ECTRIMS 2022

Congress Report | Therapy

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

26 – 28 October 2022
Amsterdam, The Netherlands

Day 1

Therapy Session 1
Hot Topic 1: High efficacy therapies

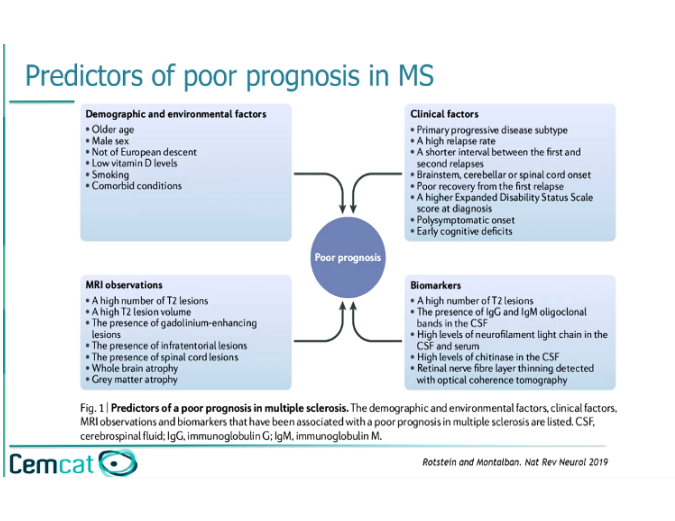
Wednesday, 26 October 10:00 – 11:00 CEST
Speakers: Xavier Montalban, Dalia Rotstein, Gavin Giovannoni
Chairs: Patricia Coyle, Eva Strijbis

Conclusion: High efficacy treatment (HET) may overcome some of the poor prognostic hurdles in people with relapsing remitting multiple sclerosis (RRMS). In theory, HET should be used in patients with poor prognostic factors as early as possible. As the majority of disability accumulation occurs independently of relapse and Magnetic Resonance Imaging (MRI) activity, from early on in the MS disease course, treatment should focus on pathological processes contributing to the slow loss of neurological function. To plan for timely treatment sequencing and escalation, vaccination status and immunologic effects of disease modifying treatments (DMTs) should be taken into account. Prolonged washout periods should be avoided to reduce the risk of new disease activity.

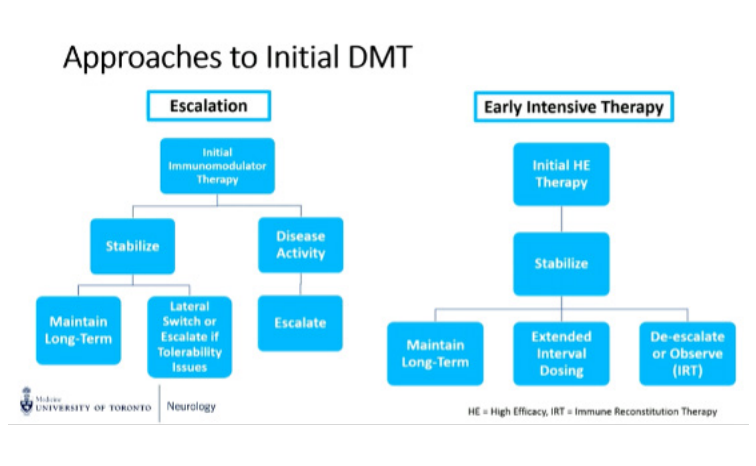
What's New: Poor prognostic factors prior to the treatment of MS include higher Expanded Disability Status Scale Score (EDSS) and inflammatory activity, older age and male gender, and may predict poor response to treatment. The treatment target in MS should go beyond focal inflammation, as recent evidence suggests that focal inflammation is a result of smouldering disease, not the cause; the majority of disability accumulation in MS occurs independently of relapse and MRI activity.

Background: There are many predictors of poor prognosis in MS, including low vitamin D levels, a high relapse rate, the presence of spinal cord lesions, male gender and higher EDSS. Compared to low efficacy treatments, evidence shows HETs are more effective, but could potentially have more severe adverse effects, as the disease activity and treatment response of MS varies between patients. Guidelines for MS recommend treatment with a HET as early on as possible. In terms of immune reconstitution therapy, it may be necessary to deescalate and observe which can impact long-term efficacy. This raises questions of how to optimise monitoring, and whether to treat stable patients with HET.

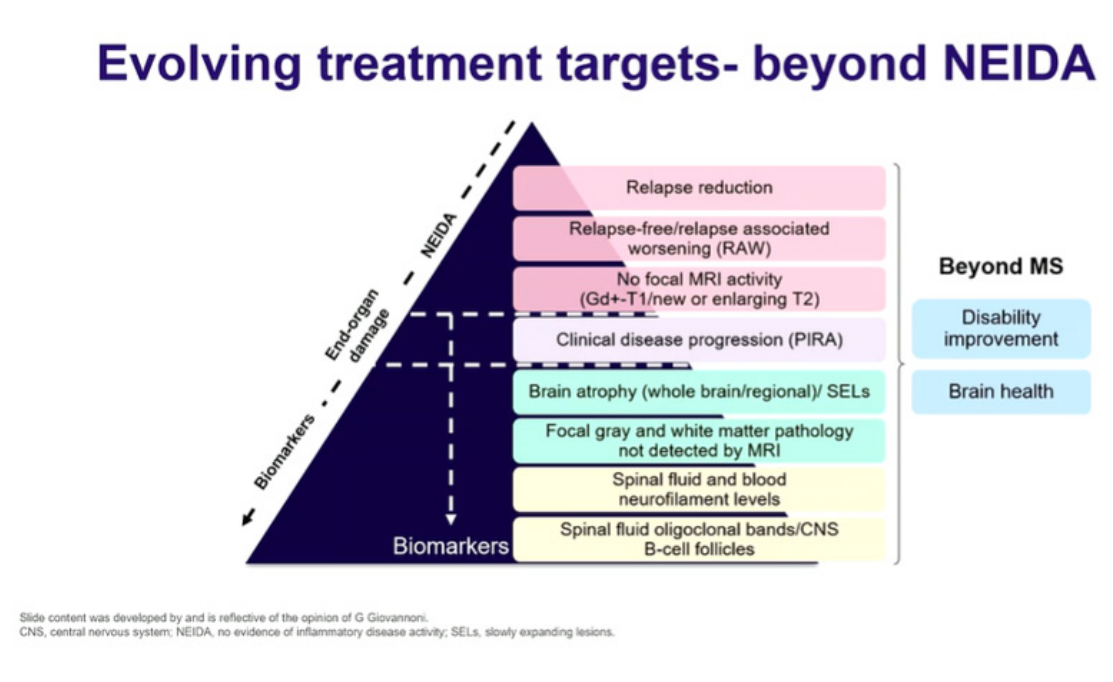
(Montalban presentation)



(Rotstein presentation)



(Giovannoni presentation)



Therapy Session 2
Scientific Session 1: Personalised treatment

Wednesday, 26 October 14:30 – 16:00 CEST
Speakers: Jaume Sastre-Garriga, Zoé van Kempen, Marcello Moccia, Tomas Kalincik, Jan Hillert, Sarah Planchon
Chairs: Finn Sellebjerg, Eva Havrdova

Conclusion: Treating patients with MS at the first onset of disease with high efficacy (HE) agents is generally recommended over the treatment escalation approach. However, treatment should be considered on a case-by-case basis per patient according to prognosis, efficacy and long-term safety. Precision medicine has a limited role in MS compared with personalised medicine.

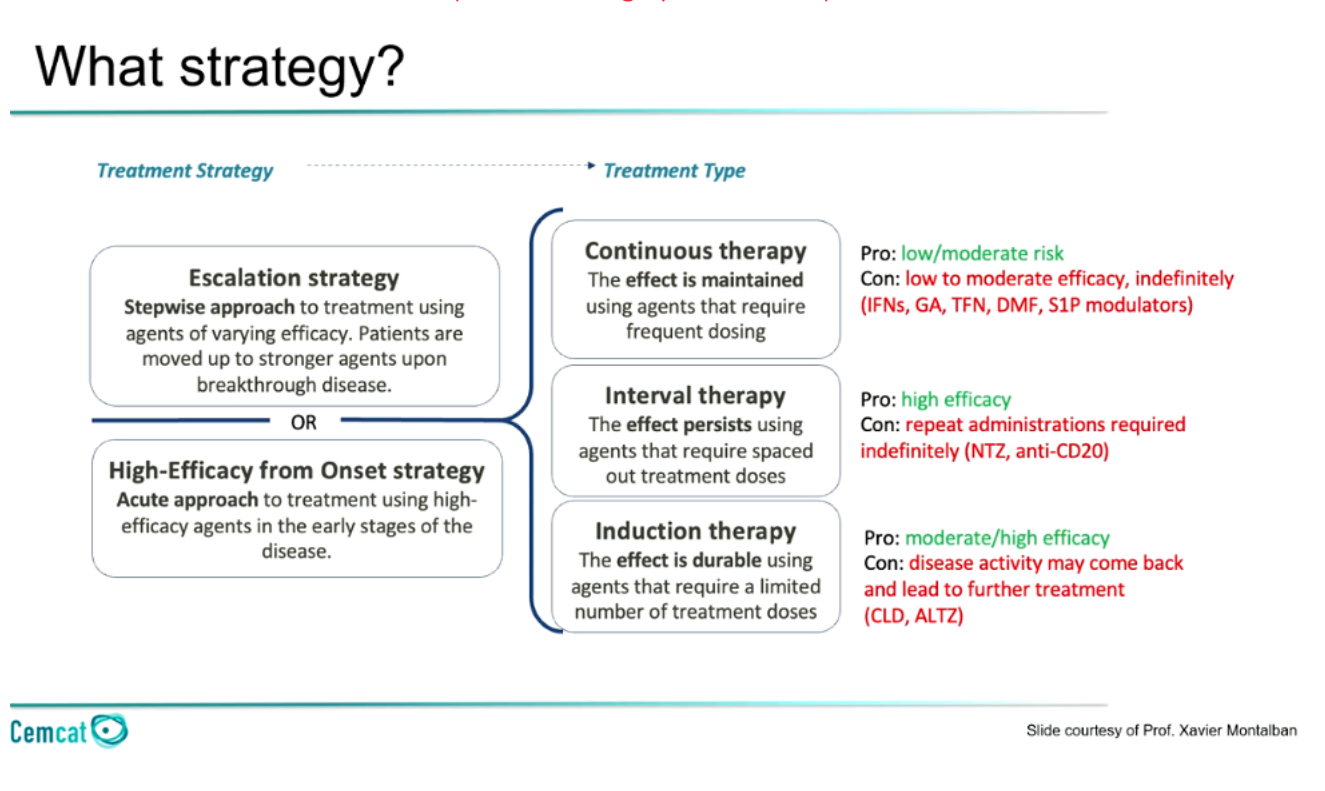
What's New: Research shows 4- and 6-week intervals for natalizumab dosing have similar efficacy, with a 6-week interval reducing the risk of progressive multifocal leukoencephalopathy (PML), hospital visits and cost. It was reported that disease-modifying therapies differ quantitatively in their ability to suppress focal inflammation, the hallmark of early MS. This suggests that MS is largely pathogenetically homogenous and indicates that precision medicine may have limited potential to treat MS.

Ocrelizumab proved superior to glatiramer acetate, dimethyl-fumarate, fingolimod and natalizumab in achieving no evidence of disease activity (NEDA-3) and reduced the worsening of the Expanded Disability Status Scale, in a real-world study using propensity score adjustment. A comparative effectiveness study was conducted for autologous hematopoietic stem cell transplantation (AHSCT) versus fingolimod, ocrelizumab and natalizumab. AHSCT was found to be superior to fingolimod and comparable with ocrelizumab and natalizumab in preventing relapses among patients with highly active MS with moderate disability. Patients treated with AHSCT had a higher rate of recovery from disability than those treated with natalizumab.

The ethnic/racial distribution enrolled in a pragmatic trial was found to be similar to the general population, suggesting that pragmatic trials may be able to overcome the typically low representation of minority groups in clinical trials.

Background: It is important to know how to treat patients with MS, what to treat patients with, and what strategy to take. Treating patients as early on as possible is recommended. There are two main treatment strategies; the escalation strategy and the HE from onset approach – both come with advantages and disadvantages. Different approaches to personalised medicine need to be understood; however, it is also important to consider the associated pros and cons, to both the healthcare system and the patients themselves.

(Sastre-Garriga presentation)



Day 2

Therapy Session 1
Hot Topic 5: Escalating and de-escalating DMTs

Thursday, 27 October 10:00 – 11:00 CEST
Speakers: Gilles Edan, Emmanuelle Waubant, Eva Strijbis
Chairs: Maria Troiano, Joep Killestein

Conclusion: Induction therapies can offer patients good disease control over a long period of time with fewer adverse effects; however, rigorous monitoring with magnetic resonance imaging (MRI) to assess the level of disease activity is imperative. Options for patients who have been stable long-term include continuing current therapy, switching to an alternate disease-modifying therapy (DMT), de-escalating to a less potent DMT, extending the dosing interval for natalizumab and anti-CD20 agents or discontinuing treatment entirely. Older patients are better candidates for discontinuation.

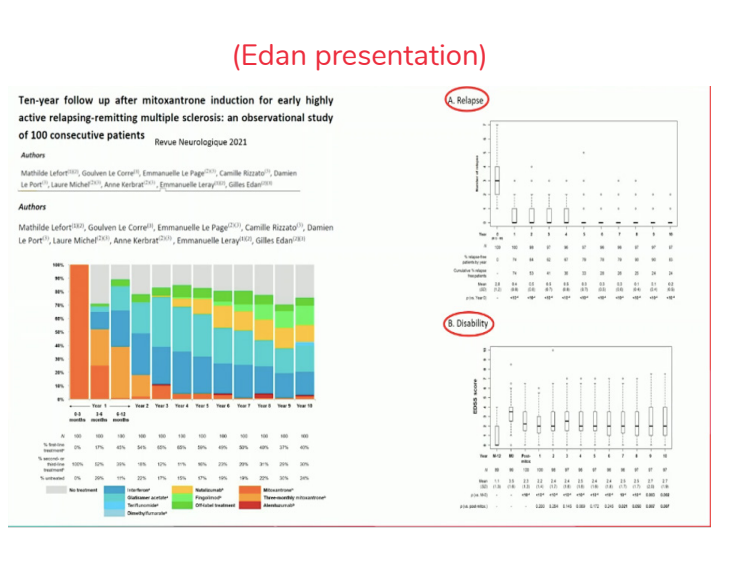
What's New: Strategies for early intensive therapy in MS include continuous intensive therapies (natalizumab, fingolimod, ocrelizumab) or induction therapies (mitoxantrone, alemtuzumab, cladribine) (Topic 1). A 10-year follow-up of 100 consecutive patients with early, active relapsing–remitting MS (RRMS) who had received mitoxantrone (3- or 6-monthly) showed that most patients did not require additional therapy or were managed with a first-line DMT; mean annual relapse rate (ARR) was low and the mean Expanded Disability Status Scale (EDSS) score remained significantly improved. In patients with aggressive RRMS, alemtuzumab showed a persistently low ARR up to 8 years and stable mean EDSS. Relapse rates were also low after induction with oral cladribine (weight-based dosing annually for 2 years), with a low risk of severe lymphopenia or clinical regression.

A proposed definition of long-term stable MS is >5 years with no relapse, no new MRI lesions and no EDSS change (Topic 2). The need to consider de-escalating therapy was highlighted during the COVID-19 pandemic when some MS treatments were associated with blunted response to COVID-19 vaccination and a higher risk of severe COVID-19 infection. The NOVA study in RRMS revealed that most patients stable on a 4-weekly dosing schedule of natalizumab could be changed to a 6-weekly schedule without impacting efficacy. Similarly, a large retrospective study demonstrated that delaying an anti-CD20 (ocrelizumab) by 4 weeks was as effective as standard dosing every 6 months. Delayed dosing and lower doses of rituximab based on memory B-cell counts are also being studied and the results appear promising.

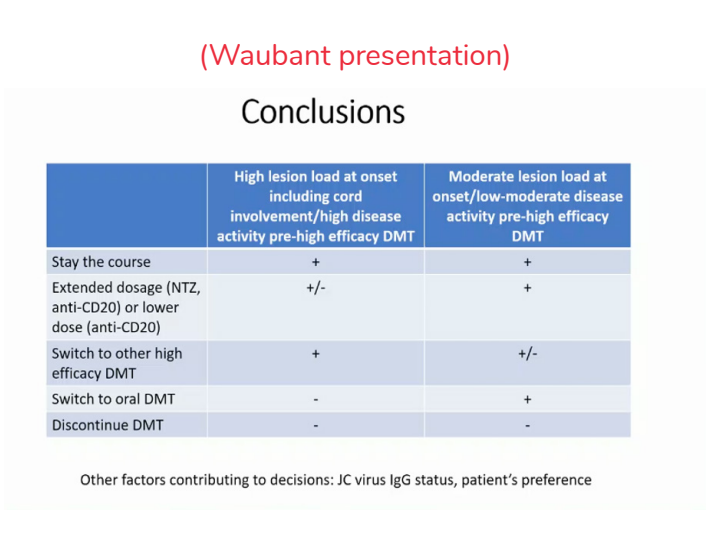
MS evolves with age as the immune system changes, leading to decreased peripheral inflammation but more compartmentalised inflammation, fewer relapses and T2 lesions, decreased impact of DMTs (lower relative efficacy), and increased risk of adverse effects from therapy (Topic 3). In observational studies, those most likely to relapse after treatment discontinuation were younger patients, those with recent active disease, and those who had been receiving natalizumab or fingolimod. Three randomised controlled studies investigating discontinuation of treatment in MS are ongoing.

Background: The range of options now available for treating MS raises important issues around choice of therapy in specific situations, management of recurrent disease activity after immune-depleting therapies and potential drug de-escalation or even discontinuation in long-term stable MS. Ongoing studies aim to provide answers to these key treatment questions.

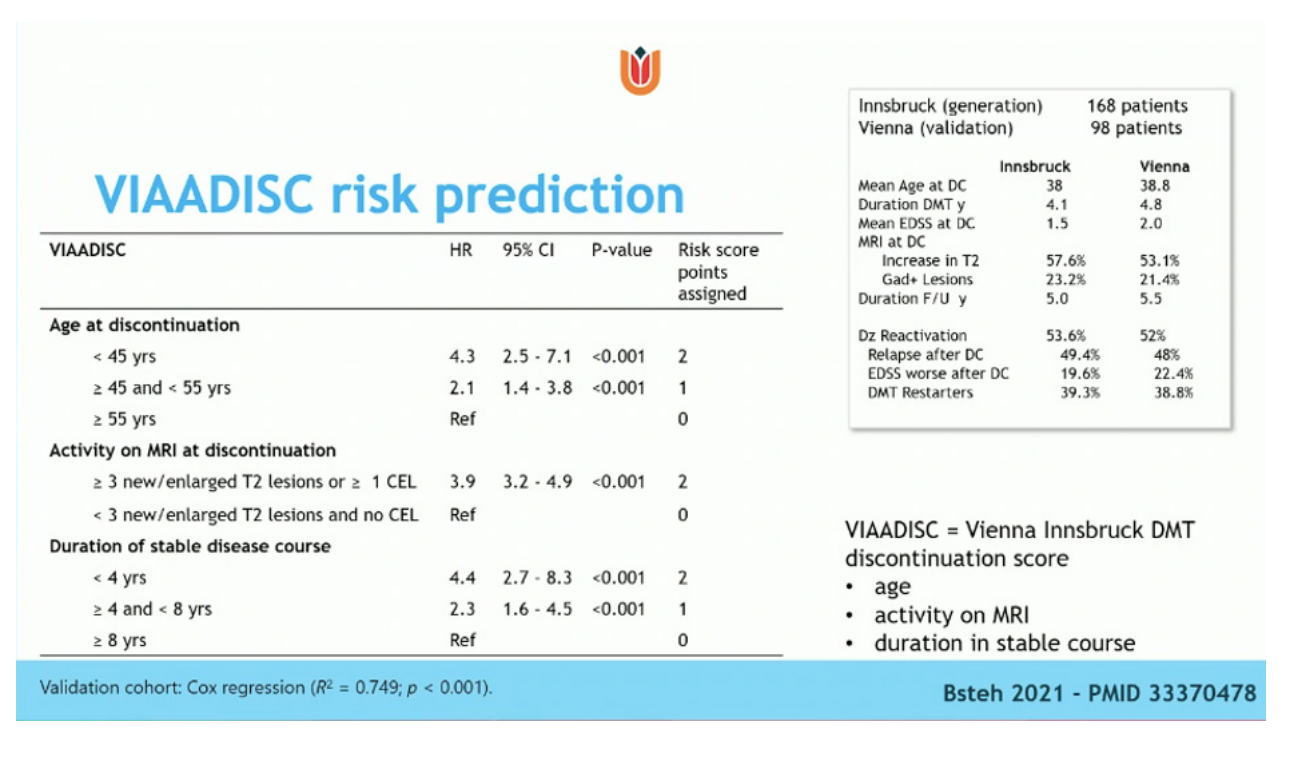
(Edan presentation)



(Waubant presentation)



(Strijbis presentation)



Therapy Session 2
Free Communications 5: Treatment

Thursday, 27 October 15:00 – 16:00 CEST
Speakers: Pietro Maggi, Agustín Pappolla, Robert J Fox, Irene Schiavetti, Fredrik Piehl
Chairs: Gabriel Bsteh, Fred Lublin

Conclusion: The Río score does predict the likelihood of relapses, disease progression, evidence of disease activity (EDA), and treatment failure in patients initiating daily oral disease-modifying therapies (DMTs). Vidofludimus 30 mg daily orally appears to be the lowest effective dose for relapsing-remitting multiple sclerosis (RRMS). After completing cladribine treatment, the rate of new treatment initiation was 3% at 12 months and 11% at 24 months. Further studies of temelimab are needed to determine its role.

What's New: A multi-centre longitudinal annual magnetic resonance imaging (MRI) study in 68 patients (42 on anti-CD 20, 26 untreated) showed that, of 346 white matter lesions, 185 were paramagnetic rim lesions (PRL) (133 treated group, 52 untreated group) (Topic 1). None of the patients in the treatment group showed resolution of PRL. Re-analysing single-cell lymphocyte sequencing from MS brain tissue revealed that few CD 20 cells were present at the chronic active lesion edge (7% of all immune cells).

In an analysis of prospectively collected data from patients with RRMS initiating a daily oral DMT (teriflunomide, fingolimod, dimethyl fumarate), the Río score was assessed based on clinical activity alone (n=187) and combined with radiographic assessment, EDA and treatment failure in a smaller subset (n=167) (Topic 2). The Río score performed well. Clinical-radiological measures integrated into the RS during the first year of treatment have an acceptable prognostic value for identifying clinical activity. Notably, if the patient experienced more than one relapse, EDSS progression or >3 new T2 lesions occurred within the first year, treatment failure rose to almost 62%.

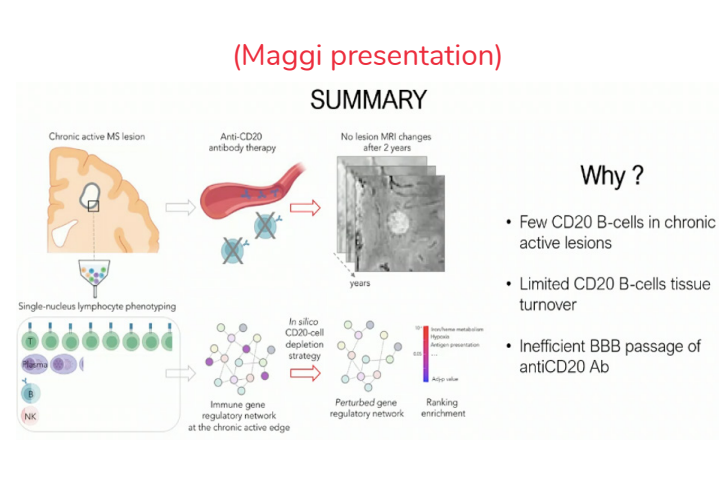
In the multi-centre, phase II, double-blind, placebo-controlled EMPhASIS study, 268 RRMS patients received 10, 30 or 45 mg of vidofludimus calcium or placebo (Topic 3). A pooled analysis revealed that the 10 mg dosage had a minimal effect on disease activity on MRI whereas the 30 and 45 mg dosages demonstrated anti-inflammatory effects, with 65%–78% reduction in combined unique active (CUA) and Gd+ lesions; median neurofilament light chain levels were reduced by 18% and 26% in the higher dose groups, respectively.

CladStop is a retrospective, observational multi-centre study assessing add-on therapy (Topic 4). A total of 139 patients who had received standard cladribine therapy (two cycles 1 month apart, repeated 1 year later), and were followed-up for a least 6 months, were included. In total, 25 patients started a new treatment within the 12-month follow-up; the majority did not start a new treatment.

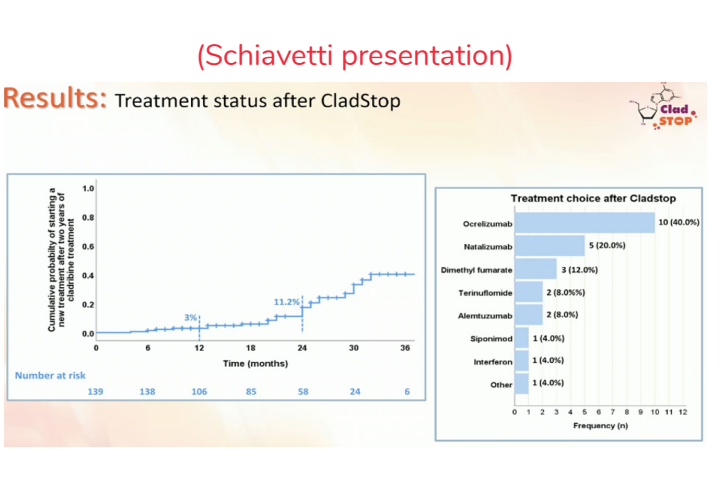
ProTECt-MS was a randomised, placebo-controlled study of three different doses of temelimab for preventing neurodegeneration in rituximab-treated patients (n=40) with relapsing MS. Temelimab improved cortical MT saturation and lowered levels of biomarkers linked to neuronal loss and astrocytic proliferation compared with rituximab alone. Temelimab-treated patients had a lower rate of brain atrophy (not statistically significant), and temelimab was well tolerated.

Background: B-cell depleting therapies are effective in relapsing-remitting MS and in young MS patients with active lesions on MRI; however, their effect on PRL is unknown. With the increasing number of oral DMTs, predictors of early treatment response are needed. Vidofludimus calcium is a second-generation, oral DHODH inhibitor that lacks off-target effects on kinases. Real-world data on the addition of therapies after completion of cladribine are limited. Temelimab is a humanized IgG4 monoclonal antibody targeting the human endogenous retrovirus-W envelope protein.

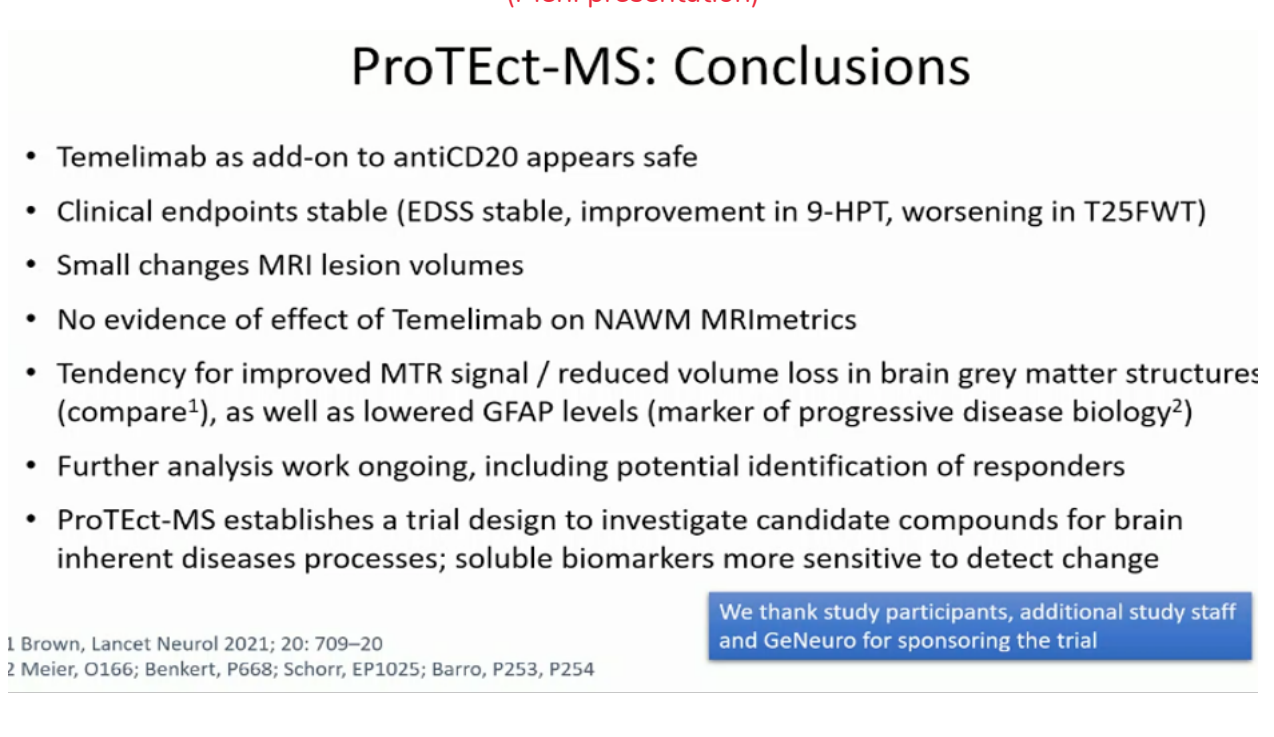
(Maggi presentation)



(Schiavetti presentation)



(Piehl presentation)



Therapy Session 3
Meet the Expert 2: Choosing therapy – similar compounds, same effect?

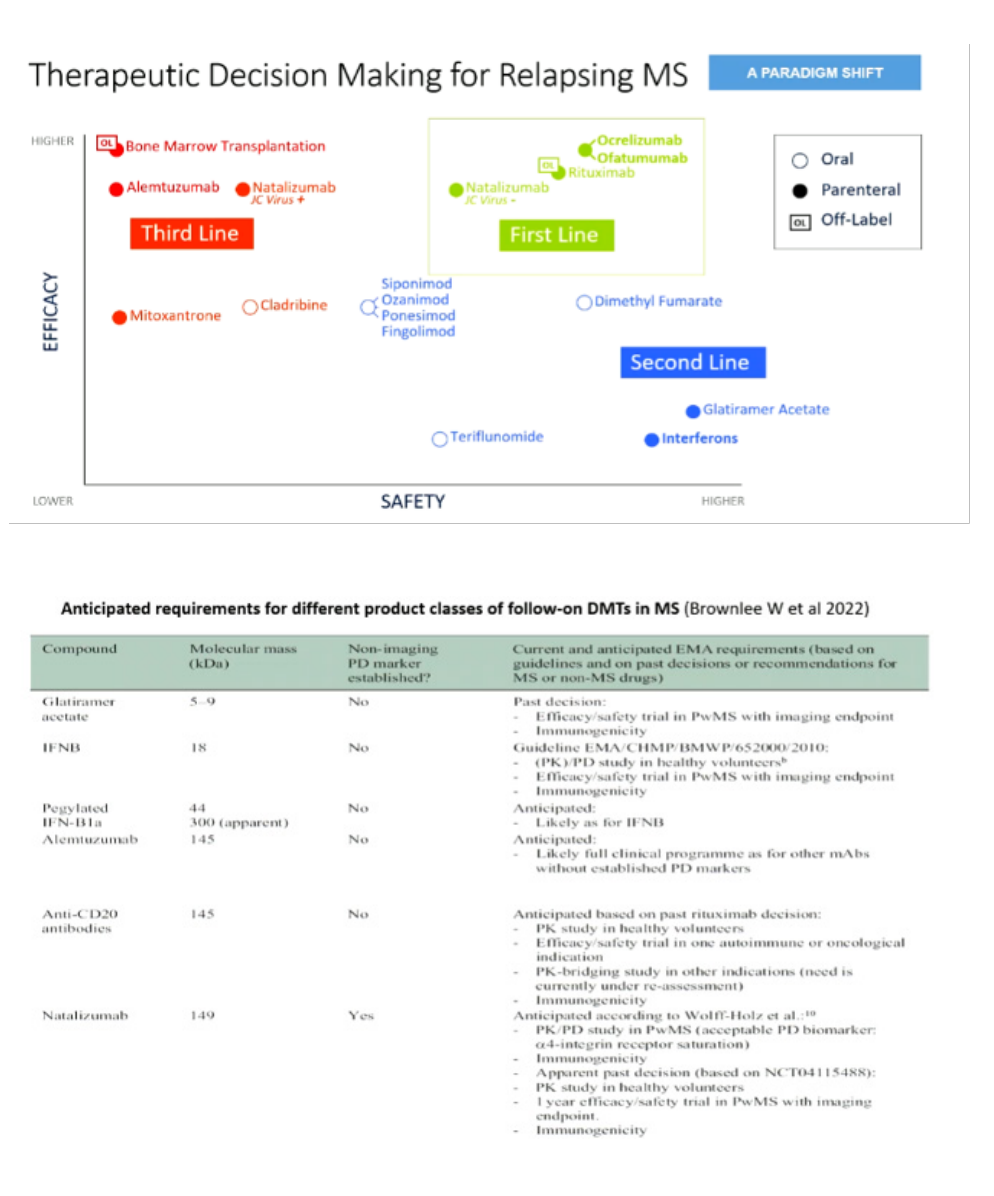
Thursday, 27 October 11:30 – 12:30 CEST
Chairs: Ludwig Kappos, Stephen Hauser

Discussion: Therapeutic decision making for relapsing MS involves weighing up safety versus efficacy, with the most desirable agent being one that is highly efficacious and very safe. The real game changer in MS was the development of B cell therapies, with better safety profiles and an extremely favourable efficacy profile for relapsing MS. These agents changed the therapeutic paradigm and should now be considered first-line therapy for newly diagnosed patients. One agent that may need to be moved in terms of its place in the efficacy versus safety equation is cladribine, which may now be considered safer than it once was, due to very impressive long-term study results.

There is a lot of discussion around follow-on products in MS, and it is important to note that such agents are not required to be identical, but rather comparable or highly similar; development of such a product is a compromise, aimed at delivering a product that is similar, safe and effective, but at a lower cost. It is necessary to trust the regulators, and education is necessary to address any remaining concerns. There can be two types of similar compounds; the follow-on attempt to replicate, and then molecules that are similar, with similar targets, but that are different – such as B-cell depleting agents.

In terms of B-cell depleting agents, there is rituximab (a chimeric that is 70% human, 30% mouse), ocrelizumab (humanized, 90% human, 10% mouse) and ofatumumab (100% human). Of note, rituximab was not developed with the expectation of being used for 20 years, and dose-finding studies were never performed for MS. These B-cell therapeutics act via different mechanisms, bind to different epitopes on CD20 and their route of delivery is different. Differences in delivery route and administration frequency may be the main factors influencing choice of agent; as more data emerge, this may change.

For the sphingosine I-phosphate receptor modulators (S1Ps), there is little to differentiate them in terms of efficacy, despite differences in the number of lymphocytes; many of the differences can be attributed to study design and patient inclusion criteria. Tolerability is somewhat better with new compounds, and the risk of bradyarrhythmia can be reduced with staged dosing, but this was already relatively low risk, so again, there is very little in terms of tolerability to differentiate agents, and little to suggest that any of these agents should be preferred over another.



Day 3

Therapy Session 1
Scientific Session 15: Global views – health care access around the globe

Date/Time: Friday, 28 October 10:00 – 11:30 CEST
Speakers: Maria Pia Amato, Lorna Galleguillos, Milena Sales Pitombeira, Reem Bunyan, Shanthi Viswanathan, Emmanuelle Waubant
Chairs: Mohammad Ali Sahraian, Alexey Boyko

Conclusion: To achieve universal access to high-quality MS care, systems must continue to evolve to overcome barriers, pivot with current and future pandemics, and expand digital/tele-healthcare.

What's New: Consensus standards for MS care have been published outlining core, achievable and aspirational levels for MS care teams in terms of referral and diagnosis, routine monitoring and support, and treatment decisions (Topic 1). Early treatment with a high efficacy disease-modifying therapy (DMT) based on degree of disease activity (clinically or on imaging) and patient characteristics – with rapid escalation as indicated – is an emerging paradigm. Early intervention can preserve brain function.

Barriers to high-quality MS care can be classified as those pertaining to clinicians, patients and the specific healthcare system (Topic 2). Early results from a survey of 78 neurologists in Latin America revealed that the majority felt that access to highly effective treatment was high and perhaps did not reflect the patient experience.

Patient surveys conducted in different countries showed that the COVID-19 pandemic notably disrupted healthcare access for people with MS; patients in Latin America were affected more than those in Europe or North America (Topic 3). Neurologists reported COVID-19-related restrictions. Global data-sharing helped develop consensus regarding COVID-19 vaccination in people with MS and approaches to management of those who contracted COVID-19 infection.

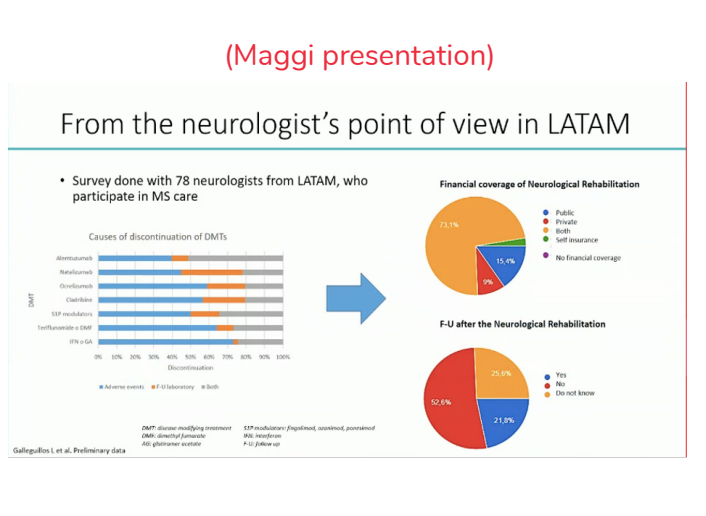
The global demand for healthcare resources is outstripping capacity (Topic 4). Although frequently implicated, the aging population is not actually the main driver of this increased demand. Digital health can help address this challenge and is defined by the World Health Organisation (WHO) as – the field of knowledge and practice associated with development and use of digital technologies to improve health. The Middle East and North Africa region is committed to adopting innovative solutions including telehealth, e-prescriptions, e-delivery, plus information collection, analysis and sharing.

In the South-East Asian regions, the use of off-label DMTs (e.g. rituximab) provide a viable MS treatment option (Topic 5). An application to add MS treatments to the WHO Essential Medicines List will be resubmitted soon.

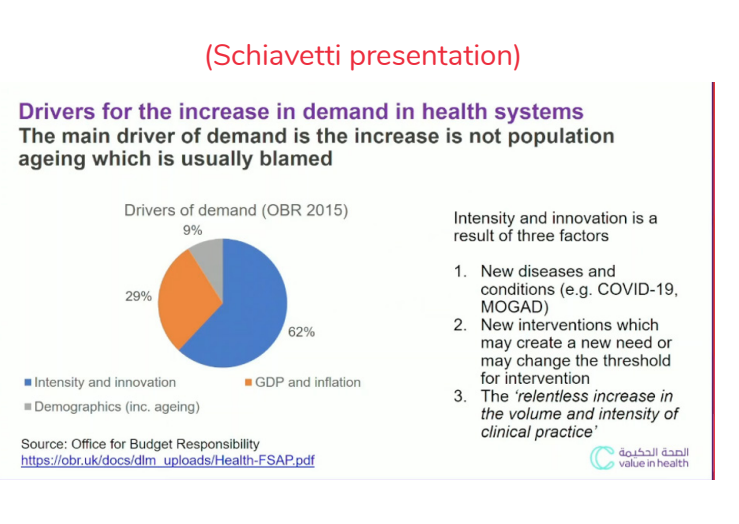
Above all, goals to improve MS care must be context-specific and realistic (Topic 6).

Background: The MS International Federation has specified that people with MS have access to and receive high quality MS care regardless of disparities such as level of disability, geographic location, socioeconomic status, gender, sexual orientation, etc. In young adults, MS is the second most common neurologic disorder leading to disability and the prevalence is increasing worldwide. MS is an expensive disease that requires specialised care.

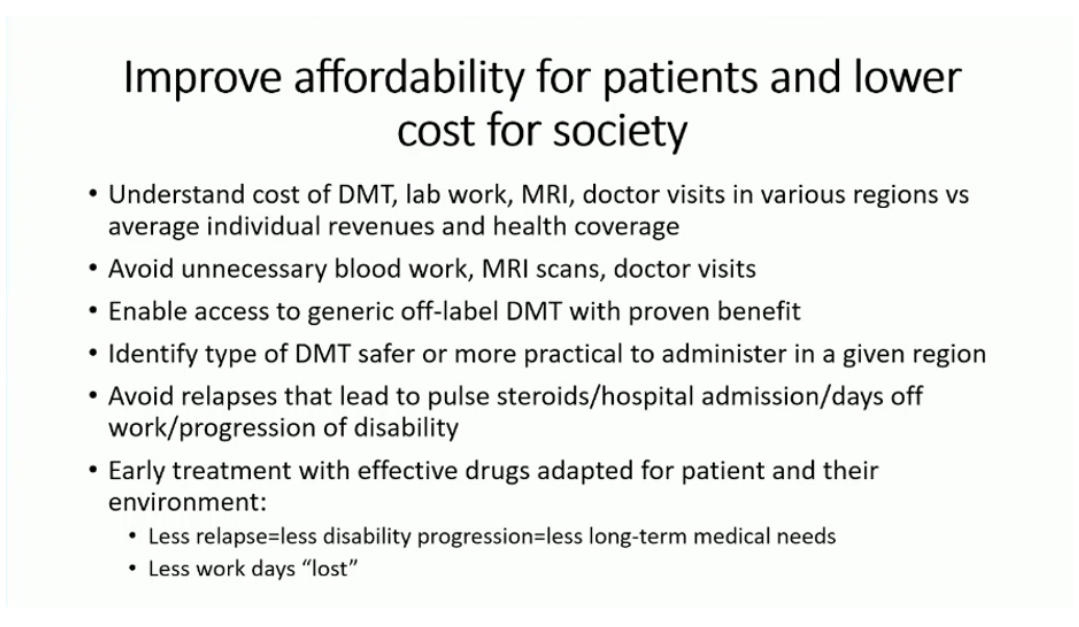
(Maggi presentation)



(Schiavetti presentation)



(Piehl presentation)



Therapy Session 2
ECTRIMS-EAN Session: 9th ECTRIMS focused workshop – autologous haematopoietic stem cell transplantation for the treatment of MS and related diseases

Friday, 28 October 12:00 – 13:30 CEST
Speakers: Giovanni Mancardi, Basil Sharrack, Riccardo Saccardi, Ellen Iacobaeus, Varun MehraViswanathan, Emmanuelle Waubant
Chairs: Bruno Stankoff, Paola Muraro

Conclusion: Autologous haematopoietic stem cell transplant (AHSCT) should be offered to all patients with highly active relapsing-remitting MS (RRMS) failing disease-modifying therapies (DMTs) and should be a clinical option in treatment-naïve patients with aggressive MS. It can also be considered in patients with progressive MS displaying clinical and radiological disease activity. Ideally, AHSCT should be carried out in MS patients as part of an ongoing randomised controlled trial or registry-based study. Appropriate patient selection and monitoring/management of complications, such as autoimmunity and viral reactivation, is key to the success of this procedure.

What's New: Based on studies carried out over the last 15 years in Europe, AHSCT in RRMS has the capacity to suppress MRI activity and relapses and to halt the progression of disability in almost 70%–80% of cases. However, important issues, such as mortality risk and long-term efficacy, remain to be addressed, and phase III studies comparing AHSCT with the more efficacious approved therapies are still ongoing. Based on preliminary evidence, the use of AHSCT for active secondary progressive MS appears to be associated with better disability outcomes than other immunotherapies.

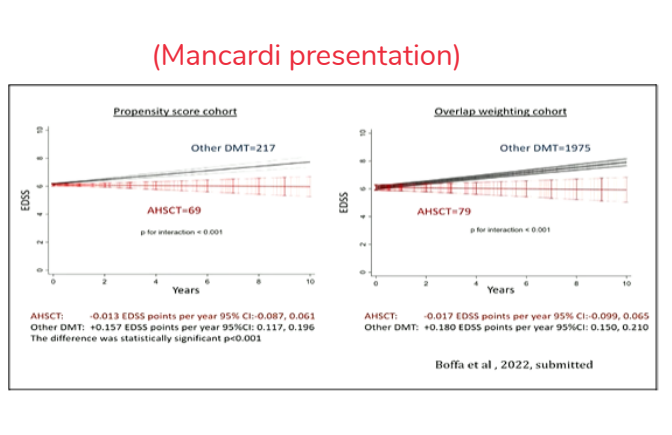
The optimal intensity of the AHSCT transplant procedure, including mobilisation and conditioning regimens as well as graft manipulation, is still to be defined. Intensity/efficacy correlation is controversial due to the wide variability of patients, clinical settings and lack of comparative trials. Three major regimens are currently in use in MS ranging from very high to intermediate/low – the latter having become the most diffused. A tailored approach may improve the overall risk:benefit ratio.

MS reactivation and breakthrough disease after AHSCT is uncommon. According to a summary of eight previous studies, the proportion of patients who remained relapse- and MRI-free after transplant ranged from 68%–100% after 3–8 years of follow-up. Lower intensity conditioning regimens appear to be associated with a higher risk of MS reactivation. However, more data are needed to assess this possible correlation and biomarkers of tolerance induction after AHSCT are also warranted. MS disease activity after AHSCT is often milder and appears easier to control with DMT (re)introduction.

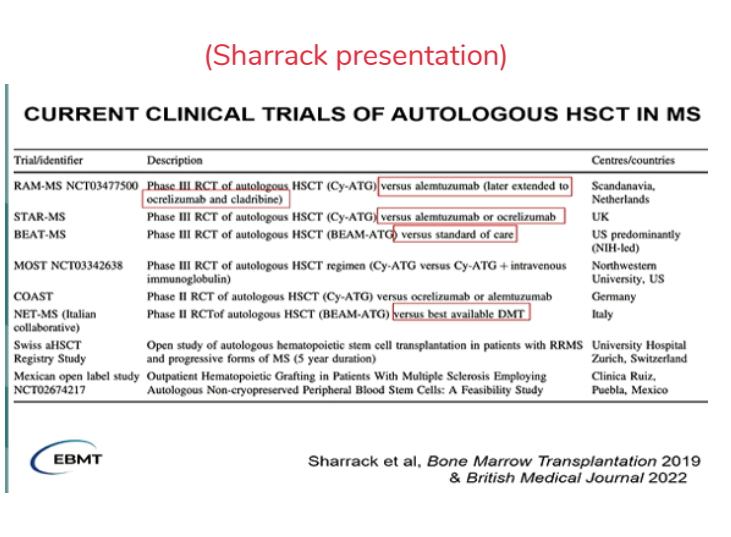
Secondary autoimmune disorders remain a concern post-AHSCT, although the risk appears lower with Cy/ATG protocols, and require long-term monitoring. Available data also confirm the need for careful monitoring of viral reactivations – which are linked to a high risk of treatment failure due to neurological toxicity – and early management with pre-emptive therapy. Weekly monitoring of Epstein–Barr virus (EBV)/cytomegalovirus DNA is recommended for the first 2 months and then fortnightly until day 100. Serum protein electrophoresis should be carried out every 4 weeks until EBV DNA is undetectable. Persistent EBV viremia >50,000 DNA IU/mL should act as a trigger for consideration of pre-emptive anti-CD20 therapy to reduce morbidity.

Background: The use of AHSCT for MS is rapidly expanding across Europe and is now a widely accepted treatment option for patients diagnosed with high-risk MS. AHSCT has been confirmed to be a very effective treatment modality in RRMS patients unresponsive to approved therapy and in those with aggressive MS. Experience so far indicates that the most favourable outcomes from AHSCT can be achieved in relapsed/refractory forms of the disease and in younger patients.

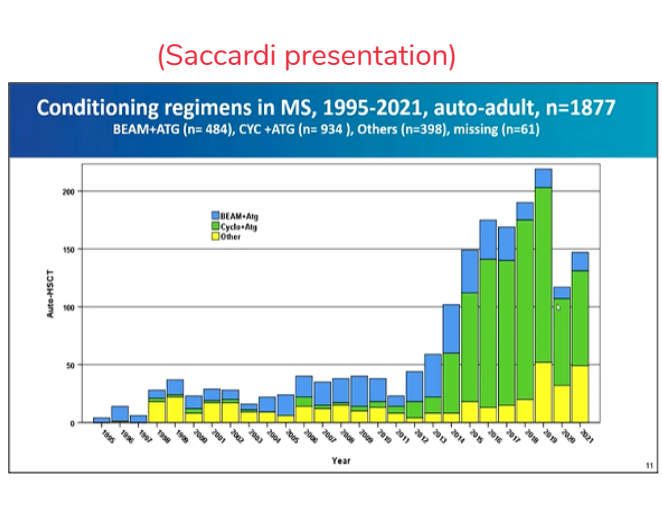
(Mancardi presentation)



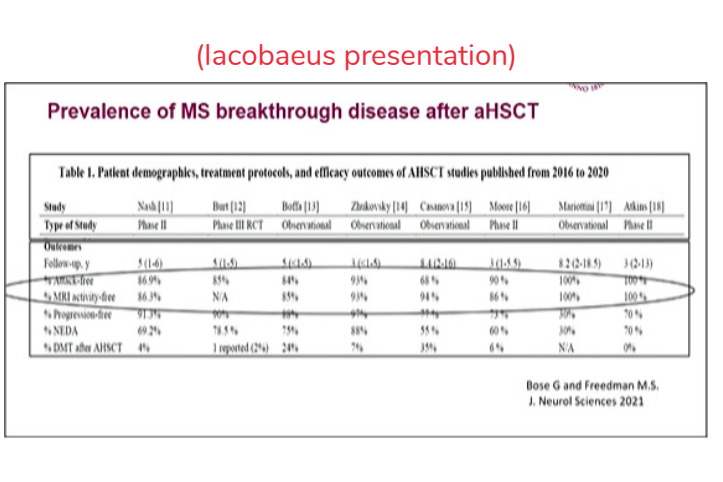
(Sharrack presentation)



(Saccardi presentation)



(Iacobaeus presentation)



Therapy Session 3
Hot Topic 9: Pharmacovigilance

Friday, 28 October 12:00 – 13:30 CEST
Speakers: Renaud Du Pasquier, Mike Wattjes, Joep Killestein
Chairs: Jorge Correale, Bruce Cree

Conclusion: The risk of long-term adverse effects (AE) with disease-modifying therapies (DMTs) used to treat MS can be mitigated by careful baseline evaluation, adhering to recommended follow-up blood/cerebrospinal fluid (CSF) tests/magnetic resonance imaging (MRI), and proactively addressing comorbidities. Interpreting imaging findings to diagnose adverse central nervous system (CNS) effects requires expertise and an interdisciplinary approach. Options for treating progressive multifocal leukoencephalopathy (PML) remain limited so early detection is key.

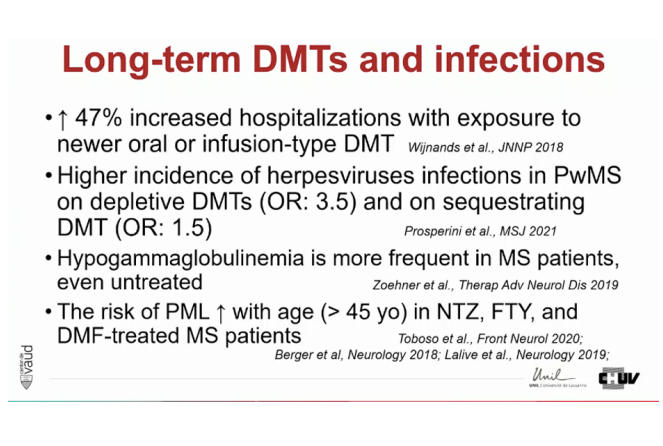
What's New: DMTs differ in their associated risk of infection (Topic 1). In a Swedish registry of 64,212 people with MS – each with five age- and sex-matched controls without MS – off-label rituximab was associated with the highest rate of hospitalisation (a marker for serious infection), followed by fingolimod, natalizumab and interferon beta/glatiramer acetate (GA). Reports examining the risk of cancer associated with long-term use of DMTs are inconclusive, apart from depletive DMTs (anti-CD20s, natalizumab), which do seem to be associated with an increased risk of cancer in individuals >45 years old. In older patients, managing comorbidities may be more valuable than using DMTs that carry increased AE risks.

Early diagnosis of CNS complications involves imaging with MRI, noting clinical symptoms and measuring CSF biomarkers (Topic 2). Vascular comorbidity is common in patients with MS and these lesions must be differentiated from MS lesions. PML can be detected before the patient is symptomatic and those who are diagnosed early have better outcomes. Frontal lobes are more commonly affected. The suggested MRI protocol for detecting/monitoring (PML) is: FLuid-Attenuated Diffusion Recovery (FLAIR; most sensitive for detecting PML), T2W (detecting vacuoles and microcysts), T1W Gd (determining degree of demyelination and inflammation) and diffusion-weighted imaging (DWI; detecting acute and active infection). PML can persist after natalizumab is stopped, and contrast-enhanced monitoring should be continued for 6–12 months after drug cessation.

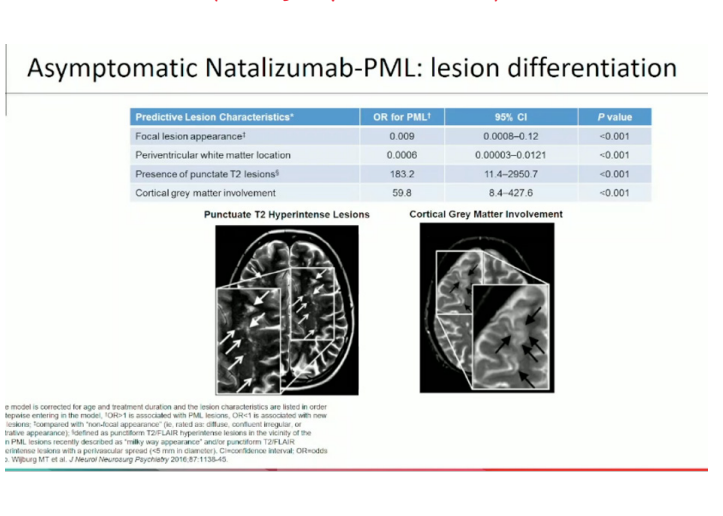
To minimise the risk of PML with natalizumab, patients should be John Cunningham (JC) virus-negative; the annual risk of converting to JC virus-positive while receiving natalizumab is 4%–15% (Topic 3). In stable patients, extending the dosing interval from every 4 to every 6 weeks can decrease PML risk. It is unclear whether extending the interval decreases the risk of JC virus seroconversion. In addition to MRI, serum neurofilament light chain monitoring can help detect PML early. To date, direct antiviral strategies have not prolonged survival or decreased disability in established PML. Steroids can dampen inflammation but may affect antiviral responses. Plasmapheresis may be helpful in late-stage PML. Results have been mixed with the CCR5+-targeting drug maraviroc and it is not currently recommended; however, BK-virus-specific T-cells appear more promising. Moving forward, more effective and less expensive means of detecting PML are needed.

Background: Long-term AEs associated with DMTs may not be well-characterised due to the limited duration of randomised, controlled trials; underreporting; lack of long-term registries; and, difficulty in separating AEs from the effects of aging. Moreover, some patient populations are not well represented in phase III trials. PML remains a recognised risk factor for five MS therapies, notably natalizumab.

(Du Pasquier presentation)



(Wattjes presentation)



(Killestein presentation)