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PEER-REVIEWED CONFERENCE REPORT

Assessment of MS Course
In the follow-up of MS patients, a comprehensive assessment of the disease course is needed. Next to EDSS, also cognition, quality of life, and other patient-reported outcome measures are relevant.

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Optimising Long-Term Treatment
Because MS is a life-long disease, information about long-term benefit and safety of MS treatment is needed.

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Pregnancy in the Treatment Era
MS is highly prevalent in young adults, especially in women. Thus, family planning is a major issue. Both maternal and foetal/child perspectives are discussed.

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Editor Prof. Hans-Peter Hartung, University of Düsseldorf, Germany

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Letter from the Editor

Prof. Hans-Peter Hartung

Dear Reader,

At ECTRIMS this year in Stockholm, about 7,000 MS specialists, neurologists, researchers, healthcare professionals gathered to present new data and exchange ideas and experiences in elucidating causes and mechanisms of MS, the genetics of this disease, new diagnostic criteria and methods, the broadening spectrum of related CNS immune disorders (NMOSD), advances in MR imaging, and fluid phase biomarkers. As always management issues were discussed extensively and data from clinical trials of new drugs were presented.

This summary attempts to identify and review the highlights of the congress.
I hope you will find this interesting reading.

Best Wishes,

Hans-Peter Hartung

Biography

Prof. Hartung has been Chair of the Department of Neurology at Hein-rich-Heine-University in Düsseldorf since 2001. He is also Director of the Center of Neuropsychiatry and the Department of Conservative Medicine at University Hospital Düsseldorf. He studied medicine at the Universities of Düsseldorf, Glasgow, Oxford, and London. After graduation he served an immunology fellowship at the University of Mainz.
Prof. Hartung's clinical and translational research interests are in the field of basic and clinical neuroimmunology and in particular multiple sclerosis and immune neuropathies. He has been involved as steering committee member in multiple clinical trials of new drugs for the treatment of multiple sclerosis, Guillain-Barre syndrome, and chronic inflammatory demyelinating polyneuropathy.
Prof. Hartung is a former President of ECTRIMS.

Conflict of Interest Statement:
Hans-Peter Hartung has received fees for consulting, speaking, and serving on steering committees from Bayer Healthcare, Biogen, GeNeuro, MedImmune, Merck, Novartis, Opexa, Receptos Celgene, Roche, Sanofi Genzyme, CSL Behring, Octapharma, and Teva, with approval by the Rector of Heinrich-Heine-University.

Towards a Comprehensive Assessment of MS Course

Cognitive assessment in MS

There are several shortcomings of the Expanded Disability Status Scale (EDSS). So, a comprehensive assessment of MS course is an important topic. Cognitive impairment has a major negative impact on the lives of people with MS. However, the clinical response to patient symptoms is not consistent. Cognitive assessment at the start of the disease is helpful in alerting patients to this aspect of MS and in highlighting the importance of activities promoting brain health.

The most prevalent cognitive problems in MS are memory and information processing speed, while language remains largely intact [1]. Cognition is not closely related to other disease variables, such as EDSS, MRI abnormalities [2], disease duration, and phenotype [3]. "Although some think that monitoring MRI is a way of understanding cognition, there is not a direct correlation", Prof. Dawn Langdon (Royal Holloway University of London, United Kingdom) mentioned. "Disease duration is also not a good clue." Furthermore, self-reporting of cognition is heavily confounded by many psychosocial issues, like depression, anxiety, fatigue, conscientiousness, perceived stress, and self-efficacy [4,5]. "Although the patient's own perception and understanding of their cognitive difficulties is very important, it is not a good guide to their objective level", said Prof. Langdon. Appropriate tools for cognitive assessment include the BRB-N, MACFIMS, and BICAMS. For the future, Prof. Langdon thinks that cognitive impairment should be quantified.

Value of cognitive assessment

Given the current limitations, what is the value of cognitive assessment? Firstly, healthcare professionals (HCPs) obtain an objective cognitive status, to separate the problems from fatigue and mood and to determine whether the patient truly has a cognitive deficit. This information enables HCPs to educate patients and encourage a positive lifestyle, and adopt an appropriate interaction style in terms of how to convey information and check understanding. It also allows HCPs to be vigilant to the increased risk of unemployment and other participation issues that MS patients with cognitive deficits are more vulnerable to. Furthermore, these patients are more likely to have falls and driving accidents, and to have poor disease management, including adherence to medication. Finally, this information can alert the HCPs to cognitive decline or relapses [6]. Currently, a number of expert committees advocate that there should be yearly assessment of cognition [7,8].

Benefits for MS patients consists of providing them with the opportunity to make positive lifestyle choices. Cognitive assessments inform people with MS about their condition and gives them the opportunity to engage, for example, in the Brain Health agenda.

1. Rao SM, et al. Neurology. 1991;41:685-91.
2. Manca R, et al. J Neurol Sci. 2018;388:115-127.
3. Brochet B, Ruet A. Front Neurol. 2019;10:261.
4. Akbar N, et al. Cogn Behav Neurol. 2011;24:115-21.
5. Beier M, et al. Rehabil Psychol. 2015;60:254-62.
6. Langdon DW, et al. Mult Scler. 2012;18:891-8.
7. Bakirtzis C, et al. Open Neurol J. 2018;12:31-40.
8. Kalb R, et al. Mult Scler. 2018;24:1665-1680.

Tool to measure quality of life in MS

Neuro-QoL is a measurement system that evaluates and monitors the physical, mental, and social effects experienced by adults and children living with a neurological condition. The development and initial validation was funded by the National Institutes of Health (NIH) and the National Institute of Neurological Disorders and Stroke (NINDS). The administration can be done in multiple forms, either as static short forms or by computer adapted testing.

The domains for adult assessment include physical, mental, and social health (see Table). "This is a very positive step in the overall approach to assess patient-reported outcomes", Dr Deborah Miller (Cleveland Clinic, OH, USA) mentioned. "We are not only looking at the negative consequences of symptoms, but also at the positive results of improvements in patient functioning."

Dr Miller emphasised the importance of HealthMeasures.net, the organisation which is responsible for the international implementation and modification of not only Neuro-QoL

Table. Domains for adult assessment in Neuro-QoL

Domains	Aspects
Physical health	• Fatigue • Sleep disturbance • Lower extremity function (mobility) • Upper extremity function (fine motor, activities of daily living) • Bowel function* • Urinary/bladder function* • Sexual function*
Mental health	• Anxiety • Depression • Positive affect and well-being • Emotional and behavioural dyscontrol • Cognitive function • Communication • Stigma • End of life concerns*
Social health	• Ability to participate in social roles and activities • Satisfaction with social roles and activities

*untested item pools

but also other measures: PROMIS®, NIH Toolbox®, and ASCQ-Me®. The website is developed and validated for common neurological conditions, using state-of-science methods which are psychometrically sound. All measures are designed to each be completed within 1 minute. They are also flexible regarding method of administration: there are pen-and-paper, web-based, or interviewer-based methods. Official translations are also available in Spanish and other languages. This set of measures is available without license, fee, or royalty. Neuro-QoL short forms and computerised adaptive test have been validated in MS [1,2].

MS-PATHS

Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS-PATHS) is a technology-enabled network of MS centres through which researchers have access to patient data generated from a broad MS population. It functions as a learning health system. The aim is to better quantify the value of various treatment approaches and improve patient outcomes in MS. Dr Miller thinks that this is a very exciting concept. "At ECTRIMS, there has been a lot of relevant discussion about the importance of clinical practical trials. MS-PATHS is used both for clinical purposes, and for research." Together with her team she studied symptoms of depression and use of anti-depressants in MS-PATHS patients (n=1,352). Around 40% were prescribed antidepressants and 23% met criteria of major mood disorder. "That suggests that we are doing a pretty good job in determining who has depression and who needs treatment. Unfortunately, we found that 31% of those prescribed antidepressants continued to meet the criteria for major mood disorder. This suggests that we are not paying enough attention to depression and that we are not adequately managing the consequences of depression in a vulnerable patient population."

Next to Neuro-QoL, no other assessment platform provides unidimensional measures of MS symptoms and functions. There is growing evidence of international interest in the MS community to implement Neuro-QoL. The HealthMeasures organisation provides an infrastructure for an international collaboration to harmonise and optimise Neuro-QoL. The question of Neuro-QoL's acceptance as tomorrow's standard patient-reported outcome measure is up to the community of researchers.

1. Miller DM, et al. Mult Scler. 2016;22:830-41.
2. Healy BC, et al. Mult Scler. 2018:1352458518810159.

Novel ways to assess MS

Until recently, MS clinical trial endpoints have focused primarily upon measures of disease activity instead of patient-reported outcome measures (PROMs). There is a growing desire, especially from regulatory authorities, to include endpoints measuring disease activity as seen from the patient's perspective.

MS performance test

The Multiple Sclerosis Performance Test (MSPT) is a novel, iPad®-based disability assessment tool that resembles the Multiple Sclerosis Functional Composite (MSFC) [1,2]. It includes a computer-adapted version of Neuro-QoL, and 4 self-administered neuroperformance tests, providing measurements of walking speed, manual dexterity, low contrast visual acuity, and cognitive processing speed.

Convergent validity studies comparing the MSPT and MSFC subtests have been published [3] or are under editorial review. MSPT is being used as part of the international MS-PATHS network of MS centres, where over 40,000 MSPT assessments have already been conducted to date. Normative databases are commonly used in neuropsychology because performance on cognitive tests can be influenced by demographic variables, such as age, education, and sex. Demographics may also influence tests designed to measure vision and motor function.
Dr Megan Sokolowski (Cleveland Clinic, OH, USA), analysed a demographically stratified normative database of healthy individuals (n=517) who self-administered the 4 MSPT neuroperformance modules [4]. Age was a significant ($P<0.05$) predictor for all MSPT modules: Walking Speed Test (WST), Manual Dexterity Test (MDT), Contrast Sensitivity Test (CST), and Processing Speed Test (PST). Compared to raw scores, adjusted z-scores correct for differences in performance due to demographic variables, thereby allowing

a more accurate representation of the impact of MS on cognitive, visual, and motor neuroperformance. Adjusted z-scores align performance on all the neuroperformance measures to the same scale and allow for the development of meaningful cut-scores for clinical interpretation [4].

Advancing walking measurement

According to Prof. Jeremy Hobart (University of Plymouth, United Kingdom), who presented a study evaluating PROMs [5], there are strong clinical, scientific, and regulatory justifications for advancing the currently available MS walking PROMs. "We believe that these instruments have strong conceptual underpinnings: concept of interest and context of use. We used a hypothesis-testing psychometric approach rather than modelling approach, to determine the strength of the concept. We believe that it meets requirements for clinical trials and provides a more comprehensive assessment of MS walking than existing scales. It was demonstrated to be conceptually and empirically superior to MS walking scale (MSWS)-12. Finally, we can compare two instruments, i.e. MSWS-32 and MSWS-12 scores, on exactly the same metric."

Remotely monitored ambulatory activity

Another proposed outcome measure for clinical trials is remote ambulatory activity monitoring. A prospective, longitudinal, observational cohort study has already validated this instrument [6]. Step-count monitoring is also an exploratory endpoint (average daily step count from the first 30 days; STEPS) of SPI2, a phase 3 trial investigating the efficacy and safety of high-dose, pharmaceutical-grade biotin (MD1003) in patients with inactive primary and secondary progressive MS.

In this study, STEPS correlated to clinical measures of ambulation (EDSS, timed 25-foot walk), cognitive function (Symbol Digit Modalities test), brain and spinal cord MRI atrophy metrics, and quality of life. Dr Valerie Block (University of California San Francisco, CA, USA) stated that these data support the study of STEPS as an exploratory outcome measure in clinical trials for progressive MS [7]. She thinks that remote gait monitoring via Fitbit could become a surrogate for MS disability in clinical trials. Longitudinal analysis of STEPS in the SPI2 study is on-going; results will be presented next year.

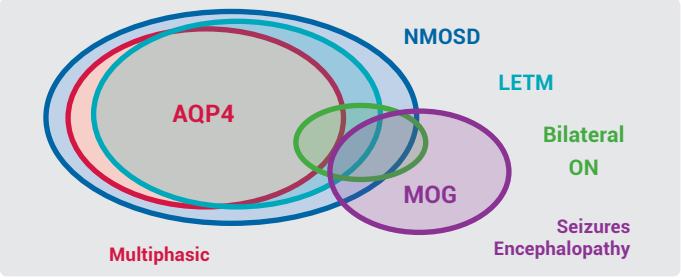
1. Rudick RA, et al. J Vis Exp. 2014;:e51318.
2. Rhodes JK, et al. Adv Ther. 2019;36:1741-1755.
3. Rao SM, et al. Mult Scler. 2017;23:1929-1937.
4. Sokolowski M, et al. ECTRIMS 2019, abstract 215.
5. Hobart J, Burke L. ECTRIMS 2019, abstract 216.
6. Block VJ, et al. JAMA Netw Open. 2019;2:e190570.
7. Block V, et al. ECTRIMS 2019, abstract 217.

Late-breaking: Role for CSF markers in autoimmune astrocytopathies

Recent results of an international study confirm that concentrations of the glial fibrillary acidic protein (GFAP) are elevated in neuromyelitis optica spectrum disorder (NMOSD) and adds a novel astrocytic biomarker, glutamine synthetase (GS), to the laboratory test panel.

NMOSD is a group of immune-mediated central nervous system disorders, including optic neuritis, acute myelitis (LETM), and area postrema syndrome (see Figure). The pathogenesis of NMOSD is better understood since the identification of pathogenic aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) antibodies. However, despite a compatible clinical phenotype some patients remain seronegative.

Figure. Autoantibodies broadened the clinical spectrum, which facilitates diagnosis and guides treatment decisions [1]



AQP4, aquaporin; LETM, acute myelitis; MOG, myelin oligodendrocyte glycoprotein; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis

In an international study, Dr Iris Kleerekooper (University College London, United Kingdom) and colleagues investigated astrocytopathy across NMOSD using 2 biomarkers: the astrocytic enzyme GS, and the structural astrocytic protein GFAP [2]. The aim was to explore levels of astrocytic injury across NMOSD in patients with NMOSD (n=43), MS (n=69), optic neuritis (n=5), and non-neurological control subjects (n=37).

In patients with NMOSD, both median GFAP and GS levels were significantly elevated compared with controls (P=0.021 and P<0.001, respectively). Only GFAP levels significantly distinguished NMOSD from MS (P=0.037) and only GS levels distinguished controls from MS (P=0.001). GFAP and GS levels correlated significantly (P<0.001) and did not differ significantly between AQP4-Ab-seropositive and -seronegative NMOSD, although GFAP levels of AQP4-Ab-seronegative NMOSD patients were markedly increased.

This study confirmed that GFAP concentrations are elevated in NMOSD. GS is a novel astrocytic biomarker, although it

is less specific than GFAP. The increased GFAP levels in seronegative NMOSD patients suggests that the spectrum of autoimmune astrocytopathies may be wider than only AQP4-Ab-seropositive cases, and there could be merit in hunting for novel autoimmune targets in these patients. As additional astrocytic autoimmune target(s) potentially exist in double-antibody-seronegative NMOSD, identification of these targets would facilitate diagnosis and clinical decision making.

1. Misu T, Fujihara K. Clin Exp Neuroimmunol. 2019;10:9-17.
2. Kleerekooper I, et al. ECTRIMS 2019, abstract 340.

Targeted therapies for NMOSD in development

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, relapsing, autoimmune, inflammatory disorder that typically affects the optic nerves and spinal cord and therefore causes blindness and paralysis. NMOSD relapses can cause significant and irreversible neurologic disability. No approved therapies exist for NMOSD. However, some targeted therapies are in development and promising results recently presented or published.

Eculizumab in AQP4-IgG-positive NMOSD

At least two thirds of NMOSD cases are associated with aquaporin-4 antibodies (AQP4-IgG) and complement-mediated damage to the central nervous system. Eculizumab, a terminal complement inhibitor, reduced the risk of NMOSD relapse in patients with AQP4-IgG-positive NMOSD. In the phase 3 PREVENT trial, 143 adults were randomised to receive intravenous eculizumab or placebo. The mean annualised relapse rate (ARR) in the 2 years before enrolment was 1.99. It was permitted to continue stable-dose immunosuppressive therapy during the trial period; 76% of patients did.

The trial was stopped prematurely after the occurrence of 23 of the 24 prespecified adjudicated relapses, the primary endpoint (3% in the eculizumab group vs 43% in the placebo group; HR 0.06; P<0.001) [1]. Secondary outcomes included the adjudicated ARR (0.02 and 0.35 for eculizumab and placebo; rate ratio 0.04; P<0.001) and Expanded Disability Status Scale (EDSS) score (mean change -0.18 for eculizumab and +0.12 for placebo; least squares mean difference -0.29). So, no significant between-group difference in measures of disability progression was found. With respect to adverse events (AEs), upper respiratory tract infections and headaches were more common in the eculizumab group [1].

At ECTRIMS, Dr Dean Wingerchuk (Mayo Clinic, Rochester, United States) presented the combined long-term safety and effectiveness data from the PREVENT study and the ongoing open-label extension of PREVENT [2]. The 137 patients who were treated with eculizumab were followed for approximately 2 years (median 107.8 weeks). A high percentage (approximately 94%) of relapse-free patients remained relapse-free through 192 weeks [2]. Rates of AEs and serious AEs per 100 patient-years were 758.5 and 32.9, respectively. "In this long-term safety and effectiveness analysis, eculizumab was well tolerated", Dr Wingerchuk concluded. "Reported AEs were consistent with the established safety profile of eculizumab in other indications" [2].

Inebilizumab in N-MOmentum trial

B-cell depletion may benefit patients with NMOSD. Inebilizumab is an anti-CD19 monoclonal antibody that depletes a broad range of B cells, including some CD20-negative antibody-secreting cells. In the phase 2/3 N-MOmentum trial, efficacy and safety of inebilizumab in reducing the risk of attacks and disability in adult patients with NMOSD were evaluated. At baseline, participants had an EDSS score of ≤8.0 in combination with either a history of ≥1 attack requiring rescue therapy in the year before screening or ≥2 attacks requiring rescue therapy in the 2 years before screening. In total, 230 patients were randomly allocated (3:1) to intravenous inebilizumab or placebo. The study population was 91% AQP4-IgG-positive, 91% female, and mean age was 43 years at study entry [3]. The primary endpoint was time to onset of an NMOSD attack, as determined by the adjudication committee.

Because of a clear demonstration of efficacy, the randomised controlled period was stopped before complete enrolment. Only 12% of participants receiving inebilizumab had an attack versus 39% receiving placebo (HR 0.272; P<0.0001). AEs occurred in 72% in the inebilizumab group and in 73% in the placebo group. Serious AEs occurred in 5% and 9% of the groups, respectively [3].

At ECTRIMS, Prof. Bruce Cree (University of California, San Francisco, USA) presented results from both the randomised controlled period and the open-label extension period of the N-MOmentum study [4]. He calculated that to prevent one attack, the number needed to treat for 6.5 months was 3.2 for the AQP4-IgG-positive group and 3.7 for the total population. On top of that, inebilizumab significantly reduced risk of worsening disability on EDSS and modified Rankin scale, number of new MRI lesions, and NMOSD-related hospitalisations. After one year, 85% of inebilizumab-treated patients were free of an NMOSD attack.

The most common AEs included urinary tract infection (19.6%), nasopharyngitis (12.9%), and infusion-related reactions (11.6%), which were most common with the first infusion. "The efficacy of inebilizumab was sustained at one year and was associated with an acceptable safety profile", Prof. Cree concluded [4].

Satralizumab in SAkuraStar

In the immune pathology of NMOSD, the pro-inflammatory cytokine interleukin-6 (IL-6) is involved. Satralizumab is a monoclonal antibody that binds to the IL-6 receptor. In the SAkuraStar and SAkuraSky trials, satralizumab reduced relapse rate in patients with NMOSD, given as monotherapy and as add-on, respectively.

In SAkuraStar, 95 patients with NMOSD and ≥1 documented relapse in the year prior to screening, were randomised to satralizumab or placebo. Results were presented at ECTRIMS by Prof. Jeffrey Bennett (University of Colorado School of Medicine, Aurora, USA). The primary endpoint was time to first relapse. Overall, satralizumab reduced relapse risk by 55% compared with placebo (HR 0.45; P=0.018). The response was highly dependent on AQP4-IgG-serostatus, namely:

- In AQP4-IgG-seropositive patients, the HR was 0.26; and
- In AQP4-IgG-seronegative patients, the HR was 1.19 [5]

The proportions of AQP4-IgG-seropositive and -seronegative patients who were relapse-free at weeks 48 and 96 are listed in the Table. Prof. Bennett concluded that satralizumab was effective in reducing relapse risk in patients with NMOSD, particularly in AQP4-IgG-seropositive patients. Because this study was not powered for subgroup analyses, these results should be interpreted with caution [5].

Table. Efficacy results of satralizumab in SAkuraStar [5]

Relapse-free	AQP4-IgG-positive		AQP4-IgG-negative	
	Satralizumab	Placebo	Satralizumab	Placebo
Week 48	82.9%	55.4%	63.3%	77.8%
Week 96	76.5%	41.1%	63.3%	77.8%

1. Pittock SJ, et al. N Engl J Med. 2019;381:614-625.
2. Wingerchuk DM, et al. ECTRIMS 2019, abstract 142.
3. Cree BAC, et al. Lancet. 2019;394:1352-1363.
4. Cree B, et al. ECTRIMS 2019, abstract 139.
5. Bennett JL, et al. ECTRIMS 2019, abstract 141.

Monitoring and Treatment of Progressive MS

Challenges in diagnosing and treating progressive MS

One of the main questions neurologists ask about progressive MS is whether it is easy to recognise it early. Dr Xavier Montalban (University of Toronto, Canada) thinks this is very complex, elaborating on the example that "some patients with an apparent clinically isolated syndrome (CIS) and incomplete recovery, do in fact have progressive MS. This is typical for male patients in their forties or fifties, who generally have primary progressive MS." Also, in patients with relapsing-remitting MS, it can be difficult to identify progression because EDSS is not very sensitive nor commonly used, even in experienced MS clinics. This also applies to other tests, such as the 9-Hole Peg Test and Timed 25-Foot Walk. Cognition is not studied in many centres either. Digital health technology is now evolving as very useful tool, Dr Montalban mentioned. "Typically, neurologists see MS patients every 6 months or every year, and a number of events happening during the year are not captured." The use of digital and remote communication technologies are useful tools for MS management because they provide more complete information about the patient. [1].

In describing the treatment landscape for patients with progressive MS, Dr Montalban started to mention 3 reasons why drugs fail in progressive MS. Firstly, pathogenic mechanisms in the progressive phase are completely different from those in the relapsing phase of MS (see Table). A second reason is that patient populations included in trials are

Table. Pathological mechanisms in progressive MS [2]

Pathological mechanisms	Aspects
Inflammation	• Compartmentalised inflammation • T and B cells • Lymphoid follicles • Relatively intact blood-brain barrier
Axonal degeneration	• Demyelination • Loss of trophic support • Anterograde degeneration • Retrograde degeneration • Transsynaptic degeneration • Histotoxic hypoxia
Microglial activation	• Surrounding chronic active lesions • Clustering at pre-active lesions • Tracking along axons (repair versus degeneration) • Oxidation products
Mitochondrial injury	• Nuclear/ mitochondrial DNA mutations • Clonal expansion and amplification • Decreased energy production and axonal degeneration • Amplification of oxidation
Oxidation by-products	• Accumulation of reactive oxygen species • Poor clearance by defective mitochondria • Microglial oxidative burst
Glutamate excitotoxicity	• Direct demyelinating effects • Dysregulation of calcium homeostasis in axons and oligodendrocytes

not appropriate, "probably because they are either too old or it is too late to intervene", he added. Thirdly, clinical outcomes are not sensitive enough and clinical trials are not smart enough to detect the worsening of disease over this period of time.

A recent study showed an association of chronic active MS lesions with disability *in vivo*. Chronic active, slowly expanding, smouldering lesions are visible on an MRI scan. This type of lesion is of special clinical and biological interest for its accumulation of microglia and/or macrophages at the lesion edge, subtle opening of the blood-brain barrier, and repair/remyelination failure with axonal loss [3].

According to Dr Montalban, the most important question is: Do we have any treatment for progressive MS? Over the years, many drugs have been approved for the treatment of relapsing MS (see Figure). "For primary progressive MS, the only drug we have available is ocrelizumab." Dr Montalban ended by recommending reading the ECTRIMS-EAN clinical practice guidelines for pharmacological management of MS [4], as well as a recently published review regarding treatment approaches for progressive MS [5].

1. Marziniak M, et al. JMIR Rehabil Assist Technol. 2018;5:e5.
2. Ontaneda D. Continuum (Minneap Minn). 2019;25:736-752.
3. Absinta M, et al. JAMA Neurol. 2019 Aug 12.
4. Montalban X, et al. Mult Scler. 2018;24:96-120.
5. Faissner S, et al. Nat Rev Drug Discov. 2019 Aug 9.

Risk factors for conversion to secondary progressive MS

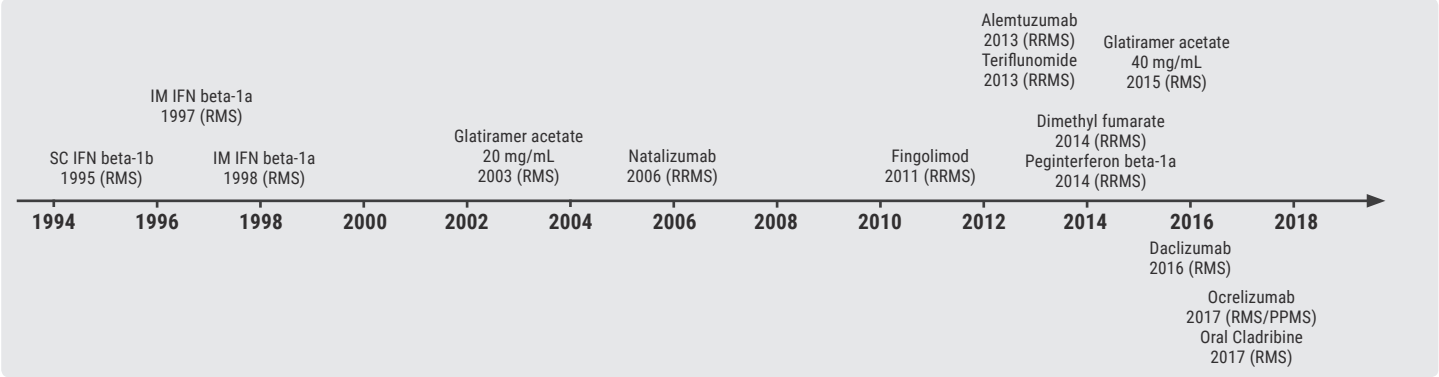
To date, according to the Lublin definition, secondary progressive MS and its diagnosis are retrospective, based on a history of gradual EDSS worsening [1,2]. There are no clear metrics for sensitive and reliable identification of the transition from relapsing-remitting MS to secondary progressive MS available to assist neurologists in daily clinical practice.

In 2016, an objective definition of secondary progressive MS was proposed, based on the application of a mathematical algorithm to longitudinally recorded EDSS score evaluations in the MSBase platform [3]. Caution should be taken, because the way conversion is defined may affect the risk and protective factors eventually associated with the disease course transition. So far, no studies have evaluated the risk factors for conversion using different secondary progressive MS definitions.

In a large cohort of relapsing-remitting MS patients (n=19,318) extracted from the Italian MS Registry, two different definitions of secondary progressive MS were applied:

- Firstly, the date of conversion annotated in the database, which was based on the subjective judgement of the neurologists, was extracted;
- Secondly, a data-driven definition based on an EDSS increase, in the absence of a relapse, with a minimum EDSS ≥4 and pyramidal score ≥2 at time of conversion [4].

Figure. Evolving therapeutic landscape in MS



The risk of reaching the secondary progressive MS was assessed by using multivariate Cox proportional hazards models. A data-driven definition of secondary progressive MS seems to select a population more likely to be in the progressive phase of the disease in comparison to the diagnosis of the neurologist.

By using both the definitions, Dr Pietro Iaffaldano (University of Bari Aldo Moro, Italy) and colleagues confirmed that the most important risk factors for the transition of relapsing-remitting MS to secondary progressive MS are a multifocal onset, an older age of onset, and a higher number of relapses. Furthermore, they confirmed that the most important protective factor against the transition to secondary progressive MS is disease-modifying treatment exposure. "The higher the exposure, the lower the risk of progression", he added.

After transition, disease-modifying treatment exposure does not have an impact on the risk of disability accrual. The major driver of disability accumulation in this phase of the disease are relapses. So, an accurate and less ambiguous secondary progressive MS definition is warranted to assist the neurologists and the scientific community in the efforts to find newer treatment strategies against progressive MS [4].

1. Lublin FD, Reingold SC. Neurology. 1996;46:907-11.
2. Lublin FD, et al. Neurology. 2014;83:278-86.
3. Lorscheider J, et al. Brain. 2016;139(Pt 9):2395-405.
4. Iaffaldano P, et al. ECTRIMS 2019, abstract 156.

Transplantation of autologous mesenchymal stem cells

Mesenchymal stem cells (MSCs) induce both immune-modulatory and neurotrophic effects, and are safe when administered to patients with MS or amyotrophic lateral sclerosis (ALS). The current phase 2b double blind randomised trial, presented by Prof. Dimitrios Karussis (Hebrew University of Jerusalem, Israel), evaluated the safety and efficacy of transplantation of autologous bone marrow-derived MSCs in patients with active progressive MS. Furthermore, this study evaluated the optimal route of administration of MSCs, comparing intrathecal to intravenous administration [1].

This trial enrolled 48 patients with progressive MS (EDSS range: 3.5-6.5). The participants randomly received autologous MSCs or placebo via intrathecal or intravenous administration. At 6 months, treatment groups were crossed over, and patients re-treated with either MSC or placebo.

Per-protocol analysis of the pre-determined primary endpoint showed that significantly fewer patients experienced treatment failure, i.e. increase in EDSS or deterioration in any functional system, in the MSC intrathecal and MSC intravenous groups compared with the placebo-treated patients (6.7%, 9.7%, and 48.4%, respectively, P=0.0003). Additionally, 58.6% of patients treated with MSC intrathecally and 40.6% of those treated with MSC intravenously exhibited no evidence of disease activity (NEDA, i.e. no relapses, no EDSS progression, no new T2 activity, no gadolinium-enhancing lesions in MRI) for 6 months, compared with 9.7% in the placebo groups [1]. Beneficial effects were also noted, mainly in the intrathecal MSC group, with several secondary endpoints, such as 25-foot timed walking, 9-hole peg test, cognitive tests, and the rate of change of MRI T2 lesion load, as well as in newer biomarkers (retinal nerve fibre layer optic coherence tomography and functional MRI-motor network) [1]. Intravenous and intrathecal administration of autologous MSCs was well-tolerated, with no observed serious treatment-related adverse events. A phase 3 trial is warranted to confirm these findings.

1. Petrou P, et al. ECTRIMS 2019, abstract 157.

Siponimod delays time to wheelchair

Secondary progressive MS is associated with insidious worsening of walking disability, which eventually results in increased wheelchair dependence [1]. Recently, it was shown that siponimod is efficacious in slowing down disability progression and cognitive decline in a typical secondary progressive MS population [2].

EXPAND was the largest phase 3 trial conducted in a typical secondary progressive MS population (n=1,651), with >50% of patients needing a walking aid (EDSS ≥6.0) at baseline. An open-label extension for up to 10 years is ongoing [2]. A significant delay in the risk of 3- and 6-month confirmed disability progression (CDP) was observed in siponimod-treated patients compared to the placebo group.

In the current study, the effect of siponimod in delaying time to wheelchair dependence was evaluated. In the survival analysis, a significantly lower proportion of siponimod-treated patients with baseline EDSS of 6.5 (19.8% vs 26.1%) progressed to EDSS ≥7 compared to placebo (HR 0.64; P=0.0483). Under the assumption of the model, i.e. a stable effect over time, siponimod extended the median time to EDSS ≥7 by 4.3 years in the overall population compared to placebo (12.0 years vs 16.3 years) [3].

Time to wheelchair is a highly clinically relevant endpoint. Prof. Patrick Vermersch (Lille University, France) thinks that results from this analysis translate to potential long-term benefits beyond the core part of the EXPAND trial. "Off course, extrapolation beyond the study duration is a limitation", he added.

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2. Kappos L, et al. Lancet. 2018;391:1263-1273.
3. Vermersch P, et al. ECTRIMS 2019, abstract 158.

Sustained reduction in disability progression with ocrelizumab

Ocrelizumab is a humanised monoclonal antibody (mAb) that targets and selectively depletes CD20-positive B cells. In the phase 3 ORATORIO study, the efficacy and safety of ocrelizumab in primary progressive MS were demonstrated compared with placebo. In the double-blind phase of ORATORIO, ocrelizumab was associated with lower rates of clinical and MRI progression than placebo.

The current analysis, presented by Prof. Jerry Wolinsky (University of Texas, TX, USA), assessed the effect of switching to, or earlier initiation of, ocrelizumab therapy on confirmed disability progression (CDP) for at least 24 weeks, in patients starting or continuing ocrelizumab in the open-label extension of ORATORIO.

After 6.5 study years (312 weeks) of follow-up, CDP outcomes favoured patients receiving earlier and continuous treatment with ocrelizumab in comparison with those with a delayed initiation. Earlier initiation of ocrelizumab therapy significantly reduced the risk of becoming wheelchair-confined by 42% compared with those who switched from placebo. So, the benefit of ocrelizumab in reducing disability progression in patients with primary progressive MS in the ORATORIO study persisted up to 6.5 years of follow-up [1]. "This is the first controlled trial showing positive results in primary progressive MS", Prof. Wolinsky finished his lecture. "Because the results were durable for up to 6.5 years, it will take some time before these results can be challenged."

1. Wolinsky JS, et al. ECTRIMS 2019, abstract 159.

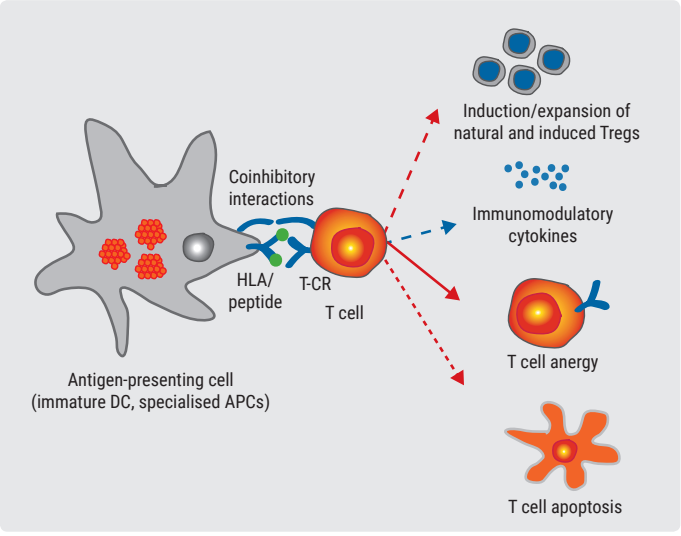
Late-breaking: Myelin-peptide coupled red blood cells

Induction of antigen-specific immune tolerance is a promising therapeutic approach in autoimmune diseases. Peptide-coupled cell tolerance is effective in several animal models of autoimmune disease, allergies and transplantation. Prof. Andreas Lutterotti (University of Zurich, Switzerland) and colleagues developed a therapeutic regimen employing autologous blood cells, chemically coupled with 7 myelin peptides, to induce antigen-specific tolerance in MS patients [1].

After a successful trial with myelin peptide-coupled peripheral blood mononuclear cells (PBMCs) in MS patients, the researchers optimised the approach using red blood cells (RBCs) as tolerogenic carriers (see Figure) [2]. ETIMS^{red} is the first-in-human phase 1b trial, to test the safety and tolerability of increasing doses of autologous peptide-coupled RBCs. Ten relapsing-remitting MS patients (mean age 38.5; 70% female) were treated with increasing doses of peptide-coupled RBCs.

The trial met its primary endpoint, demonstrating feasibility, safety, and excellent tolerability. There were no adverse events within the 24 hours after infusion and no serious adverse events occurred in the trial. Patients remained stable in all clinical parameters. The trial was accompanied by mechanistic studies to assess *in vivo* immunological effects of the therapy [2]. Frequency of myelin peptide-specific T cells reduced after tolerization (more pronounced in high-dose patients), which suggests there was antigen-specific tolerization. Increases in regulatory T cells and IL-10, as well as a reduction of neurofilament light chain, point towards active mechanisms of immune tolerance [2]. The next step is to expand the peptide cocktail to novel antigens. A phase 2a trial to assess the efficacy of the approach is being developed.

Figure. Tolerance induction with peptide-coupled RBCs or white blood cells [2]



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Optimising Long-Term Benefit of MS Treatment

Induction therapy over treatment escalation

Prof. Alasdair Coles (Cambridge University Hospitals, United Kingdom) discussed why induction therapy is the preferred principle over treatment escalation. "I have to admit that there is no perfect induction therapy in humans", he mentioned at the beginning of his talk.

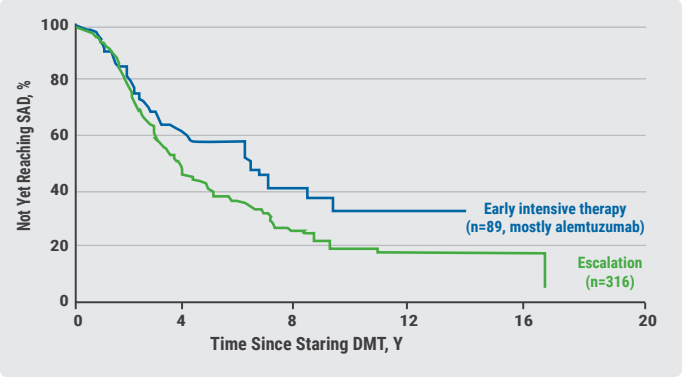
The ideal induction therapy for an autoimmune disease is one "short sharp shock" of treatment with a restricted period of adverse effects, leading to long-lasting disease-specific immunological tolerance. This approach leaves the remaining immune system competent to fight infections and the patients free of infectious diseases risk.

"How close are we to this ideal model in the management of MS?" Prof. Coles asked. "There are only 3 therapies which come close to what we might consider induction therapies of MS: autologous haematopoietic stem cell therapy (aHSCT), alemtuzumab, and cladribine. I want to make a point that not all high-efficacy therapies are induction therapies by the provided definition. Clearly, natalizumab and ocrelizumab have high efficacy, but they have to be delivered continuously. It is true that induction therapies are, by definition, early therapies, given after the first identification of an abnormal immune response."

Evidence for induction therapy

It is not possible to demonstrate immunological tolerance in MS, because the underlying pathogenic immune process is not known. "So, we have to infer the induction of tolerance by disease suppression", Prof. Coles said. The question is whether one of the above-mentioned 3 induction therapies can lead to long-lasting disease suppression with restricted window of risk. And if so, is this better than continuous dosing with treatment escalation? Two ongoing trials are testing early intensive versus escalation in MS treatment: TREAT-MS and DELIVER-MS. "But they don't directly address the issue of today", Prof. Coles added, "because in the intensive therapy arm, natalizumab and ocrelizumab are included, which I don't think count as induction therapies." Recently published real-world data, which, according to Prof. Coles, are "exciting", show that early, high-efficacy treatment using alemtuzumab and natalizumab slow the rate of secondary progression over 8-11 years [1]. "Nevertheless, these data cannot directly address our question", he admitted. Another study showed that early intensive therapy, mainly using alemtuzumab, does offer benefits compared to escalation over a period of 15-16 years (see Figure 1) [2].

Figure 1. Early intensive therapy vs escalation. Median time to sustained accumulation of disability was 6.0 years for treatment with high-efficacy disease-modifying treatment (early intensive treatment) vs 3.14 years for moderate-efficacy disease-modifying treatment (escalation treatment) [2]



Prof. Coles thinks that the alemtuzumab trials are most relevant for the question at hand. In a phase 2 trial, MS patients (n=60) with a disease duration of median 1.3 years (age 32 years) either received IFN-beta or two cycles of alemtuzumab, and were subsequently followed for over 12 years. During that period, 33% of alemtuzumab-treated patients did not need a further line of therapy, 38% needed an additional three days of therapy, and 29% needed more cycles [3]. "There is prolonged suppression of relapses", Prof. Coles concluded. "12 years after starting this induction therapy, 71% of patients either had stable or improved disability. So, we see prolonged disease suppression following alemtuzumab induction."

Two phase 3 trials evaluated alemtuzumab therapy in either prior untreated MS (CARE-MS1; n=581, median age 33 years, and 1.7 years since onset), or in somewhat older patients with breakthrough disease activity under disease-modifying treatment (CARE-MS2; n=628, median age 35 years, and 4 years since onset). Patients who initially received IFN-beta, were offered to switch to alemtuzumab. In CARE-MS1, 58%

of patients who received alemtuzumab induction therapy needed no further treatment, 22% needed one additional cycle, and 20% multiple additional cycles. Data of 9 years of patient experience, after receiving only 8 or 11 days of alemtuzumab treatment, were presented: In previously untreated patients (CARE-MS1 trial, see Figure 2, left curves) disability progression was comparable for patients receiving alemtuzumab induction therapy versus those starting with IFN-beta and then switching to alemtuzumab [4]. "However, if you leave the patient for 2 more years, give them IFN-beta and afterwards start alemtuzumab in case of recurrent disease activity, they never recover the disability advantage (CARE-MS2 trial, see Figure 2, right curves) [5]."

Safety issues

During the treatment cycles with alemtuzumab, there is serious risk of infection and infusion reactions for about a month, Prof. Coles emphasised. "After each cycle of therapy, there is a risk, with a window of 4 years, for autoimmune disease. Furthermore, patients are advised to not become pregnant for 4 months after each cycle of therapy. In an ideal situation, we have the possibility from year 5-10 to have the benefit of treatment, i.e. disease suppression, in the absence of any risks. There are also windows of disease suppression, with freedom from risks, in which it is safe to become pregnant."

There are definitely possibilities to improve current induction therapies of MS. Firstly, one could combine induction therapy with lower-efficacy and low-risk treatments. Another option is trying to maintain immunological tolerance and reduce risk with Physician Guided Reconstitution.

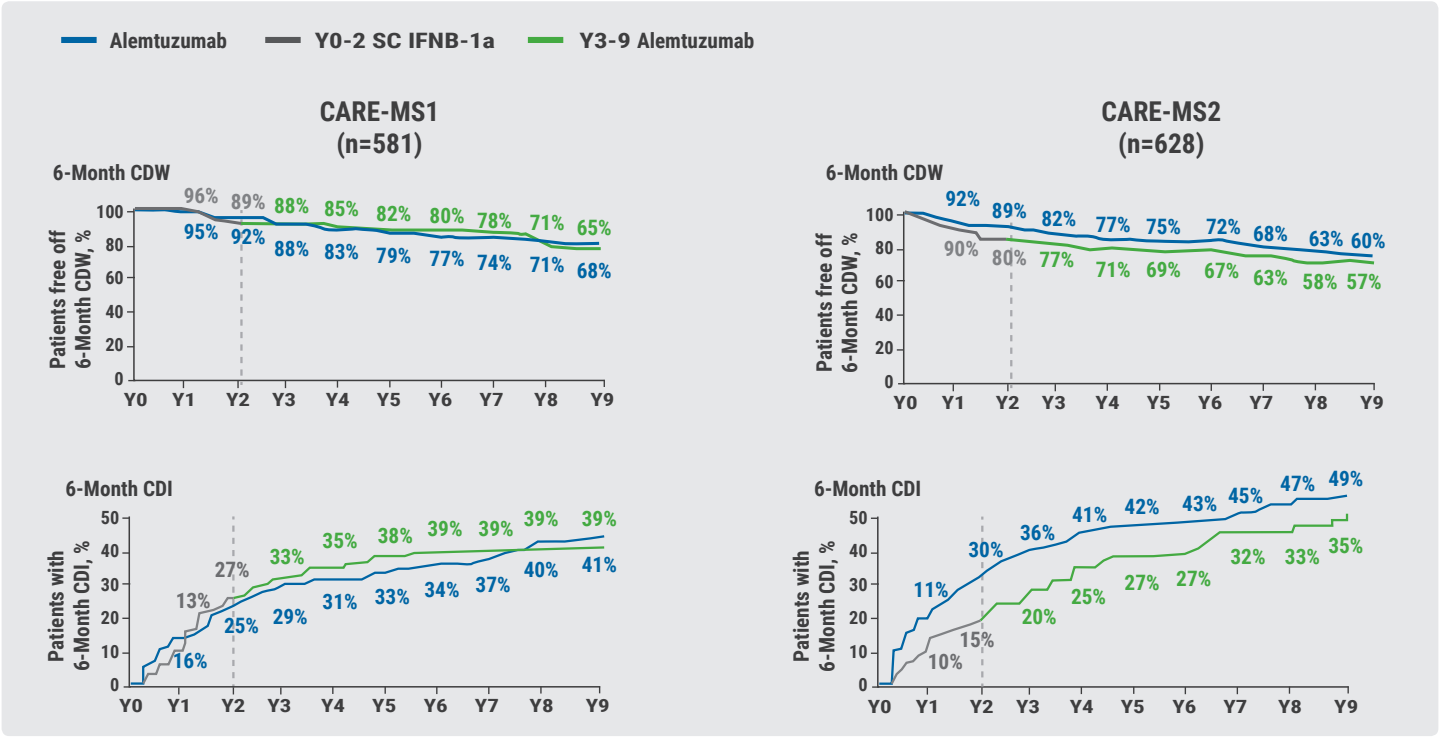
1. Brown JWL, et al. JAMA. 2019;321:175-187.
2. Harding K, et al. JAMA Neurol. 2019;76:536-541.
3. Coles A, et al. ECTRIMS 2019, abstract P651.
4. Montalban X, et al. ECTRIMS 2019, abstract P974.
5. Comi G, et al. ECTRIMS 2019, abstract P645.

Treatment escalation over induction therapy

Dr Emmanuelle Waubant (University of California, San Francisco, CA, USA) discussed why treatment escalation is the preferred principle over induction therapy.

With respect to long-term outcomes in MS, there is a lot of heterogeneity. Patients can have different clinical and anatomical relapse locations, as well as different relapse frequency, severity, and recovery. Up to 20% of patients have "benign" disease, defined as having an EDSS ≥2.0 after 10-year duration. Although untreated MS may shorten life span by 6 years on average, many patients on moderately effective disease-modifying treatments (DMTs) have good outcomes in the long term. For example, it was shown that 69.8% of patients with clinically isolated syndrome on IFN-beta had EDSS <3.0 by year 11 [1].

Figure 2. Disability data of 9-year extension studies of CARE-MS1 and CARE-MS2 [4,5].



Several clinical and MRI characteristics at onset predict poor outcome in cohorts, but not always in individual patients. Very little is known about the long-term safety and efficacy of oral and intravenous induction therapies. "For the treatment of classical MS, there is consensus that you have to start the therapy early, using either injectable or oral therapies", Dr Waubant told. "Escalation is a very reasonable strategy, when there is breakthrough either clinically or on the MRI. In severe MS, early aggressive treatment using monoclonal antibodies is recommended."

Progression and safety

IFN-beta, glatiramer acetate, and fingolimod were recently shown to decrease the risk of progression to secondary progressive MS, especially if initiated within 5 years of onset, Dr Waubant mentioned (HR 0.77; P=0.03; 5-year absolute risk of 3% vs 6% after follow-up of median 13.4 years) [2]. "So, early intervention is key. A nice meta-analysis has clearly shown reduced disability progression based on EDSS" [3]. Furthermore, recently published analyses showed that early escalation was associated with lower lifetime cost per patient, prolonged quality-adjusted survival, and longer median time to sustained increased disability [4,5].

In the short-term, there is an increased risk of auto-immune complications after initiating alemtuzumab. IFN-beta, glatiramer acetate, fingolimod, dimethyl fumarate, and natalizumab have all shown a good safety profile (if JC-virus-negative). There is limited long-term data (i.e. >5 years) for haematopoietic stem cell therapy (HSCT), alemtuzumab, ocrelizumab, and cladribine.

In contrast: induction therapy

Induction therapy often means first-line treatment with the goal of increasing the rate of complete remission. However, no currently available MS drug induces complete remission. Rates of no evidence of disease activity (NEDA) are quite low, according to Dr Waubant. Natalizumab was associated with 34% NEDA at year 2, alemtuzumab with 40% NEDA at year 5, and autologous HSCT (open label) with 60% NEDA at year 5. Patients who achieve NEDA often have a less active initial disease, whereby induction therapy was not needed [6]. Prior informative studies did not involve early MS, had a relatively short follow-up (<3 years) and small sample size, and were not always randomised with a control group. On top of this, they focused on early effect, not what happened years after discontinuing treatment.

Early initiation of traditional DMTs is effective and safe for most patients with clinically isolated syndrome or relapsing-remitting MS. Carefully monitoring these patients clinically and with yearly MRI is important to detect possible breakthrough. In case of disease activity, early escalation using more effective agents has proven beneficial. Data on true induction therapy with long-term safety and efficacy are not yet available.

1. Kappos L, et al. Neurology. 2016;87:978-87.
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3. Signori A, et al. Mult Scler Relat Disord. 2016;6:57-63.
4. Furneri G, et al. BMC Health Serv Res. 2019;19:436.
5. Harding K, et al. JAMA Neurol. 2019;76:536-541.
6. Prosperini L, et al. J Neurol Sci. 2016 May 15;364:145-7.

Influence of age on disease progression

Patients with paediatric-onset MS (POMS) have initially slower disability progression rates [1], but higher relapse rates compared with adult-onset patients [2,3]. An important outstanding question is: What is the impact of age at DMT start on time to first relapse and time to first confirmed EDSS progression across the full age spectrum? Factors that need to be taken into account are gender, year of DMT start, type of DMT, pre-DMT relapses, EDSS, time since first MS symptom, and MS severity score [4]. Dr Viktor von Wyl (University of Zurich, Switzerland) tried to answer this question using the Swiss Association for Common Tasks of Health Insurers database which contains data from 14,718 MS patients who initiated their first DMT between 1995 and 2017 (69% women; 85% relapsing-remitting MS; mean age 39±11.5 years; disease duration 6±8 years; 80% IFN-beta or glatiramer acetate) [5].

Data from 9,705 MS patients were eligible for this analysis. The association between age at disease onset and EDSS progression had a sigmoidal shape: EDSS progression hazard remained stable in patients with disease onset from early childhood to about 32 years; then increased sharply around the age of 45 years; and afterwards remained stable at a relatively high level [6]. In contrast, the association between age at disease onset and relapse risk was almost linear: the risk for relapse was highest at younger ages and decreased continuously from childhood to around 35 years of age. For example, a 20-year old patient with first symptoms of MS had a 1.5-fold higher risk for relapse on DMT than a 38-year old patient, after adjustment for other factors (gender, relapse-activity before DMT initiation, EDSS, pyramidal functional system score, and MS severity score). Risk of relapse remained constant for a decade and then continuously decreased from age 45 years onwards.

So, age at DMT start is an important factor affecting relapse and confirmed disability progression, independent of other characteristics and possibly type of DMT. Age at first symptom onset and disease duration are also relevant and correlated with age at DMT start. The age between 37 and 40 years seems critical with regard to the compensation of damage in the central nervous system caused by MS. Patients older than 40 years who start with a DMT have a higher risk of disability progression, when controlling for important clinical disease characteristics [6].

1. Renoux C, et al. N Engl J Med. 2007;356:2603-13.
2. Benson LA, et al. Mult Scler Relat Disord. 2014;3:186-93.
3. Gorman MP, et al. Arch Neurol. 2009;66:54-9.
4. Roxburgh RH, et al. Neurology. 2005;64:1144-51.
5. Lorscheider J, et al. Mult Scler. 2018;24:777-785.
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Exposure to DMTs reduces disability progression

Recent real-world findings of the Italian MS Registry E-MUSIC suggest the existence of different impactful periods of intervention [1]. There was an apparent higher impact for paediatric onset (POMS ≤18 years) and adult onset MS (AOMS 18-49 years), and a lower -but still detectable- impact in late onset MS (LOMS ≥50 years). So, age is a critical factor in the evaluation of benefit-risk ratio in the decision-making process regarding treatment initiation and outcome.

Age at onset is one of the factors that can predict evolution of MS or risk of disability accumulation over time. In clinic- and population-based studies, the onset of the progressive phase is seemingly age-dependent [1-3]. The earlier the onset of the disease, the younger the age at which various landmarks are reached. The effectiveness of disease-modifying treatments (DMTs) on reducing disability worsening decreases with age.

A real-world analysis from the Early MS Italian cohort (E-MUSIC), presented by Dr Mattia Fonderico (University of Florence, Italy), evaluated how the traditional prognostic predictors vary in 3 subgroups of relapsing MS patients defined by age at onset: POMS (n=646), i.e. age ≤18 years; AOMS (n=8,473), i.e. age 18-49 years; and LOMS (n=448), i.e. age ≥50 years [4]. DMTs reduced the risk of CDP in all the cohorts. This appeared to be related to the cumulative exposure to DMTs in a dose-dependent manner, with progressive risk reduction in different quartiles of exposure. The risk ratios for disability progression at 3 months in non-exposed versus exposed >62% of the time in the 3 age groups were: POMS 8.1; AOMS 6.7; and LOMS 7.5 (P<0.0001) [4]. Results were consistent for CDP at 12 months in POMS and AOMS. Relapses, considered as time-dependent covariate, were a risk factor for 3- and 12-month CDP in POMS (HR 2.5; P=0.002) and AOMS (HR 1.3; P<0.0001) but not in LOMS (HR 0.98) [4].

The current, real-world data from the Italian MS Registry suggests that DMTs can reduce the risk of irreversible disability progression. In different quartiles of exposure, risk reduction was related to the cumulative time spent under therapy. In all 3 cohorts, untreated patients were at higher risk of disability progression, independent of their age of onset [4].

1. Kantarci OH. Continuum (Minneap Minn). 2019;25:636-654.
2. Scalfari A, et al. Neurology. 2011;77:1246-52.
3. Tedeholm H, et al. J Neurol. 2015;262:1148-63.
4. Fonderico M, et al. ECTRIMS 2019, abstract 303.

Predicting long-term sustained disability progression

The ultimate treatment goal in MS is to prevent disability over the long term. However, randomised clinical trials (RCTs) usually evaluate short-term effect of therapies on disability, in the form of confirmed disability progression (CDP) after 3 and 6 months. Additionally, CDP events overestimate the accumulation of irreversible disability by up to 30% [1]. Changes in bowel and bladder function, and in pyramidal, cerebellar, and cerebral domains contribute more to confirmed EDSS worsening than other neurological domains [2].

Using the global MSBase registry, Prof. Tomas Kalincik (University of Melbourne, Australia), studied 6-month CDP events as indicators of long-term disability worsening. A total of 11,435 CDP events were identified in 6,902 patients.

This study showed that CDP can be defined in more detail at the occurrence of a CDP event. A low probability of recovery from a CDP event is associated with several factors, such as older age, male sex, progressive disease course, no recent MS relapse preceding the event, higher EDSS or greater change in disability, number of affected neurological domains, and worsening in pyramidal and cerebellar domains.

CDP events can be stratified with respect to their likelihood of being sustained in the long term. This approach can be applied using data that are routinely acquired in trials, thus enabling reanalysis of previously completed RCTs [3].

1. Kalincik T, et al. Brain. 2015;138(Pt 11):3287-98.
2. Stewart T, et al. Mult Scler. 2017;23:266-276.
3. Sharmin S, et al. ECTRIMS 2019, abstract 304.

Treatment response scoring systems to assess long term prognosis

DMTs may influence the natural history of MS [1]. "It is important to provide our patients information about long-term prognosis, during the first months of therapy", Dr Jordi Río (University Hospital Vall d'Hebron, Barcelona, Spain) advised. Although different scoring systems have been used in the assessment of response in the short-term, little data exists regarding the long-term predictive power of these scores [2,3]. There is evidence that MRI activity, relapses, and EDSS worsening are good predictors of short-term treatment response, i.e. during the first 2-3 years after initiation of therapy [4]. Based on these clinical and imaging parameters, several scoring systems have been developed. Dr Río and colleagues compared different treatment response scoring systems to assess long-term prognosis in treated relapsing-remitting MS patients (n=319), and to describe diagnostic properties of the different scores.

Prediction model analysis showed that all scoring systems could significantly identify patients with an EDSS of 6 after 10 years of follow-up. Survival analysis showed that patients with a Rio score >1, modified Rio score >0, ROAD score >3, and MAGNIMS score >0 had a significant probability of achieving an EDSS of 6.0. The ROAD score showed the best sensitivity (85%), whereas the modified Rio score showed the best specificity (88%). The Rio score showed the best positive predictive value (42%), and the ROAD score the best negative predictive value (94%). Finally, the Rio score demonstrated the best accuracy (81%) [5].

These data reinforce the concept of early treatment optimisation in order to minimise the risk of long-term disability. Data regarding the role of these sources in patients receiving non-injectable drugs are needed.

1. Trojano M, et al. Ann Neurol. 2007;61:300-6.
2. Río J, et al. Mult Scler. 2018;24:322-330.
3. Gasperini C, et al. Neurology. 2019;92:180-192.
4. Río J, et al. Mult Scler. 2009;15:848-53.
5. Río J, et al. ECTRIMS 2019, abstract 305.

Late-breaking: Ofatumumab versus teriflunomide in relapsing MS

Ofatumumab is the first fully human anti-CD20 mAb, which is under development for the treatment of MS. Ofatumumab binds to CD20, resulting in B-cell depletion and reduced B- and T-cell interactions, which may reduce inflammation in the central nervous system. Anti-CD20 therapy may preserve pre-existing humoral immunity and B-cell reconstitution [1].

Two phase 3 trials, identical in design and conducted in parallel, ASCLEPIOS I and II (n=1,881 totally), evaluated the effect of ofatumumab in patients with relapsing MS. Ofatumumab demonstrated significant reduction of adjusted annualised relapse rate (ARR):

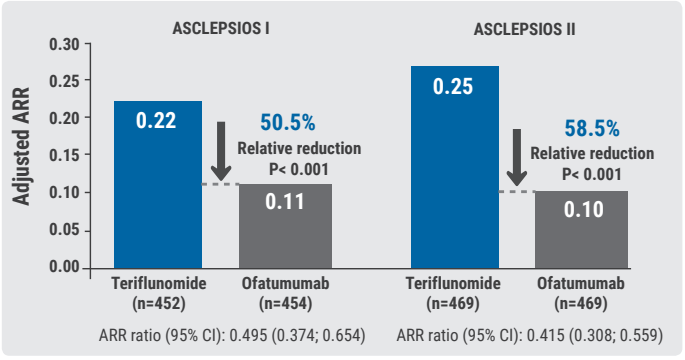
- ASCLEPIOS I: 0.22 in teriflunomide group vs 0.11 in ofatumumab group (relative reduction of 50.5%; P<0.001);
- ASCLEPIOS II: 0.25 in teriflunomide group vs 0.10 in ofatumumab group (relative reduction of 58.5%; P<0.001, Figure) [2].

Furthermore, ofatumumab showed a significant reduction in 3- and 6-month confirmed disability worsening (CDW) and a favourable, but non-significant trend to achieve 6-month confirmed disability improvement (CDI):

- 3-month CDW: 15.0% in teriflunomide group vs 10.9% in ofatumumab group (relative reduction of 34.4%; P=0.002; HR 0.656);
- 6-month CDW: 12.0% in teriflunomide group vs 8.1% in ofatumumab group (relative reduction of 32.5%; P=0.012; HR 0.675); and
- 6-month CDI: 8.1% in teriflunomide group vs 11.0% in ofatumumab group (relative increase of 35.2%; P=0.094; HR 1.352) [2].

The ASCLEPIOS I and II trials demonstrated, in a broad population of patients with active, somewhat advanced relapsing MS, that ofatumumab has superior efficacy compared with teriflunomide in lowering relapse rates and MRI activity. Treatment with ofatumumab leads to substantial and significant reductions in 3- and 6-month CDW, and to lower levels of neurofilament light chain (NfL) already at month 3 and at all subsequent visits. Ofatumumab also had a favourable safety profile with no unexpected safety signals. There was no imbalance in the rates of infections or malignancies (low on both arms of the trial).

Figure. Ofatumumab demonstrated significant reduction in ARR (primary endpoint in full analysis set) [2]



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Safety Assessment in the Post-Approval Phase

Use of clinical registries in phase 4 of DMT

At the time of authorisation, information on the safety of a medicinal product is relatively limited. This is due to the conditions in which in clinical trials are performed when compared with real life, including a smaller number of subjects, restricted population in terms of age (usually no children and older people), gender and ethnicity, restricted co-morbidity, co-medication, conditions of use, and relatively short duration of exposure and follow-up. Therefore, phase 4 research is very important.

The first step in phase 4 research is pharmacovigilance, i.e. the detection, assessment, understanding, and prevention of adverse events and other medicine-related problems. "The problem with pharmacovigilance is that it mainly relies on spontaneous identification", Prof. Sandra Vukusic (Lyon University Hospital, France) mentioned. "Usually, pharmacovigilance research is very time-consuming. Furthermore, it is limited by reporting bias." These challenges led to the introduction of risk-management plans by the EMA, a second step in phase 4 research. These plans are designed to identify, characterise, and prevent or minimise risks related to medicinal products, including the assessment of effectiveness. The next step comprises the secondary use of registry data. The rationale is to increase in the number of post-approval safety studies. "This is very time consuming, but, investigators have limited time." Secondary use of registry data mostly means the application of data collected in routine clinical practice for all patients. This could fill the requirements of each individual risk-management plan on safety, efficacy, good use, and risk/benefit balance. Furthermore, phase 4 research is useful to mutualise human, financial, methodological, and technical means. The protocols of these studies can be designed collaboratively with health authorities, academics, and industry. An important aspect of phase 4 research is to reassure the quality of the data.

Alignment of research worlds

Compared to traditional post-marketing studies, the number of patients is much higher in drug registries (see Table). "Furthermore, in post-marketing studies, patients are selected, but for example children are excluded because age <18 years is an exclusion criteria in such studies. However, we need information about those patients", Prof. Vukusic emphasised. "That is the case in registry studies, which deliver long-term data." A shortcoming of registries is that there might be more patients lost to follow-up and missing data. The regulators in Europe are very interested in using registry data. This led to the publication of a discussion paper regarding the use of patient disease registries for regulatory purposes in November 2018 [1].

Table. Characteristics of clinical trials, traditional post-marketing studies, and drug registries

	Clinical trials	Traditional post-marketing studies	MS drug registries
Phase	Pre-marketing	Post-marketing	Post-marketing
Driven by	Industry +++	Industry +++ Health authorities/ Academics +	Academics +++ Health Authorities/ Industry +
Number of patients	Limited (hunderds to 1-2 thousands)	Extended (several thousands)	Tend to exhaustivity
Type of patients	Highly selected	Selected	"Real life settings"
Co-treatments	0	+	+
Co-morbidities	0	+	+
Age groups	0	±	+
Pregnancy	0	+	+
Duration	Short term (2-4 years)	Mean term (5 years)	Long term (not limited)
Lost to follow-up and missing data	±	+	++
Efficacy	+++	+	+
Safety (detection of adverse events)	+++	+++	+++
Frequent AE	+++	+++	+++
Rare AE	+	++	+++

BigMSData registry

The BigMSData registry initiative started in 2011. "Between 2012 and 2016, we had a large pilot phase with 5 MS registries from Italy, Sweden, Denmark, France, and the international MSBase", Prof. Vukusic added. In a feasibility phase, the differences and commonalities among the 5 registries were evaluated. Afterwards, it was decided to standardise the definitions and procedures, to ensure the possibility of merging data from different sources. Initially, 3 projects were proposed to validate the feasibility of pooling data:

- Impact of early treatment on long-term disability in relapsing-remitting MS patients [2];
- Treatment discontinuation in the BigMSData Network, a descriptive analysis, presented at ECTRIMS 2018 [3]; and
- Use of DMTs in the progressive phase (ongoing study by H. Butzkueven et al.).

"Because the quality of the data was good, it was possible to pool them", Prof. Vukusic continued. "We can work together, so we can answer questions which we cannot answer using only our own data." The next step was to create a core study protocol, aimed to assess and characterise the risk of certain safety events in MS patients who were exposed and unexposed to approved DMTs for the treatment of MS, by collecting serious adverse events in specific disease registries. An increasing number of DMTs are currently available, but, are yet to undergo post-approval safety studies. Several MS registries are currently mature, according to Prof. Vukusic. This includes the BigMSData network, which is open to other national registries in the future. There is a favourable context with an EMA initiative on disease registries and pharma agreeing to collaborate. "The direction is towards a more active, but less time-consuming participation of MS neurologists to the risk/benefit assessment of DMTs in the future."

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3. Spelman T, et al. ECTRIMS 2018, abstract P1195.

Genes, environment, and safety monitoring in using registries

"For an MS registry to be useful, it should deliver a clinical tool for the day-to-day care of individual patients", stated Prof. Tomas Olsson (Karolinska Institute, Sweden) at the beginning of his lecture. Compliance with entering data into the MS registry depends on the benefit for the clinician and the person with MS. Registries are a tool for quality assessment and development of MS care. Nationwide data obtained can be used for numerous research purposes.

The interface of the Swedish MS registry shows the "whole evolution of a certain patient", Olsson continued, "such as the EDSS course and the different drugs given." This has led to a widespread use of these rates in Sweden, with 17,397 of 20,500 current MS patients included (85% coverage). The data are used for research in genetics, neuroimmunology, epidemiology, post-marketing follow-up, and biobanks [1]. Subsequently, Prof. Olsson mentioned some selected examples of research projects using the Swedish MS registry as a platform. After the introduction of natalizumab and knowing the influence of JC virus on progressive multifocal leukoencephalopathy (PML) risk, he started the Immunomodulation and MS Epidemiology (IMSE) studies. "Since then, a lot of new drugs have come to the market, so post-marketing surveillance was warranted. Furthermore, several genetics, lifestyle, and environmental factors in MS (EIMS) studies are based on the Swedish data."

Genetics, lifestyle, and environmental factors

The pathophysiological cascade of MS is characterised by many factors. "We need precise knowledge on causes of MS to provide prevention and more precise therapy. This has been a neglected area", according to Prof. Olsson. This includes risk genes, lifestyle, and environmental factors, and the interactions between them [2]. Lifestyle and environmental factors have a modest influence (odd ratios of approximately 1.5-2), although their influence is mostly higher compared to the influence of non-HLA genes (ORs of approximately 1.1-1.2). Some factors act during adolescence and early adulthood, such as Epstein-Barr virus (EBV), obesity, brain concussion, and disturbed diurnal rhythm. Many factors interact with MS risk genes; all factors can be argued to act on the immune system.

Further research on the aetiology of MS is warranted to achieve prevention and more selective therapy. Perhaps there should be new emphasis on the adaptive immunity, including ways to define specificities and functions to auto-aggressive T and B cells. The combination of genetics and epidemiology may lead us into testable hypotheses, as exemplified by the interaction between smoking and HLA genes. Thus, combined studies are warranted. Upcoming genetics research should take environmental exposures into account; upcoming epidemiology research should take genetics into account.

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Risk of hypogammaglobulinemia and rituximab

Rituximab, an anti-CD20-therapy that depletes B cells with high efficacy and tolerability, is used off-label for MS (in Sweden) [1]. From studies in rheumatology [2] and in other autoimmune diseases, such as neuromyelitis optica spectrum disorders [3], hypogammaglobulinemia is a well-known side effect associated with rituximab which can lead to treatment discontinuation and susceptibility for infections.

Dr Susanna Hallberg (Karolinska Institute, Sweden) and colleagues investigated the risk of developing decreased levels of IgG and IgM during long-term treatment with rituximab in MS patients (n=1,933). They found that the risk of hypogammaglobulinemia is an important side-effect in long-term treatment with rituximab in MS, which is consistent with previous findings in other autoimmune diseases [2,3].

The main predictors for treatment-induced Ig decrease were total accumulated dose of rituximab, treatment duration, and

initial level of IgG. IgG levels decreased significantly in women during rituximab treatment. Furthermore, previous immune-modulatory treatment influenced initial IgG. Therefore, Dr Hallberg thinks that IgG and IgM levels should monitored regularly [4].

Finally, she suggested some treatment options for anti-CD20-induced hypogammaglobulinemia:

- Longer intervals or dose reduction of rituximab;
- Treatment discontinuation with clinical and MRI assessment, or consider other DMTs than anti-CD20 therapy;
- Regular follow up of patients with low IgG levels after cessation of rituximab [4].

Dr Hallberg advocated against using a continuous treatment in case of a trend towards lower levels of IgG. Intravenous Ig (IVIg) substitution is recommended in case of severe hypogammaglobulinemia (<4.0 g/L; or <6.7 mg/L in patients who are suspectable to infections). It is not known whether rituximab-induced hypogammaglobulinemia is reversible or not [4].

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2. van Vollenhoven RF, et al. Ann Rheum Dis. 2013;72:1496-502.
3. Marcinnò A, et al. Neurol Neuroimmunol Neuroinflamm. 2018;5:e498.
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Determinants of outcomes for natalizumab-associated PML

Natalizumab is an effective treatment for patients with active MS, but is associated with an increased risk of progressive multifocal leukoencephalopathy (PML) [1,2]. "We are concerned as clinicians about PML risk and how to manage it", Prof. Chris McGuigan (University College Dublin, Ireland) stated.

Following a diagnosis of PML, various interventions, such as rapid natalizumab clearance by plasma exchange (PLEX), have been adopted in clinical practice [3,4]. PLEX is associated with increased clearance of natalizumab [5]. "However, the impact of PLEX on clinical outcomes was based on pharmacokinetic data and not on clinical evidence or real-world experience", Prof. McGuigan added.

In the current analysis, the impact of PLEX and patient characteristics on the outcome of natalizumab-associated PML was investigated. Of the 787 confirmed natalizumab PML cases, 725 had a known PLEX status (PLEX-positive in 85.0%). A higher percentage of PLEX positive patients than PLEX-negative patients were symptomatic at diagnosis (87.8% vs 78.9%) and had a high JC virus viral copy number (33.3% vs 17.4%). The cumulative probability of survival 2 years post-PML diagnosis for PLEX-positive vs PLEX-negative patients was 88.2% vs 89.3% (P=0.857). Death within 2 years was less likely for patients who were asymptomatic (HR 0.38; P=0.012); and more likely for patients aged >50 years (HR 1.56; P=0.014), with widespread MRI lesions (HR 1.61; P=0.007), or higher JC virus load (HR 2.86; P< 0.001) [6].

It should be noted that pharmacovigilance data has some limitations. "This dataset was entirely dependent on physicians providing the data", Prof. McGuigan mentioned. "We had missing data in terms of EDSS scores at baseline and after the confirmed diagnosis of PML." Furthermore, there is possible indication bias secondary to lack of baseline EDSS data, whereby patients with more severe functional impairment pre-PML might be more likely to receive PLEX. For PLEX-positive (n=177) and PLEX-negative (n=31) patients who had an EDSS score reported in the 6 months before PML diagnosis, the median EDSS score was 3.5 in both groups. "We also included all-cause mortality in the study", Prof. McGuigan added. "So, we can not specify whether the cause of death was the PML itself or another cause, such as immune reconstitution inflammatory syndrome (IRIS) or recurrence of the MS itself." Due to limited data, it is not known whether the severe disability impairment in survivors was transient or long lasting. Finally, the potential impact of DMT use in the post-PML phase in patients with functional data is not accounted for [6].

In conclusion, even though the majority of patients with natalizumab-associated PML received PLEX, this analysis showed no beneficial effects of PLEX on PML outcomes. PLEX treatment did not have a significant effect on 2-year survival rates. The risk of advanced disability or death appeared to be worse in patients who received PLEX, but missing data and selection biases may have contributed to these findings. Consistent with prior analyses [7,8], asymptomatic detection, more localised MRI lesions, and fewer copies of JC virus were associated with better PML outcomes. These data support early, vigilant monitoring for PML as an important component of improving post-PML outcomes.

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Serum immunoglobulin levels and risk of serious infections

Patients with MS have a higher risk of infections and hospital admission rates for infection compared with the general population [1]. The risk of serious infections is influenced by diverse factors, such as age, body weight, comorbidities (e.g. diabetes), disability level, concomitant treatments (e.g. steroids), and neutrophil and lymphocyte count [1,2]. "This is true for the general population, but also for MS patients", Prof. Tobias Derfuss (University Hospital Basel, Switzerland) mentioned. Immunoglobulins also play a major role in adaptive immunity. The risk of certain types of infection is increased when immunoglobulin levels are low [3]. Reduced blood concentration of IgG, IgM, and/or IgA is known to occur in patients treated with B-cell-depleting therapy, including ocrelizumab [4,5].

In clinical trials evaluating ocrelizumab in MS patients, infections were one of the most frequently reported adverse events. In phase 3 trials, rates of serious infections were low, and there was no increased risk compared with IFN-beta-1a and placebo observed. In an open-label extension analysis of the OPERA I and II and ORATORIO trials, evaluating patients with relapsing-remitting MS and primary progressive MS respectively, Prof. Derfuss and others assessed serum Ig levels over 5.5 years and evaluated a potential association between a decrease in IgG, IgM, or IgA levels and serious infections.

Over 5.5 years of ocrelizumab treatment, the reduction in serum levels (relative reduction from baseline to 264 weeks) were:

- In relapsing MS: IgG, 17.0%; IgA, 21.3%; and IgM, 58.1%;
- In primary progressive MS: IgG, 16.9%; IgA, 20.5%; IgM, 56.3% [6].

At week 264, the proportions of patients reaching IgG, IgA, and IgM levels under the lower limit of normal (<LLN) were 5.7%, 5.4% and 29.2%, respectively.

After approximately 6 years of ocrelizumab exposure, rates of serious infections remained low and consistent with rates of infection-related hospitalisations in real-world MS cohorts. Overall, 14 serious infections occurred during a drop in IgG levels <LLN (6.50 adverse events per 100 patient years), which was higher compared with IgG levels ≥LLN (2.11 adverse events per 100 patient years). A reduction in serum Ig levels was observed at an approximate mean rate of 3-4% per year for IgG, but for the majority of patients, Ig levels remained above LLN. "IgM levels dropped quite fast, while the drop of IgG took a lot longer", Prof. Derfuss added. There is an apparent association between decreased levels of IgG (and less so for IgM or IgA) and serious infections, but overall incidence was low. The majority of serious infections following episodes of decreased Ig levels <LLN were urinary tract infections, cellulitis and pneumonia. Most infections resolved with standard of care, and in most cases patients remained on ocrelizumab treatment [6].

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EAN guideline on palliative care

Optimising the care of people with severe MS is hindered by fragmented and varied care across Europe. The availability and involvement of palliative care services also vary between and within European countries. A guideline was devised by a task force appointed by the European Academy of Neurology in partnership with the European Association for Palliative Care (EAPC) and the European network for best practice and research in MS Rehabilitation (RIMS) [1].

From a literature search, expert survey, and direct engagement of MS patients and caregivers from seven European countries, 10 clinical questions were formulated about the following topics:

1. Symptomatic treatments;
2. Multidisciplinary rehabilitation;
3. Advanced care planning;
4. General palliative care;
5. Specialist palliative care;
6. Caregiver training and education;
7. Caregiver practical and emotional support;
8. MS healthcare professionals' training/education in palliative care;
9. Palliative care healthcare professionals' training/ education in MS care; and
10. Discussion with healthcare professionals about the wish of hastening death.

Dr Alessandra Solari (Carlo Besta Neurological Institute, Italy) and co-authors found no studies related to only 4 of these 10 questions. Meta-analysis was possible for 1 question (symptom management) and individual participant data meta-analysis for 2 questions (general and specialist

palliative care). Of ten publications on palliative care, three were randomised controlled studies and one qualitative study. Of these, two compared home-based specialist palliative care to usual care, and one compared home-based general palliative care to usual care [2].

Recommendations about palliative care and hastened death discussion were:

- People with severe MS should be offered home-based palliative care, either by healthcare professionals with good basic palliative care skills and knowledge (general palliative care) or a multi-professional team of palliative care specialists (specialist palliative care).
- People with severe MS should be offered in- or outpatient palliative care. Patient preference, conditions, and availability of palliative care services should be taken into account.
- MS patients should be encouraged to discuss their wishes about future care, including the restriction of treatment or interventions and the wish of hastened death.
- Healthcare professionals should be aware of the risk factors for the wish of hastened death, including depression, isolation, restricted abilities, and encourage the discussion of these issues and the appropriate management.

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Pregnancy in the Treatment Era

The maternal perspective: when to stop/ resume treatment and risks for progression

Over the last few decades, pregnancy decision-making in MS (Table) has become increasingly challenging, as mentioned by Dr Emilio Portaccio (University of Florence, Italy), "We have to deal with different disease- and patient-related factors". In his talk, he focused on the treatment decisions in relation to maternal risks of progression during and after pregnancy.

To determine when to stop and when to resume MS treatment, it is important to consider the disease course during and after pregnancy. The European multicentric Pregnancy in Multiple Sclerosis (PRIMS) study, which was conducted in the period before the introduction of disease-modifying drugs (DMTs), clearly showed that disease activity reduced during the gestational period (P=0.03) and increased thereafter, particularly during the first trimester postpartum [1].

Since the publication of the PRIMS study, several DMTs have been introduced (Table). "With respect to disease course and maternal risk of progression during pregnancy, that risk is generally limited for the newer drugs", Dr Portaccio said. "These drugs may be valuable as first-line therapies, particularly the injectables, and among the high-efficacy therapies, natalizumab." Several studies showed that disease activity during and after pregnancy was reduced in patients receiving first-line therapies, in comparison with the observations in the previous PRIMS study. Therefore, early DMT resumption should be encouraged, particularly in patients with a more active disease [3].

Table. DMTs for the treatment of relapsing-remitting MS [2]

First-line therapies		High-efficacy therapies	
Injectables	**Oral agents**	**Infusions**	**Oral agents**
Glatiramer acetate IFN-beta1a IFN-beta1b PEG-IFN-beta1a	Dimethyl fumarate Teriflunomide	Alemtuzumab Natalizumab Ocrelizumab	Cladribine Fingolimod

Postpartum period

The postpartum period is a critical phase in which disease reactivation is expected. "Treatment should be aimed to prevent disease reactivation", Dr Portaccio advised. "We should take into account possible predictors of disease reactivation after delivery. The occurrence of relapses during pregnancy is found to be associated with a higher risk of disease reactivation after delivery. Interestingly, in the Italian pregnancy dataset [3], early restart of disease therapy after delivery reduced the risk of relapses after pregnancy." However, it was also stated that disease activity after pregnancy is not limited to relapses. "Although the median disease activity (EDSS score) remains stable before and after pregnancy, at the individual level, 13% of patients were observed to have progression of disability

after 1-year follow-up [3]. This progression was related to higher disease activity before pregnancy and the occurrence of relapses during the year before delivery." However, published literature to-date reveals that more studies report no effect of pregnancy on MS disability than those reporting reduced disability or a delay in progression. One of the major limitations is the possibility of reverse causality, i.e. women with more aggressive disease may choose not to conceive due to concerns about their current symptoms, disability, or choice of treatment during pregnancy [4].

In conclusion, pregnancy should be planned after a period of clinical stability, i.e. no relapses in the year before conception. "Next, we should consider risk of postpartum disease activity: relapses before pregnancy, relapses during pregnancy, and higher disability level. Particularly in high risk women, continuation of therapy until conception or during gestational period and early restart of therapy after delivery are recommended."

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Foetal/child perspective: risks related to drug exposure and breastfeeding

In general, around 60% of pregnant women take prescribed medication during pregnancy, 50% during the first trimester, with even more patients using over-the-counter medication. For most drugs, it is known whether they are safe for the foetus or not. However, data is lacking for MS treatments specifically. Fortunately, teratogenic effects have only been demonstrated with 30 treatments in humans, some of which are used in neurology, such as the anti-epileptic drug valproic acid, and some off-label use of the neuroimmunological agents mycophenolate mofetil and methotrexate.

MS drugs and pregnancy

Specific treatments are relatively new in MS, with the first drugs approved "only" 30 years ago, and the last drug in 2017. In the publications regarding the use of DMTs during pregnancy, the sample sizes are much larger for patients who had first trimester exposure compared to those with exposure throughout pregnancy. The former meaning: becoming pregnant, taking a pregnancy test, and then stopping medication. "This is what generally happens", Dr Kerstin Hellwig (Ruhr-Universität Bochum, Germany) stated. "Most data we have is for IFN-beta and glatiramer acetate, with several thousand pregnancies evaluated. Both drugs have the best safety profile. We are awaiting a new EMA label. Dimethyl fumarate seems to have a good safety profile, but only 300 pregnancies have been analysed. Recently, the EMA published an updated restriction to use fingolimod during pregnancy [1]. So far, no teratogenicity is found for teriflunomide in humans, but data is missing." With respect to the monoclonal antibodies (mAb) and cladribine, a lot of data is still missing, especially with the newer drugs. Despite a lack of data, Dr Hellwig argues to opt for depleting antibodies, at least in patients with highly active MS, "because they have a long-lasting effect. This might also be true for cladribine." In patients with highly active disease who became pregnant on natalizumab, she advises to consider continuing natalizumab. "In the case of stopping natalizumab, there might be a risk of rebound, but the exact magnitude of the rebound risk, especially of severe rebounds, is not known yet. There might be the possibility to continue natalizumab, but then there is a risk for haematological abnormalities in the baby and there might be an aberrant birth weight." Therefore, it is advised to stop treatment in gestational week 34 and check haematology. Dr Hellwig concluded that none of the current MS drugs justifies an elective termination of pregnancy per se.

Breastfeeding

It is recommended by the WHO that women breastfeed, and Dr Hellwig thinks that more women using MS medication should be recommended to breastfeed. "At least for mild MS, there is no reason to believe that breastfeeding is harmful. A systematic review published a couple of years ago [2], that is also supported by more recent data, showed that breastfeeding is not harmful. Women who want to breastfeed, should be supported to do so."

She advised that not all MS patients need medication during or after pregnancy, meaning that they can safely breastfeed. But breastfeeding should also not be discouraged in favour of resuming MS medications in most women. The size of a molecule mainly determines if it enters the breastmilk, so there is the possibility to choose treatments compatible with breastfeeding (injectables and mAbs), even in patients with highly active MS. With respect to the oral DMTs, cladribine is the first drug which advises on the label that breastfeeding is safe 1 week after the intake of the last tablet. If a woman does not want to breastfeed, Dr Hellwig advised to begin with MS treatment early after delivery (after 7-14 days), especially in cases of active disease. More data on breastfeeding under medication and a longer follow up of exposed children is needed.

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Patient awareness about family planning represents a major knowledge gap

For patients with MS, family planning is important. According to the definition of the WHO, family planning allows individuals and couples to anticipate and attain their desired number of children, and the spacing and timing of births. Family planning is achieved through use of contraceptive methods and treatment of involuntary infertility. "It is good to consider that", Prof. Marie D'Hooghe (National MS Center, Belgium) said. "However, family planning is planning the future. How can we plan the future, if someone is diagnosed with MS?"

Reproductive decisions

When people are diagnosed with MS, it comes with a great deal of uncertainty, Prof. D'Hooghe emphasised. "They don't know what is going to happen. They have to redefine their personal identity and modify their lifestyle (e.g. smoking and diet). Furthermore, they have to consider MS treatment and take into account factors such as way of administration, side effects, complications, and teratogenicity.

Family planning appears to be a major knowledge gap for patients. An online survey in Denmark (n=590) showed that 10% of men and women with MS indicated that there were unplanned pregnancies on DMTs. About half of these pregnancies were terminated and 18% ended in a spontaneous abortion. Only half of the surveyed patients felt well informed about the teratogenic risk of DMTs and family planning. However, 42% female and 74% male patients were not aware of potential teratogenic effects of their current DMTs [1].

MS has a clear impact on reproductive decisions, as there is an increased risk of nulliparity among MS patients, having no children (25.6%) compared with a reference population (19.9%). Furthermore, MS patients have on average fewer children: in females both before and after diagnosis, and in males only after diagnosis [2]. As much as 79% of MS patients indicated that following MS diagnosis there was no pregnancy or fathering pregnancy. It should be noted that this was due to MS-related reasons in only on third of patients; two thirds answered that their family was already complete [3]. The most frequent MS-related reason for not becoming pregnant was the presence of symptoms that might interfere with parenting (71.2%). Other reasons included burdening their partner (50.7%), financial issues (39.4%), worries about children inheriting MS (34.7%), and risks associated with exposure to medication (30%) [3].

Associated disease prognosis

Women of reproductive age have a higher incidence of relapsing-remitting MS, including mild forms (benign MS). They have more relapses, but less disability progression, namely a longer time from onset to EDSS score 6.0 when compared with men. "Women somehow appear to be protected against progression with respect to cognitive impairment, thalamic atrophy, and the occurrence of primary progressive MS during reproductive age", Prof. D'Hooghe stated. "We really don't know why this is the case." There is also no indication that pregnancy has an adverse effect on long-term prognosis of MS, at least according to most studies. "Nevertheless, we know that there is an increased relapse risk in the postpartum period, especially when MS is very active before pregnancy. So, we should be very careful when stopping highly effective DMTs with potential rebound before and during pregnancy."

Assisted reproductive therapies have also been introduced for MS patients. There appears to be an increased relapse risk following these hormonal treatments, at least when having led to pregnancy. There is no adverse effect of epidural analgesia. MS itself does not appear to have a major effect on reproductive outcomes, i.e. fertility, pregnancy outcomes (abortion, ectopic pregnancy, and delivery), and neonatal outcomes. "We cannot exclude minor effects, but there are no major effects", Prof. D'Hooghe reassured. "However, DMTs may affect these outcomes due to gonadal/foetal toxicity, birth defects, rebound activity, and autoimmune thyroiditis", she added, referring to the EMA recommendation about restricted use of fingolimod [4].

Successful pregnancy planning

The trends are that both pregnancy rates and number of annual live births in MS are increasing. However, it appears that women with MS become pregnant with a delay of 2-3 years compared to reference persons, indicating increased risk for the foetus and the mother. Furthermore, there is an increasing number of pregnancies conceived under DMTs. "This is really impressive", according to Prof. D'Hooghe. "Data from MSBase shows an increase from 26% to 62% with respect to the number of pregnancies conceived under DMTs in recent times."

Overall, it is important to manage MS with patient preference and reproductive decisions taken into consideration. Before starting, stopping, or switching DMT, it is very relevant to consider the risk of long-term MS disability, to actively ask

for pregnancy plans and contraceptive use, to include the mother's preferences and risk avoidance, and to discuss how contraceptive choice impacts DMT selection. "In case of a pregnancy planning, we should monitor whether disease activity is under control", Prof. D'Hooghe advised. "We should consider treatment, if needed, with modestly effective DMTs, that are safe to continue taking through to conception. As previously mentioned, that could be injectables rather than orals or second-line therapy. We could also consider not starting with DMT." Furthermore, Prof. D'Hooghe emphasised the need to restrict the use of highly teratogenic drugs. "These drugs need to be stopped in time, but then there is a risk of relapse. We also have to take into account that there is a variable period to become pregnant (6-24 months). Furthermore, we should restrict the use of highly effective drugs with risk of rebound disease activity 8-16 weeks after cessation, because pregnancy is not protecting against this rebound, so we really have a risk of relapse during pregnancy."

On the other hand, it is important to avoid unplanned pregnancy under DMT, the motto is: safety first. "During treatment with all DMTs, patients need safe and effective contraception", D'Hooghe mentioned. "We should be aware that gastrointestinal side effects may reduce effectivity or oral contraceptives. Intrauterine devices may be considered, because they have a long-term effect and are safe. Some highly teratogenic DMTs need double contraceptive method, at least temporarily."

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Late-breaking: Continuation of natalizumab or interruption during pregnancy

Pregnancy in female MS patients treated with natalizumab can expose the patients to high risk of relapses and sustained disability progression. Maintaining natalizumab, at least until conception, and re-starting treatment early after delivery was confirmed to be the optimal strategy when looking at maternal risk. The decision must take into account possible foetal risks and breastfeeding choice. The effects of different timings of natalizumab suspension before and during pregnancy were presented as late-breaking news [1].

Pregnancy is an emerging issue in MS, which influences treatment choice. Dr Doriana Landi (Tor Vergata University, Italy) started her lecture by stating It is well known that pregnancy is not compatible with all high-efficacy treatments, "especially second-line treatment, used to treat women with highly active MS. So, there is a need to accumulate data on how to manage these patients, and planning a pregnancy."

There are several anecdotal reports and previous studies showing that suspension of natalizumab due to pregnancy is associated with dramatic disease worsening. "This is mainly due to the fact that the pharmacodynamic effects of natalizumab start to decline 8-12 weeks after the last infusion", Dr Landi explained. Currently, wash-out of natalizumab in women with MS planning a pregnancy is discouraged due to high risk of disease reactivation. Natalizumab suspension early after the last menstrual period, whilst producing a 3-fold reduction of relapses during pregnancy, does not rule out the risks. Continuation of natalizumab is a promising strategy to minimise the occurrence of relapses during pregnancy and postpartum. However, there is a need for new evidence supporting the efficacy and safety of this strategy.

In the current analysis, women with MS treated with natalizumab and undergoing pregnancy, followed in 19 Italian MS centres, were analysed. They were divided into 3 groups according to time of last infusion of natalizumab with respect to last menstrual period:

- Group 0: before last menstrual period;
- Group 1: within the first trimester of pregnancy; and
- Group 2: continuing treatment after the first trimester [1].

A total of 92 completed pregnancies were evaluated, from 84 women with MS (mean age 31.4 years, median EDSS 2.0) and giving birth to 94 new-borns (mean gestational age 38.4 weeks, birthweight 2,878 gram, length 48.23 cm). The median interval between last dose of natalizumab and last menstrual period was -70 days for group 0, +21 days for group 1, and +189 days for group 2. Group 2 received a median of 5 natalizumab infusions during pregnancy with a median last prepartum-delivery dose interval of 81 days [1].

For women restarting natalizumab in the postpartum period, median interval between last prepartum and first postpartum dose was 411 days in group 0, 288 days in group 1, and 103 days in group 2. Annualised relapse rate (ARR) during pregnancy was median 1.06 in group 0, 0.49 in group 1, and 0.09 in group 2 (see Figure). ARR postpartum was median 0.39 in group 0, 0.23 in group 1, and 0.10 in group 2 (see Figure). ARR was lower in pregnancies exposed to natalizumab after conception and became zero in pregnancies exposed

for >90 days. ARR was higher in the postpartum period in unexposed pregnancies and reliably depended on delayed treatment resumption. The mean gestational age (P=0.523), birthweight (P=0.896) and length (P=0.331) of the new-borns were not different in these 3 groups [1].

It was concluded that continuation of natalizumab beyond conception reduced the risk of relapse during pregnancy and was not associated with major foetal risks. Although this study was underpowered to detect statistically significant differences among pregnancies exposed up to the first trimester and beyond, the investigators observed that prolonging treatment protected from relapse occurrence in a time-dependent manner. Dr Landi noted that in case of treatment prolongation up to the third trimester, it is likely desirable to restart infusions within 12 weeks from the last prepartum infusion, to minimise the risk of "doubled" disease rebound. It needs to be assessed whether extended dosing is as protective as regular dosing, although no differences were seen in this cohort [1].

Foetal parameters did not vary according to different exposure to natalizumab, however, birthweight was numerically slightly lower in the 3 groups compared to general pregnancies. Anaemia was recorded only in newborns exposed beyond the first trimester, but there were confounding factors. No malformations cluster has been identified according to European Surveillance of Congenital Anomalies (EUROCAT) registry [1]. A larger sample is needed to correctly estimate the incidence of foetal complications in exposed pregnancies and provide conclusive data useful for patients counselling.

1. Landi D, et al. ECTRIMS 2019, abstract 338.

Figure. ARR before and during pregnancy and postpartum [1]