ECTRIMS 2022 **Congress Report | Therapy**

ECTR PEAN COMMITTEE FOR TREATMI RESEARCH IN MULTIPLE SCLERC

Day 1

Day 2

Amsterdam, The Netherlands

26 – 28 October 2022

Day 3

Please click on the sections in the navigation bar to go to the content.

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,

(Montalban presentation)

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.

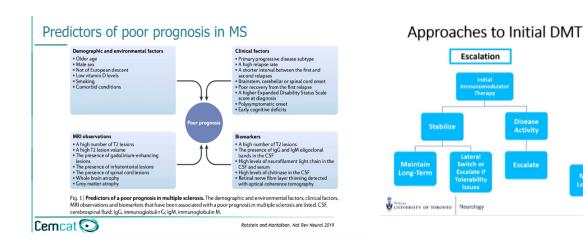
Background: There are many predictors of poor prognosis in MS, including low vitamin D levels, a high relapse rate, the presence of spinal cord lesions, male gender and higher EDSS. Compared to low efficacy treatments, evidence shows HETs are more effective, but could potentially have more severe adverse 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.

(Rotstein presentation)

Early Intensive Therapy

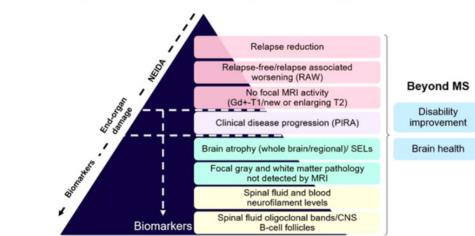
HE = High Efficacy, IRT = Immune Reconstitution Therapy

nitial H



(Giovannoni presentation)

Evolving treatment targets- beyond NEIDA



Slide content was developed by and is reflective of the opinion of G Giovannoni. CNS, central nervous system; NEIDA, no evidence of inflammatory disease activity; SELs, slowly expanding lesi

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 diseasemodifying therapies differ guantitatively 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, dimethylfumarate, 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

Escalation strategy

Stepwise approach to treatment using

agents of varying efficacy. Patients are

moved up to stronger agents upon breakthrough disease.

OR

High-Efficacy from Onset strategy

Acute approach to treatment using highefficacy agents in the early stages of the

disease.

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)

What strategy?

Treatment Strategy

Treatment Type

Continuous therapy

frequent dosing Interval therapy The effect persists using agents that require spaced

The effect is maintained

using agents that require

out treatment doses Induction therapy

The effect is durable using agents that require a limited number of treatment doses

Pro: low/moderate risk Con: low to moderate efficacy, indefinitely (IFNs, GA, TFN, DMF, S1P modulators)

Pro: high efficacy Con: repeat administrations required indefinitely (NTZ, anti-CD20)

Pro: moderate/high efficacy Con: disease activity may come back and lead to further treatment (CLD, ALTZ)

Cemcat 🛈

Slide courtesy of Prof. Xavier Montalban

Day 2

Therapy Session 1

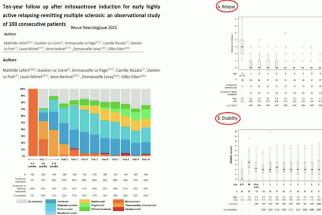
Hot Topic 5: Escalating and de-escalating DMTs Thursday, 27 October 10:00 - 11:00 CEST Speakers: Gilles Edan, Emmanuelle Waubant, Eva Strijbis Chairs: Maria Troiano, Joep Killestein

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 longterm 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

(Edan presentation)



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.

(Waubant presentation)

Conclusions

| High lesion load at onset including cord involvement/high disease activity pre-high efficacy DMT | Moderate lesion load at onset/low-moderate disease activity pre-high efficacy DMT |
|---|--|
| + | + |
| +/- | + |
| + | +/- |
| | + |
| | - |
| | involvement/high disease ictivity pre-high efficacy DMT + +/- + - |

(Strijbis presentation)

Ŵ Innsbruck (generation) 168 patients Vienna (validation) 98 patients Innsbruck Vienna VIAADISC risk prediction Mean Age at DC 38 38.8 Duration DMT 4.1 4.8 Mean EDSS at DC 1.5 2.0 MRI at DC VIAADISC HR 95% CI P-value Risk score 57.6% Increase in T2 53.1% points 21.4% Gad+ Lesions 23.2% assigned Duration F/U y 5.0 5.5 Age at discontinuation Dz Reactivation 53.6% 52% Relapse after DC EDSS worse after DC 49.4% 19.6% 48% 22.4% 2 < 45 yrs 4.3 2.5 - 7.1 < 0.001 ≥ 45 and < 55 yrs 2.1 1.4 - 3.8 < 0.001 1 DMT Restarters 39.3% 38.8% ≥ 55 yrs 0 Ref Activity on MRI at discontinuation ≥ 3 new/enlarged T2 lesions or ≥ 1 CEL 3.9 3.2 - 4.9 < 0.001 2 < 3 new/enlarged T2 lesions and no CEL Ref 0 VIAADISC = Vienna Innsbruck DMT Duration of stable disease course discontinuation score < 4 yrs 4.4 2.7 - 8.3 < 0.001 2 age ≥ 4 and < 8 yrs 1.6 - 4.5 < 0.001 2.3 1 activity on MRI 0 duration in stable course ≥ 8 yrs Ref Validation cohort: Cox regression ($R^2 = 0.749$; p < 0.001). Bsteh 2021 - PMID 33370478

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

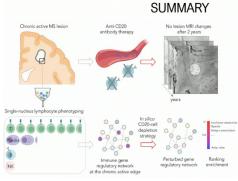
Conclusion: The Río score does predict the likelihood of relapses, disease progression, evidence of disease activity (EDA), and treatment failure in patients initiating daily oral disease-modifying therapies (DMTs). Vidofludimus 30 mg daily orally appears to be the lowest effective dose for relapsingremitting 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. Clinicalradiological 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

(Maggi presentation)



Why? Few CD20 B-cells in chronic active lesions

- Limited CD20 B-cells tissue
- turnove Inefficient BBB passage of antiCD20 Ab

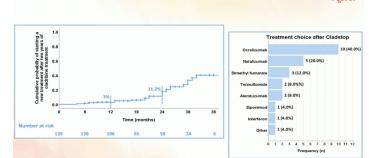
analysis revealed that the 10 mg dosage had a minimal effect on disease activity on MRI whereas the 30 and 45 mg dosages demonstrated anti-inflammatory effects, with 65%-78% reduction in combined unique active (CUA) and Gd+ lesions; median neurofilament light chain levels were reduced by 18% and 26% 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 secondgeneration, 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.

(Schiavetti presentation) Results: Treatment status after CladStop



(Piehl presentation)

ProTEct-MS: Conclusions

- Temelimab as add-on to antiCD20 appears safe
- Clinical endpoints stable (EDSS stable, improvement in 9-HPT, worsening in T25FWT) Small changes MRI lesion volumes
- No evidence of effect of Temelimab on NAWM MRImetrics
- Tendency for improved MTR signal / reduced volume loss in brain grey matter structures (compare¹), as well as lowered GFAP levels (marker of progressive disease biology²)

- · Further analysis work ongoing, including potential identification of responders
- ProTEct-MS establishes a trial design to investigate candidate compounds for brain inherent diseases processes; soluble biomarkers more sensitive to detect change

1 Brown, Lancet Neurol 2021; 20: 709-20 2 Meier, O166; Benkert, P668; Schorr, EP1025; Barro, P253, P254 We thank study participants, additional study staff and GeNeuro for sponsoring the trial

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 longterm 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.

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.

A PARADIGM SHIFT

Therapeutic Decision Making for Relapsing MS



| Compound Molecular ma (kDa) | | Non-imaging PD marker established? | Current and anticipated EMA requirements (based on guidelines and on past decisions or recommendations for MS or non-MS drugs) | | | | |
|--------------------------------|----------------|--|---|--|--|--|--|
| Glatiramer acetate | 5-9 | No | Past decision: - Efficacy/safety trial in PwMS with imaging endpoint - Immunogenicity | | | | |
| IFNB | 18 | No | Guideline EMA/CHMP/BMWP/652000/2010: - (PK)/PD study in healthy volunteers ^b - Efficacy/safety trial in PwMS with imaging endpoint - Immunogenicity | | | | |
| Pegylated | 44 | No | Anticipated: | | | | |
| IFN-B1a | 300 (apparent) | | Likely as for IFNB | | | | |
| Alemtuzumab | 145 | No | Anticipated: - Likely full clinical programme as for other mAbs without established PD markers | | | | |
| Anti-CD20 antibodies | 145 | No | Anticipated based on past rituximab decision: PK study in healthy volunteers Efficacy/safety trial in one autoimmune or oncologica indication PK-bridging study in other indications (need is currently under re-assessment) Immunogenicity | | | | |
| Natalizumab | 149 | Immunogenicity Anticipated according to Wolff-Holz et al.¹⁰ PK/PD study in PwMS (acceptable PD biomarker: a4-integrin receptor saturation) Immunogenicity Apparent past decision (based on NCT04115488): PK study in healthy volunteers I year efficacy/safety trial in PwMS with imaging endpoint. Immunogenicity | | | | | |

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.

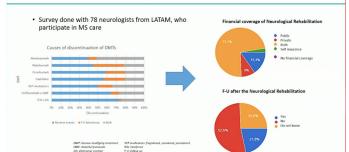
What's New: Consensus standards for MS care have been published outlining core, achievable and aspirational levels for MS care teams in terms of referral and diagnosis, routine monitoring and support, and treatment decisions (Topic 1). Early treatment with a high efficacy disease-modifying therapy (DMT) 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.

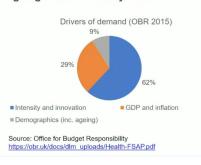
Barriers to high-quality MS care can be classified as those pertaining to clinicians, patients and the specific healthcare system (Topic 2). Early results from a survey of 78 neurologists in Latin America revealed that the majority felt that access to highly effective treatment was high and perhaps did 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

(Maggi presentation)

From the neurologist's point of view in LATAM





contracted COVID-19 infection.

collection, analysis and sharing.

realistic (Topic 6).

Medicines List will be resubmitted soon.

The global demand for healthcare resources is outstripping

population is not actually the main driver of this increased

capacity (Topic 4). Although frequently implicated, the aging

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

In the South-East Asian regions, the use of off-label DMTs

An application to add MS treatments to the WHO Essential

(e.g. rituximab) provide a viable MS treatment option (Topic 5).

Above all, goals to improve MS care must be context-specific and

Background: The MS International Federation has specified that

people with MS have access to and receive high quality MS care

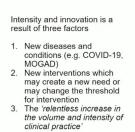
location, socioeconomic status, gender, sexual orientation, etc. In

leading to disability and the prevalence is increasing worldwide.

MS is an expensive disease that requires specialised care.

young adults, MS is the second most common neurologic disorder

regardless of disparities such as level of disability, geographic



الصحة الجكيمة

(Piehl presentation)

Improve affordability for patients and lower cost for society

- Understand cost of DMT, lab work, MRI, doctor visits in various regions vs
- average individual revenues and health coverage Avoid unnecessary blood work, MRI scans, doctor visits
- · Enable access to generic off-label DMT with proven benefit
- Identify type of DMT safer or more practical to administer in a given region
- Avoid relapses that lead to pulse steroids/hospital admission/days off work/progression of disability
- · Early treatment with effective drugs adapted for patient and their
 - environment: Less relapse=less disability progression=less long-term medical needs Less work days "lost"

Therapy Session 2

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

(Schiavetti presentation)

Drivers for the increase in demand in health systems The main driver of demand is the increase is not population ageing which is usually blamed

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

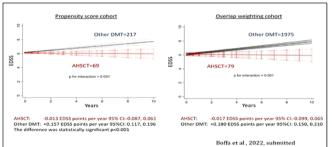
Conclusion: Autologous haematopoietic stem cell transplant (AHSCT) should be offered to all patients with highly active relapsing-remitting MS (RRMS) failing disease-modifying therapies (DMTs) and should be a clinical option in treatmentnaïve patients with aggressive MS. It can also be considered in 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

(Mancardi presentation)



(Saccardi presentation)

BEAM+Atg Cyclo+Atg

Conditioning regimens in MS, 1995-2021, auto-adult, n=1877

00, 00

uncommon. According to a summary of eight previous studies, the proportion of patients who remained relapse- and MRIfree 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.

(Sharrack presentation)

CURRENT CLINICAL TRIALS OF AUTOLOGOUS HSCT IN MS

| Trial/identifier | Description | Centres/countries |
|---|--|--|
| RAM-MS NCT03477500 | Phase III RCT of autologous HSCT (Cy-ATG) versus alemtuzumab (later extended to ocrelizumab and cladribine) | Scandanavia, Netherlands |
| STAR-MS | Phase III RCT of autologous HSCT (Cy-ATG) versus alemtuzumab or ocrelizumab | UK |
| BEAT-MS | Phase III RCT of autologous HSCT (BEAM-ATG) versus standard of care | US predominantly (NIH-led) |
| MOST NCT03342638 | Phase III RCT of autologous HSCT regimen (Cy-ATG versus Cy-ATG + intravenous immunoglobulin) | Northwestern University, US |
| COAST | Phase II RCT of autologous HSCT (Cy-ATG) versus ocrelizumab or alemtuzumab | Germany |
| NET-MS (Italian collaborative) | Phase II RCTof autologous HSCT (BEAM-ATG) versus best available DMT | Italy |
| Swiss aHSCT Registry Study | Open study of autologous hematopoietic stem cell transplantation in patients with RRMS and progressive forms of MS (5 year duration) | University Hospital Zurich, Switzerland |
| Mexican open label study NCT02674217 | Outpatient Hematopoietic Grafting in Patients With Multiple Sclerosis Employing Autologous Non-cryopreserved Peripheral Blood Stem Cells: A Feasibility Study | Clinica Ruiz, Puebla, Mexico |
| | | |

Sharrack et al, Bone Marrow Transplantation 2019 & British Medical Journal 2022

(lacobaeus presentation)

Prevalence of MS breakthrough disease after aHSCT

| Table 1. Patient demographics, treatment protocols, and efficacy outcomes of AHSCT studies published from 2016 to 2020 | | | | | | | | |
|--|---|-----------------|---------------|------------------------------------|--------------------------------|------------------------|----------------------------------|-------------------------|
| Study | Nash [11] Burt [12] Phase II Phase III RCT | Burt [12] | Boffa [13] | Zhikovsky [14] ad Observational | Casanova [15] Observational | Moore [16] Phase II | Mariottini [17] Observational | Atkins [18] Phase II |
| Type of Study | | Phase III RCT | Observational | | | | | |
| Outcomes | | | | | | | | |
| Follow-up, y | 5(1-6) | 5(1-5) | 5 (<1.5) | 3 (<1.5) | 8.4 (2-16) | 3 (1-5.5) | 8.2 (2-18.5) | 3 (2-13) |
| Amerik-free | 86.9% | 85% | 84% | 93% | 68 % | 90 % | 100% | 100 ** |
| 5 MRI activity-free | 86.3% | N/A | 85% | 93% | 94 % | 86 % | 100% | 100 % |
| h Progression-free | 91.3% | 50% | 19% | 97% | 114 | 73 % | 30% | 70.96 |
| % NEDA | 69.2% | 78.5 % | 75% | 88% | 55 % | 60 % | 30% | 70 % |
| S DMT after AHSCT | 4% | 1 reported (2%) | 24% | 7% | 35% | 6 % | N/A | 0% |



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

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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

(Du Pasquier presentation)

Long-term DMTs and infections

- newer oral or infusion-type DMT Wijnands et al., JNNP 2018
- Higher incidence of herpesviruses infections in PwMS on depletive DMTs (OR: 3.5) and on sequestrating
- DMT (OR: 1.5) Prosperini et al., MSJ 2021 · Hypogammaglobulinemia is more frequent in MS patients,
- Zoehner et al., Therap Adv Neurol Dis 2019 even untreated • The risk of PML ↑ with age (> 45 yo) in NTZ, FTY, and
- DMF-treated MS patients Toboso et al., Front Neurol 2020; al, Neurology 2018; Lalive et al., Neurology 2019; Berge Vaud Unil C:UV

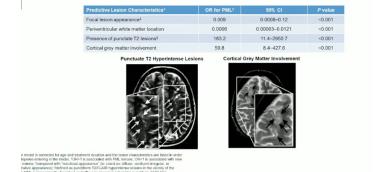
(FLAIR; most sensitive for detecting PML), T2W (detecting vacuoles and microcysts), T1W Gd (determining degree of demyelination and inflammation) and diffusion-weighted imaging (DWI; detecting acute and active infection). PML can persist after natalizumab is stopped, and contrast-enhanced monitoring 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.

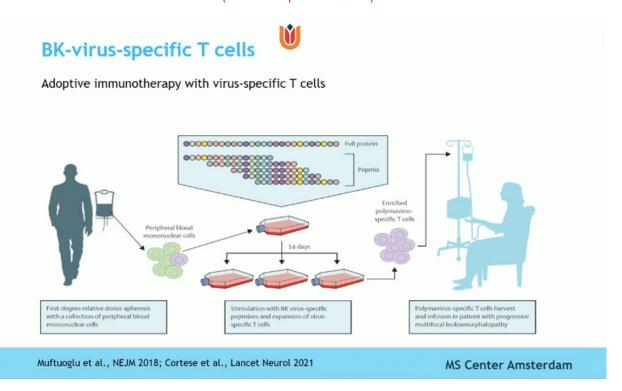
Background: Long-term AEs associated with DMTs may not be well-characterised due to the limited duration of randomised, controlled trials; underreporting; lack of long-term registries; and, difficulty in separating AEs from the effects of aging. Moreover, some patient populations are not well represented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

(Wattjes presentation)

Asymptomatic Natalizumab-PML: lesion differentiation



(Killestein presentation)



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