ECTRIMS 2022

Review of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress 2022

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THIS YEAR'S European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) congress was the 38th, and the first ever hybrid congress organised by ECTRIMS. The congress, which is the world's largest for research into the pathogenesis, diagnosis, and treatment in multiple sclerosis (MS) and related neurological disorders, is held in collaboration with Rehabilitation in Multiple Sclerosis (RIMS). This year's hybrid congress brought together 2,000 participants online, as well as 7,000 participants in-person in Amsterdam, the Netherlands, a city that has a history of neurological research going back almost 115 years, and one of the largest neuroscience communities in Europe.

President Maria Pia Amato opened the congress by looking back. After the pandemic first began, this congress was a celebration of the opportunity to get together again, while building on the experience of the past years. At the opening ceremony, Amato stated: "Despite the challenging times over the past 2 years, we have witnessed an ongoing evolution in both the treatment and the journey for people living with and impacted by MS. ECTRIMS has also been working hard to evolve, and this is reflected in the organisation, the programme, and the activities on offer at our first hybrid conference."

The theme of this year's congress was 'Experience the Evolution'. Amato explained that despite challenging times, we have seen ongoing evolution in many fields of medical research. In order to support this evolution, ECTRIMS strives to improve connections, create synergies, and promote learning opportunities for professionals, while working to evolve at the same time. Amato introduced the ECTRIMS 365 model, a new concept that was designed to provide continuous learning and connecting opportunities throughout the year for the entire community. These include a range of new programmes and activities, such as ECTRIMS Insights and News, providing the latest news, announcements, and sponsored articles; a webinar series, in which MS experts can connect and discuss advances in research; and a new podcast that brings together experts to break down the latest insights into MS research, treatment, and care, and offers a collaborative platform for healthcare experts, with the aim of being a sounding board for experts and advocates to discuss innovative work within the MS research community. Further activities include the Summer Schools, and the newly introduced Winter School, which took place for the first time in November in Barcelona, Spain. ECTRIMS also organises annual focused workshops,

the last of which happened in March and focused on autologous haematopoietic stem cell transplantation for the treatment of MS. While the regional teaching courses, which take place all over the world, were suspended since the pandemic began, they will resume in 2023. Furthermore, ECTRIMS continues to offer fellowship programmes, providing training opportunities to young researchers and clinicians, as well as nurses, psychologists, physiotherapists, and other healthcare professionals.

ECTRIMS is leading the way by continuing to develop guidelines on MS and related disorders. Recent guidelines have included topics such as treatments, vaccinations, the treatment of neuromyelitis optica spectrum disorders, and cognition in MS. All of these programmes will continue to evolve, accelerating impact to benefit those affected by the disease. The congress shared all progress made in every field of basic and clinical research on MS and related disorders. Amato also expressed the hope that interactions and exchange of participants' scientific knowledge will help to inspire new avenues for research, collaborations between experts, and enable them to find more advanced solutions for care.

This year's host, Bernard Uitdehaag, reminded participants of the importance of staying connected, and the need for strong networks such as ECTRIMS. Otto van Eikema Hommes, Founder of ECTRIMS and President from 1982–1994, envisioned that bringing together people would enhance the process of finding a cure for the disease. Hommes sadly passed away this year.

At the closing ceremony, several awards were granted. First, the Young Investigators Awards were granted to Annalisa Colombi, University of Verona, Italy, and Stephanie Meier, University of Basel, Switzerland. The Poster Awards were presented to Victoria Leavitt, Columbia University, New York, USA; Mads Alexander Madsen, University of Copenhagen (KU), Denmark; Catherine Larochelle, Centre Hospitalier de L'Université de Montreal (CHUM), Canada; Christian Cordano, University of California, San Fransisco (UCSF), USA; and Samad Al-Araji, University College London (UCL), UK. Several RIMS awards were also presented. The best oral presentation award was granted to Laurits Taul-Madsen, Aarhus University, Denmark, and the best poster presentation was awarded to Marie Kierkegaard, Karolinska Institutet (KI), Sweden. Next, the European Charcot Foundation Award for Young investigator was awarded to Alexander Balcerac, Paris Descartes University, France. Finally, Krzysztof Selmaj, Olsztyn, Poland, was awarded the title of honorary member of ECTRIMS for their outstanding contributions to the field of MS.

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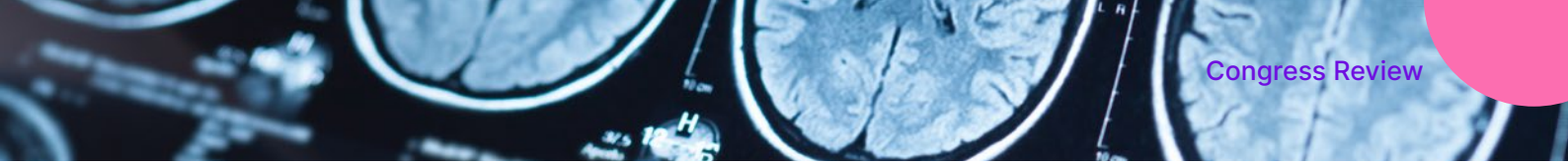
The programme of the congress was developed to enable participants to identify and attend sessions that were of interest to them, but also new topics to spark new discussions, covering 10 hot topics. With over 240 speakers, the congress included 18 scientific sessions, 22 educational sessions, and 12 satellite symposiums, covering four main topics: clinical, therapy, pathogenesis, and imaging and non-imaging biomarkers.

This review includes summaries of multiple insightful abstracts, covering topics such as a comparison between rituximab and ocrelizumab in relapsing-remitting MS, and the link between early non-disabling relapse and the risk of disability accumulation. The EMJ team was delighted to participate in this congress, and looks forward to the next one. Read on for our scientific highlights of this year's congress.



Serum Neurofilament Light Chain in Predicting Multiple Sclerosis Diagnosis

SERUM neurofilament light chain (sNfL) levels in multiple sclerosis (MS) are associated with inflammatory activity. As with IgG oligoclonal bands (OB), sNfL may support the inflammatory nature of lesions when diagnosing MS. SNfL levels in MS are less clearly associated with disability. Georgina Arrambide, Multiple Sclerosis Centre of Catalonia, Neurology Department, Vall d'Hebron University Hospital, Barcelona, Spain, and colleagues assessed the value of sNfL measured at the time of a clinically isolated syndrome (CIS) to predict MS diagnosis and future disability. The results were shared at ECTRIMS 2022.

The researchers selected patients with ≥one brain MRI and serum samples collected within 6 months of the CIS (n=593). SNfL levels were measured using a single molecule array assay. Results were measured as Z-scores, and sNfL Z-score cut-offs were estimated by bootstrapping. For MS diagnosis, this was done in all CIS cases, and in patients not fulfilling McDonald MS at baseline. Based on the calculated cut-offs, Cox regression models were conducted, with 2017 McDonald MS as the outcome. Focusing on patients who did not fulfil McDonald MS at baseline, those with a minimum follow-up of 3 years were selected to assess diagnostic properties for McDonald MS in individuals with ≥one T2 lesion or ≥two T2 lesions, either alone or in combination with OB, Z-score cut-offs, or both. For disability, Z-score cut-offs were also calculated by bootstrapping to predict secondary progressive MS (SPMS) and progression independent of relapse activity (PIRA) without inflammatory activity on MRI (non-active PIRA).

After a median follow-up of 9.2 years, approximately two-thirds of patients fulfilled 2017 McDonald MS, 7% had SPMS, and 8% had non-active PIRA. The mean sNfL Z-score was 1.3. For MS diagnosis, the Z-score cut-off for all patients (n=593) was 1.46 (adjusted hazard ratio [aHR]: 1.25; 95% confidence interval [CI]: 1.00–1.57; p=0.05). In patients not fulfilling McDonald MS at baseline (n=323), the cut-off was 0.36 (aHR: 1.64; 95% CI: 1.002–2.690; p=0.049). Adding either an OB or a Z-score of 1.46 to ≥one T2 lesion increased MS diagnosis specificity at the expense of sensitivity. If having both an OB and a Z-score of 1.46, sensitivity was 30.3 and specificity was 93.3. Results were similar when assessing ≥two T2 lesions. In this case, having both an OB and a Z-score of 1.46 yielded a sensitivity and specificity of 25.3 and 96.6, respectively. For SPMS, the cut-off was 2.89; however, significance was lost when adding T2 lesions (aHR: 1.54; 95% CI: 0.75–3.14; p=0.239). Finally, a Z-score cut-off of 1.28 decreased the risk of reaching non-active PIRA (aHR: 0.41; 95% CI: 0.20–0.86; p=0.018).

> **"Although predictive sNfL Z-score cut-offs in CIS increase MS diagnosis specificity in patients not fulfilling McDonald at baseline, their role in predicting disability milestones is superseded by MRI findings."**

In conclusion, although predictive sNfL Z-score cut-offs in CIS increase MS diagnosis specificity in patients not fulfilling McDonald at baseline, their role in predicting disability milestones is superseded by MRI findings. ●

Early Non-disabling Relapses Linked to Higher Risk of Disability Accumulation

PROGNOSTIC significance of non-disabling relapse in multiple sclerosis (MS) was discussed in a presentation that took place at the ECTRIMS 2022 Congress, by Cyrus Daruwalla, University of Cambridge, UK.

The aim of the presentation was to establish whether non-disabling relapses early in relapsing-remitting MS (RRMS) indicate faster accumulation of disability than no relapses, or slower accumulation of disability than early disabling relapses in patients treated with disease-modifying therapies (DMT) of all efficacies. In order to determine this, Daruwalla and colleagues used MSBase, the largest MS database registry, with information from over 70,000 patients with MS in 41 countries.

In this registry, the treating clinicians grade the severity of relapse as either mild, moderate, or severe. Mild relapses do not limit day-to-day activities, thus non-disabling relapse. Moderate relapses limit daily activities, and severe relapses are those that require hospitalisation; both are disabling relapses. Early MS diagnosis is defined as the 2 years after RRMS diagnosis. Researchers grouped the data of the patients into three groups: no early MS relapses, exclusively non-disabling early MS relapses, and any disabling relapses. The primary analysis of the study compared patients with no early MS relapses and exclusively non-disabling early MS relapses. The secondary analysis compared exclusively non-disabling early MS relapses and any disabling relapses.

The analytical methodology was based on the treatment strata on the highest efficacy DMT the patients received during follow-up, which was either untreated, platform DMT, or high-efficacy DMT. The results from the study showed that the patients with early non-disabling relapses had an increased risk of disability accumulation compared to the patients with no early MS relapses. Additionally, there was an increased risk of disability in the patients treated with platform DMT and with early non-disabling relapses. However, in patients with early non-disabling relapses who were treated with high-efficacy DMT, there was no significant difference in disability accumulation compared to the patients who had no early MS relapses.

The limitation of the study was that the relapse severity was non-standardised; however, the clinicians' judgment in severity reflects the clinical practice. Furthermore, there was no direct comparison between DMT efficacies after a non-disabling relapse. Daruwalla and colleagues concluded that early non-disabling relapses are linked to a higher risk of disability accumulation compared to no early relapses in patients with RRMS. However, this link is not observed in patients treated with high-efficacy DMTs. Currently, the European Medicines Agency (EMA) restricts the use of certain DMTs only to patients with disabling relapses. Daruwalla, contrary to EMA, suggested that non-disabling relapses should be considered in clinicians' decisions to start or escalate treatment such as high-efficacy DMTs.

Benefit of Disease-Modifying Therapy in Radiologically Isolated Syndrome

RADIOLOGICALLY isolated syndrome (RIS) represents the earliest detectable preclinical phase of multiple sclerosis. The impact of a given disease-modifying therapy in preventing the clinical onset of multiple sclerosis in a group of subjects with RIS is unknown. Therefore, Darin Okuda, University of Texas (UT) Southwestern Medical Center, Dallas, USA, and colleagues conducted a multicentre, randomised, double-blinded, placebo-controlled study to evaluate the efficacy and safety of dimethyl fumarate (DMF) in people with RIS. The primary endpoint was time to onset of a first clinical symptom attributable to a central nervous system demyelinating event over a 96-week period. Secondary endpoints included new or newly-enlarging T2 lesions, change in T2 lesion volume, the number of gadolinium-enhancing lesions, and whole brain volume measures. The results were shared at ECTRIMS Congress 2022.

The research team leveraged two independent committees for this study. Both committees evaluated clinical and imaging data through adjudicated consensus. If screening was successful, participants were randomised 1:1 to receive DMF in accordance with the U.S. Food and Drug Administration (FDA) approved label or a placebo. From 9th March 2016–31st October 2019, 87 individuals were assessed for eligibility and randomised into the study; 44 were randomised to DNF and 43 received placebo. An intention to treat analysis was performed on all the data.

The risk of a first clinical demyelinating event during the 96-week study period was statistically significant following treatment with DMF in the unadjusted model, with a hazard ratio (HR) of 0.18 obtained. Further, results from the adjusted model yielded an HR of 0.07. A strategy for Bayesian methodology was pursued during the trial in the event that the pace of enrolment was slower than anticipated. Within this model, 40 individuals were needed per arm to have 90% power, demonstrating a 50% therapeutic effect, assuming that 25% of individuals would experience a first clinical event within a given 96-week period. The results from this prespecified Bayesian analysis revealed an HR of 0.20.

A significant reduction in the occurrence of new or newly-enlarging T2 lesions was observed in those treated with DMF. For those exposed to DMF, there was a lower change in T2 lesion volumes in both the unadjusted and adjusted analysis; however, statistical significance was not achieved. Gadolinium enhancement was present in one individual at Week 96 and, therefore, a statistical analysis could not be performed.

There were more moderate adverse reactions present in those exposed to DMF compared to placebo. With respect to severe adverse events, there was no significant different between the two groups. Overall, there were no unexpected safety outcomes throughout the trial.

In conclusion, this was the first randomised clinical trial demonstrating the benefit of a disease-modifying therapy in preventing a first acute clinical event in people with RIS. Going forward, additional research is necessary to understand the impact on future disability outcomes.

Rituximab Versus Ocrelizumab in Relapsing-Remitting Multiple Sclerosis

IZANNE Roos, University of Melbourne, Australia, presented on a non-inferiority study of rituximab (RTX) versus ocrlizumab (OCR) in relapsing-remitting multiple sclerosis (RRMS) at ECTRIMS Congress 2022. B cell therapies are highly effective in the treatment of RRMS. OCR, a humanised monoclonal antibody targeted against CD20+ B cells that reduces disability worsening by 40%, and frequency of relapses by 46% compared to interferon-β1a in RRMS, is an approved treatment. RTX, a chimeric monoclonal anti-CD20 agent, is an off-label alternative to this treatment.

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This study aimed to evaluate the clinical non-inferiority of RTX compared to OCR in RRMS. The longitudinal, observational cohort study was conducted from two observational registries: MSBase and Danish MS Registry. Patients with RRMS that were treated for ≥6 months with RTX or OCR after 2015 were identified. They all required over 6-month pre-treatment follow-up.

To ensure comparable groups, they were matched on age, sex, MS duration, Expanded Disability Status Scale (EDSS), prior relapse rate, prior therapy, disease activity, MRI brain lesion burden, and country. The primary outcome was the annualised relapse rate with a pre-specified non-inferiority margin of 0.2 rate ratio. The secondary outcome was the cumulative hazard of relapse (6-month confirmed disability accumulation and improvement). The researchers carried out sensitivity analyses to evaluate informed censoring and registry.

In total, 710 patients treated with OCR were matched with 186 patients treated with RTX. After 1.5-years follow-up, the annual relapse rate was lower in patients treated with OCR compared to those treated with RTX (rate ratio: 1.8; 95% confidence interval: 1.4–2.4; annualised relapsed rate: 0.09 versus 0.20; $p<0.01$). Furthermore, the cumulative hazard of relapses was lower in those treated with OCR than those with RTX (hazard ratio: 2.1 [1.5-3.0]). There was no difference in disability accumulation between the two groups.

The researchers concluded that there is no non-inferiority of treating with RTX compared to OCR. There was a higher risk of relapse in patients treated with RTX than OCR. ●

Autologous Haematopoietic Stem Cell Transplantation Versus Natalizumab: Which Is Best?

THE COMPARATIVE efficacy of autologous haematopoietic stem cell transplantation (AHSCT) and natalizumab as a treatment for progressive multiple sclerosis (MS) was explored during a presentation of study data, delivered by Tomáš Kalinčík, The Royal Melbourne Hospital Neuroimmunology Centre, Australia, at ECTRIMS 2022.

The aims of the study were to compare the efficacy of AHSCT and natalizumab in controlling disability progression and relapse reduction for patients with primary and secondary progressive MS, and to consider the adverse events and treatment-related mortality following AHSCT.

The study used data from the MS Base Neuro-Immunology Registry and six specialist AHSCT MS centres to enrol a total of 158 patients with a diagnosis of moderately advanced progressive MS, defined as an average Expanded Disability Status Scale (EDSS) score of 5.7, and average relapse rate of 0.5–0.6 in the preceding 12 months. Of these patients, 119 had been treated with natalizumab and 39 with AHSCT. Following propensity score matching to overcome the lack of randomisation, patients were matched in a 1:3 variable matching ratio to help preserve the power in the small AHSCT cohort. The analysis was also adjusted for age and MS duration.

The results revealed that there was no difference in the annual relapse rate between the two cohorts, and that the overall annualised relapse rate was lower following intervention than at baseline for both AHSCT and natalizumab groups, at 0.08. In terms of disability outcomes, there was no evidence to suggest a difference in 6-month confirmed disability worsening between the two cohorts, and 6-month confirmed disability improvement was rarely seen over the 5-year follow-up period.

With respect to adverse events and treatment-related mortality following AHSCT, the observed complications were febrile neutropenia (3/39 [7.7%]), intensive care admission (6/39 [15%]), serum sickness (9/39 [23%]), and post-discharge complications (36/39 [92%]). On further stratification of post-discharge complications, 6/36 occurred early and 21/36 were secondary to infections. There were no reported cases of treatment-related mortality.

The authors noted that the study limitations included the small sample size, lack of randomisation, incomplete safety data for the natalizumab group, lack of MRI data available for baseline matching or as an outcome, and a multicentric cohort. However, the team acted to mitigate some of these limitations by using propensity score matching. Kalinčík concluded the presentation by stating that "AHSCT is not superior to natalizumab" in reducing disability progression, increasing disability improvement, or preventing relapses for patients with moderately progressive MS.

Epstein–Barr Virus-Specific T Cell Receptors in Multiple Sclerosis

THIS NOVEL research presentation opened with Tilman Schneider-Hohendorf, Department of Neurology with Institute of Translational Neurology (GERiT), University of Münster, Germany, drawing the audience's attention to recent literature about the antibody evidence for the causal relationship between Epstein–Barr virus (EBV) and multiple sclerosis (MS). This included evidence that EBV seroconversion proceeded MS diagnosis by years, and that CNS damage, measured by neurofilament light chain, is detectable after EBV seroconversion, possibly suggesting the primary EBV infection could be a trigger of the autoimmune processes behind MS.

The study aimed to investigate the peripheral blood CD8 EBV-specific T cell receptor repertoire in patients with MS. The investigators sequenced the T cell receptor variable β-chain (TRBV) in the peripheral blood of three different cohorts of patients with MS and healthy donors, including a discovery, validation, and MS twin cohort. Following this, they retrieved multimer-binding TRBV sequences for four common pathogens, including EBV and severe acute respiratory syndrome coronavirus 2, from public databases. This allowed the researchers to quantify database-derived, pathogen specific TRB sequences in peripheral blood by the matching of human leukocyte antigen, variable β-chain family, and Complementarity-determining region 3 amino acid sequence. This sequence was then modelled with the covariates of age, sex, sequencing depth, and disease status.

The researchers found a broader EBV-specific T cell receptor repertoire in patients with MS than in controls. This meant that they found more unique EBV-specific, major histocompatibility complex Class I-restricted cluster of differentiation 8 (CD8) TRBV sequences in the blood of patients with MS. This was found in all three cohorts, including the monozygotic twin cohort; this, therefore, excludes the impact of any genetic or environmental differences. The researchers suggested the difference within each of the three groups between patients with MS and the controls could be the imprint of a primary EBV infection.

To further investigate the nature of the immune cell responses, researchers investigated the phenotype of EBV-specific CD8 T cells in the cerebrospinal fluid of patients with MS compared to healthy donors. They found many more EBV-specific CD8 T cells in patients with MS. In addition to this, the EBV-specific T cells that were found in healthy donor patients were mainly confined to the T cell effector memory compartment, indicating increased immune surveillance in patients with MS.

From the data collected, the researchers concluded that broader EBV-specific T cell receptor-repertoire could indicate an aberrant immune response, possibly the remnant of a disease-triggering event or an ongoing CD8 immune response to EBV. Schneider-Hohendorf then outlined the next steps required to define whether it is the EBV activity driving disease in MS. These include expanding pathogen specific sequences, assessing tissues from the central nervous system and MS lesions, and defining healthy primary responses in paediatric cohorts. ●