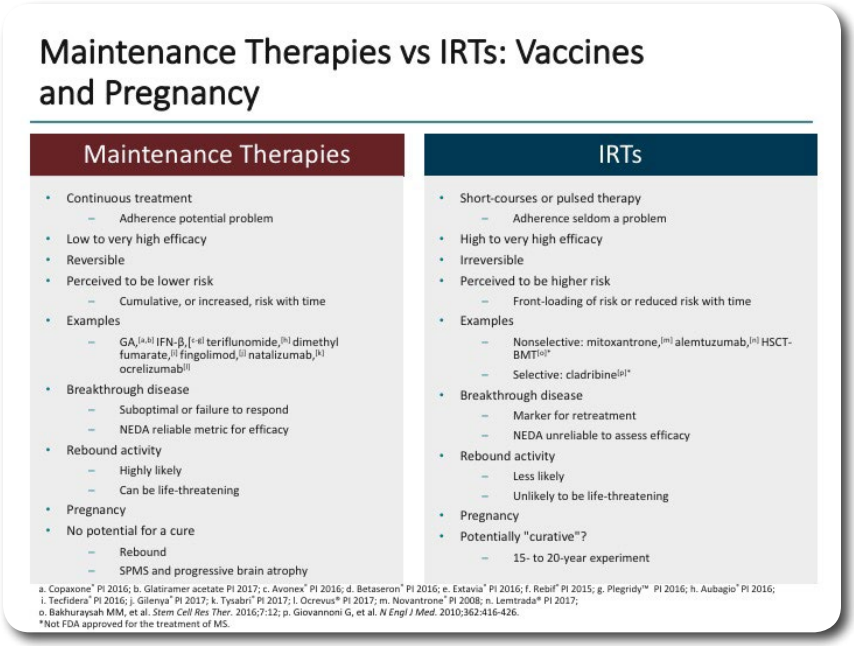


De-Risking Immunosuppression

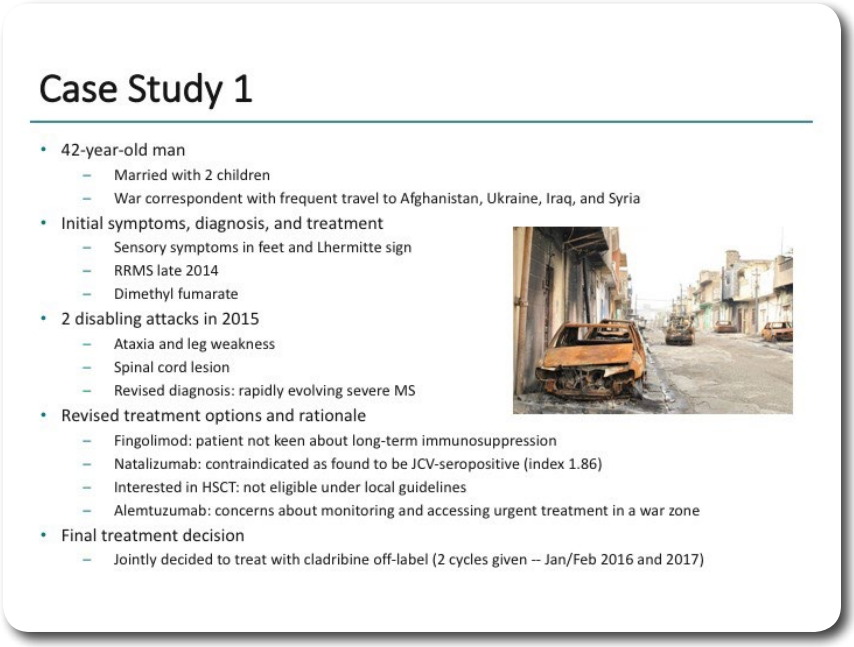
This slide summarizes the way we de-risk immunosuppression in clinical practice. At baseline, you have to do routine blood work. In our center, we assess baseline immunoglobulin levels, primarily for patients receiving the anti-CD20 DMTs. We also do a serum protein electrophoresis because, if the patient 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

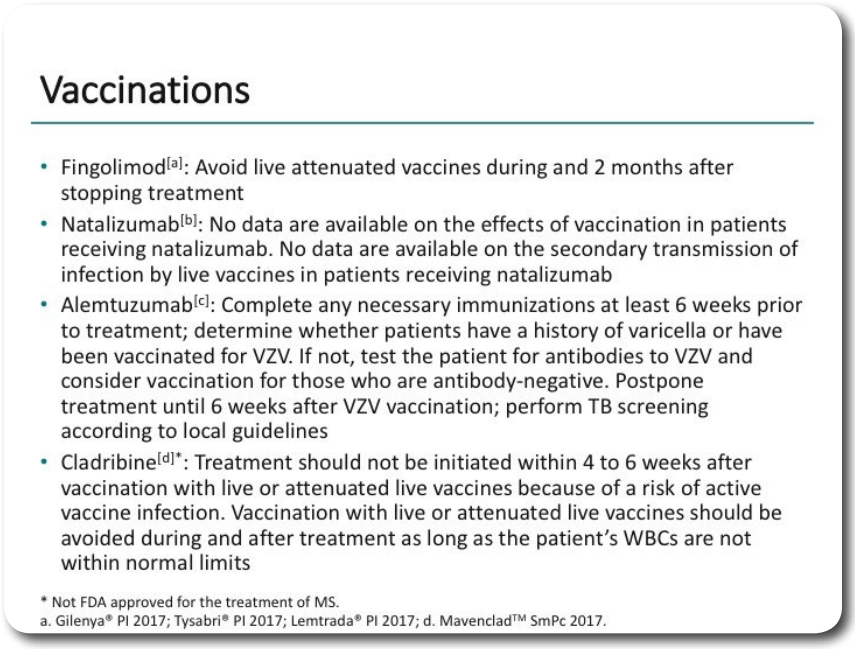


Maintenance Therapies vs IRTs: Vaccines and Pregnancy[1-16]
This slide, again, summarizes the 2 arms. I want to come back to this Table because the two things I am going to talk to you now are vaccinations and pregnancies, which I think are two important attributes that separate these arms.



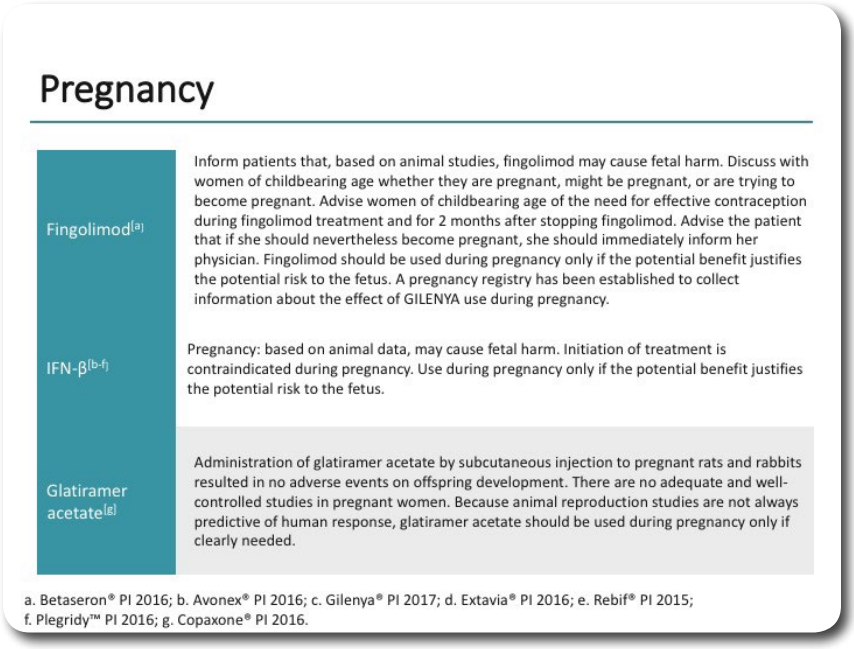
Case Study 1
This patient is a journalist on one of the television stations in the United Kingdom. He was aged 42 years and married with 2 children when he developed MS. He frequently travels to war zones, including Afghanistan, Ukraine, Iraq, and Syria. His initial symptoms were sensory symptoms in 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.



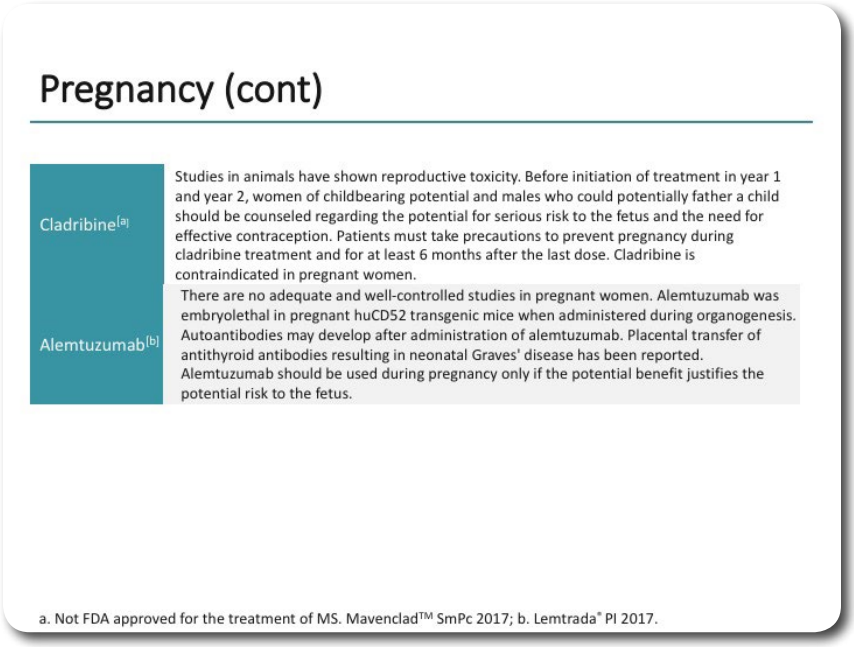
Vaccinations[6,9,12,22]

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[1-3,5,8,13]

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)[12,22]

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[a]	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[b]	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[c]	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[d]	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)[6,10,11,15]

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?

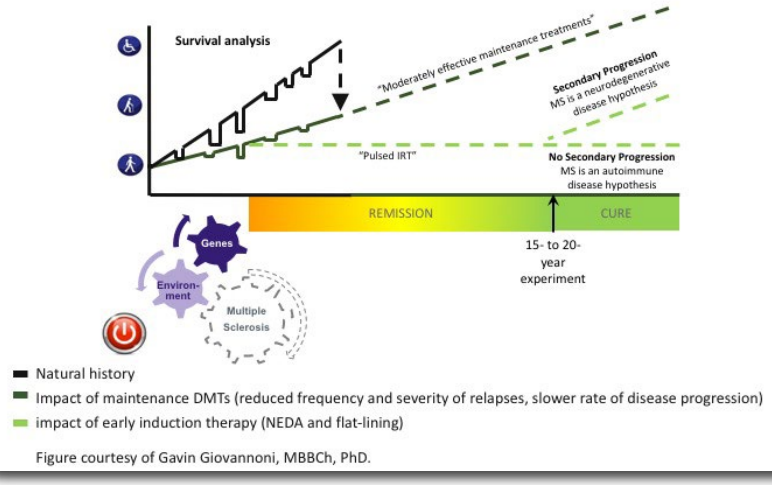
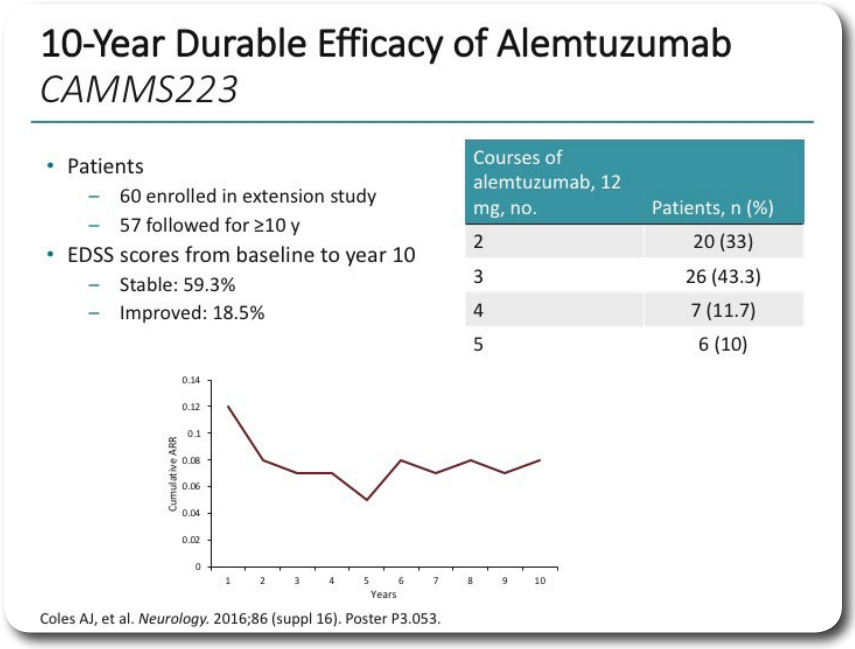


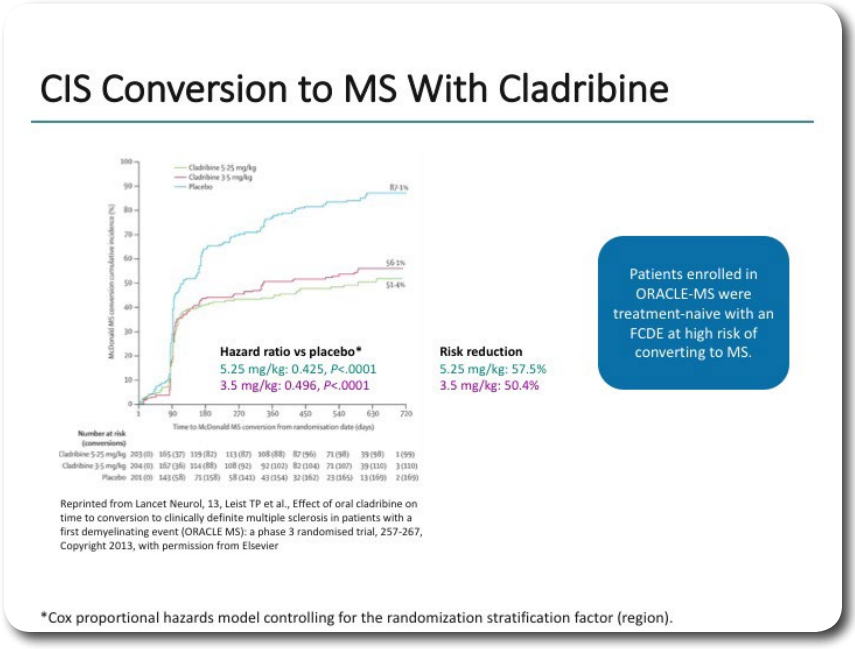
Figure courtesy of Gavin Giovannoni, MBBCh, PhD.

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[37]
This slide shows the 10-year follow-up of the phase 2 trial of alemtuzumab vs interferon β-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.

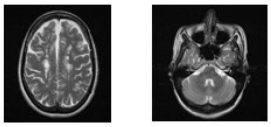


CIS Conversion to MS With Cladribine[38]
ORACLE is the study of oral cladribine in patients with clinically isolated syndrome (CIS). Most people with CIS convert to MS within the first 3 to 6 months. In this study, only half of the patients converted to McDonald-positive MS on cladribine, whereas more 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

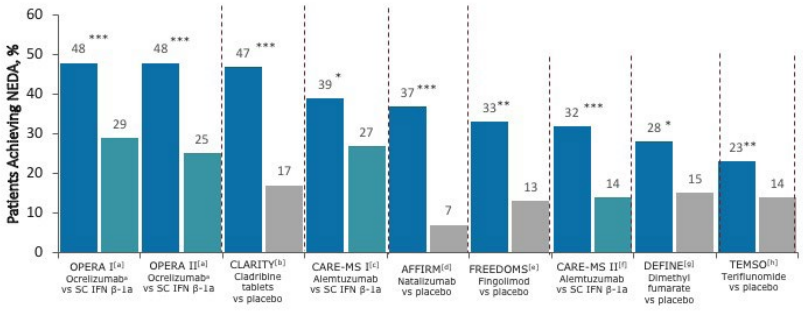


Figures courtesy of Gavin Giovannoni, MBBCh, PhD.

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).

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Figure courtesy of Gavin Giovannoni, MBBCh, PhD.

NEDA Rates in Phase 3 Trials[39-46]

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

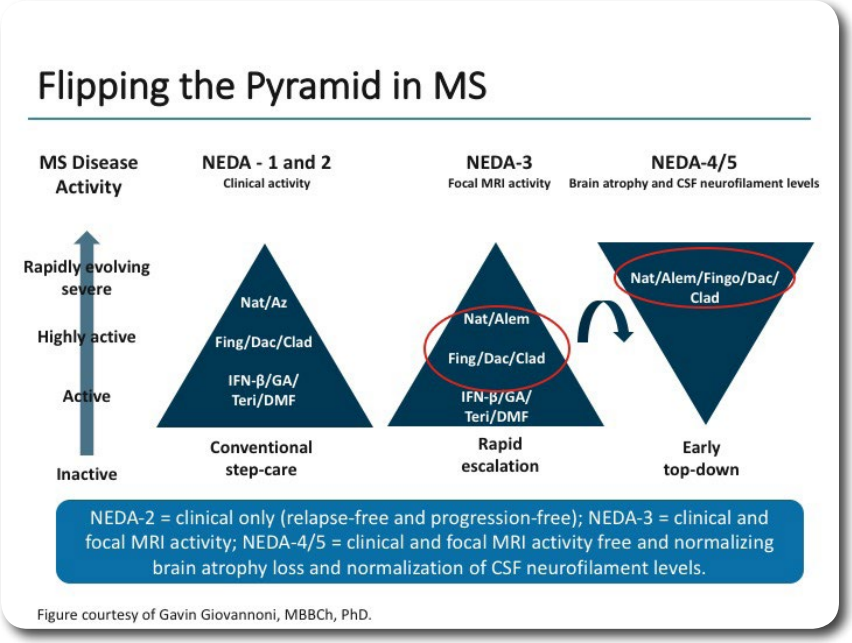
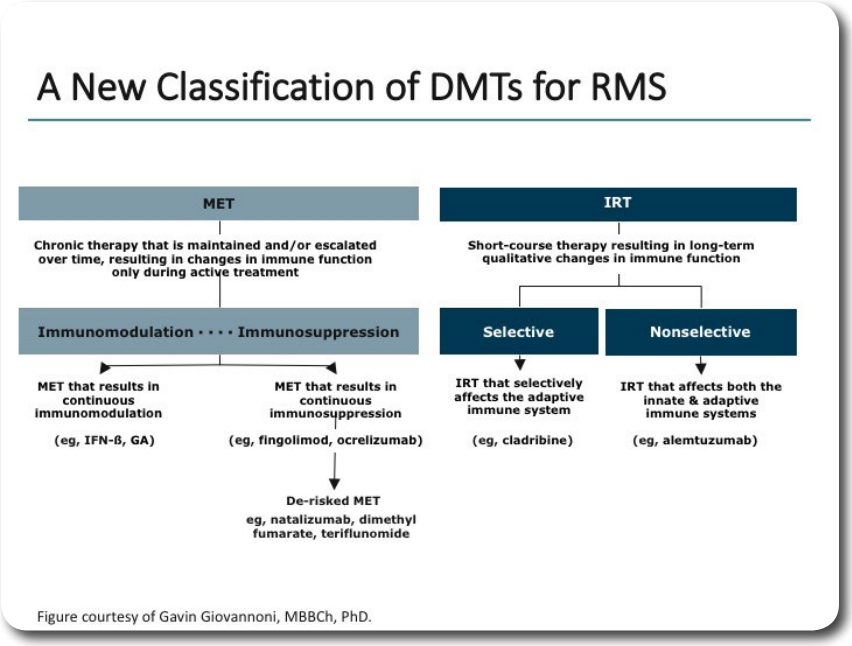


Figure courtesy of Gavin Giovannoni, MBBCh, PhD.

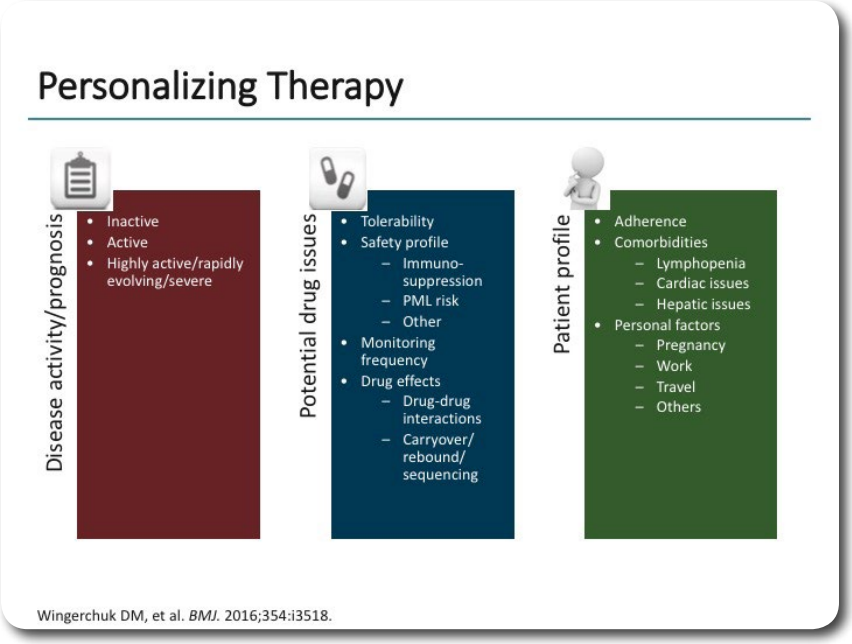
Flipping the Pyramid in MS

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

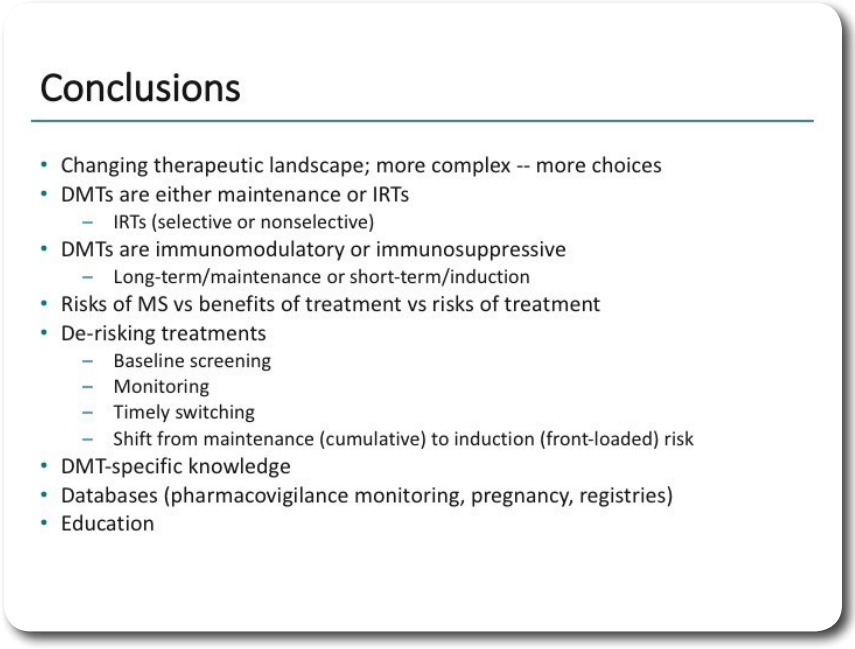
I would like to propose a new classification system to try to put this into some kind of pigeonholing to help you understand these treatments. On the left, we have the maintenance escalation treatments, which I like to divide into immunomodulatory, interferon and glatiramer acetate, vs immunosuppressive. 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[47]

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

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

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Clinical Advances in Multiple Sclerosis

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

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