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Exploratory MRI Outcomes and Plasma NfL Levels in Frexalimab-Treated Participants with Relapsing Multiple Sclerosis: Week 48 Results from the Phase 2 Open-Label Extension

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INTRODUCTION: Frexalimab, a second-generation anti-CD40L monoclonal antibody, inhibits the CD40/CD40L pathway that regulates adaptive and innate immunity. In a phase 2 trial (NCT04879628) for relapsing multiple sclerosis (RMS), frexalimab rapidly reduced new gadolinium-enhancing T1-lesions, but less is known about its effects on biomarkers of chronic neuroinflammation and neurodegeneration.

OBJECTIVES: Report exploratory MRI outcomes and changes in plasma neurofilament light chain (NfL) at Week (W) 48 in the phase 2 open-label-extension (OLE).

METHODS: Participants were randomised to frexalimab$_{1200/\text{intravenous (IV)}}$ (n=52), frexalimab$_{300/\text{subcutaneous (SC)}}$ (n=51), or matching placebo (placebo$_{IV}$: n=12; placebo$_{SC}$: n=14). Participants receiving placebos switched to respective frexalimab at W12 and entered OLE. Exploratory assessments included paramagnetic rim lesions (PRLs), new T1-hypointense lesions, and NfL levels.

RESULTS: 125/129 participants completed double-blind period and entered OLE; 112 (87%) continued the study as of 19-September-2023 (W48 cut-off). Mean baseline age±SD was 36.6±9.4 years; 66% women. At baseline, 19/46 (41%) of participants at sites with sufficient imaging capability had ≥1 PRLs. New PRLs were detected in frexalimab$_{300/SC}$ arms between W8 and W20, whereas no new PRLs were detected from baseline to W48 in frexalimab$_{1200/IV}$ arms. New T1-hypointense lesions (mean±SD) were low at W48: frexalimab$_{1200/IV}$, 0.1±0.4; frexalimab$_{300/SC}$, 0.8±1.6; placebo$_{IV}$/frexalimab$_{1200/IV}$, 0.0±0.0; placebo$_{SC}$/frexalimab$_{300/SC}$, 0.6±1.0. At W48, NfL levels (geometric mean±SD) were: frexalimab$_{1200/IV}$, 6.7±2.0; frexalimab$_{300/SC}$, 8.1±1.7; placebo$_{IV}$/frexalimab$_{1200/IV}$, 9.6±1.7; and placebo$_{SC}$/frexalimab$_{300/SC}$, 7.8±2.1 pg/ml, corresponding to 41%, 35%, 24%, and 33% reductions from baseline, respectively.

CONCLUSION: These exploratory MRI and NfL data help understand frexalimab's effect on chronic neuroinflammation and neurodegeneration, supporting further investigations in RMS and non-relapsing secondary progressive MS.

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Safety and Efficacy of Frexalimab in the Treatment of Relapsing Multiple Sclerosis: 18-Month Results from the Phase 2 Open-Label Extension

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Introduction: Frexalimab, a second-generation anti-CD40L antibody, blocks the CD40/CD40L pathway that regulates adaptive and innate immunity. In a phase-2 trial for relapsing multiple sclerosis (RMS; NCT04879628), frexalimab was well-tolerated and efficacious at reducing disease activity. Frexalimab 1200-mg intravenous (IV) every-4-weeks (q4w) decreased new gadolinium-enhancing T1-lesions by 89% vs placebo at W12. Treatment effect was sustained over W48 in open-label extension (OLE).

Objectives: Report safety and efficacy of frexalimab at W72 (18-months).

Methods: Participants were randomized (4:4:1:1) to receive 1200-mg IV q4w or 300-mg subcutaneous (SC) q2w doses of frexalimab or matching placebo. After W12, participants receiving placebos switched to respective frexalimab and entered OLE. During OLE, SC dose was increased to 1800-mg q4w to achieve a similar exposure as with the 1200-mg q4w IV dose; 7/57 participants had their W72 MRI after receiving high-dose. Key endpoints: safety and efficacy (number of gadolinium-enhancing T1-lesions and new/enlarging T2-lesions).

Results: 125/129 participants completed double-blind period and entered OLE; 111 (89%) had ongoing treatment as of 2-Feb-2024 (W72 cut-off). At W72, number of gadolinium-enhancing T1-lesions (mean±SD) remained low: frexalimab$_{IV}$, 0.1±0.4; frexalimab$_{SC}$, 0.4±0.9; placebo$_{IV}$/frexalimab$_{IV}$, 0.0±0.0; placebo$_{SC}$/frexalimab$_{SC}$, 0.2±0.4. New/enlarging T2-lesions and T2-lesion volume change remained low through W72. No new safety signals were observed; most common adverse events observed during OLE until W72 cut-off were nasopharyngitis (13%), COVID-19 (12%), and headache (11%).

Conclusions: Frexalimab continues to show favourable safety and sustained reduction in disease activity in RMS participants assessed by MRI through 18-months, supporting its further development in phase-3 MS trials as a high-efficacy, non-lymphocyte-depleting therapy.

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Diagnostic Age of Patients with Multiple Sclerosis in Azerbaijan: A Clinical and Epidemiological Study

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Introduction: Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system, characterized by inflammation and an unknown cause. MS most commonly affects individuals aged 20–40, with a female-to-male ratio ranging from 2:1 to 3:1, depending on the region. **The aim of this study** was to analyze the diagnostic age of MS patients in Azerbaijan.

Materials and Methods: This study analyzed data from 1,796 MS patients recorded under the "State Program on Measures of Treatment, Prevention, and Control of MS" over a ten-year period (2013–2022). Patients were grouped by 10-year diagnostic age intervals, and their sex, clinical course, residency, and diagnostic delay were evaluated.

Results and Discussion: Of the patients, 65.7% were female, and 34.3% were male, with an average diagnostic age of 34.9±8.9 years (range: 11–66). MS diagnoses were less prevalent in the 20, 50–59, and ≥60 age groups. The average diagnostic delay was 5.2±4.8 years. The highest proportion of diagnoses occurred in the 30–39 age group (39.15% women; 38.80% men). Women were more frequently diagnosed across all age groups, with the greatest disparity observed in those ≥60 (female-to-male ratio of 7:1). Relapsing-remitting MS was the predominant type in patients 60 (48.8%–88.6%), whereas secondary progressive MS was significantly more common in those ≥60 (75.0%, P0.001).

Conclusion: MS is most frequently diagnosed between the ages of 20–49 in Azerbaijan. Younger patients predominantly present with relapsing-remitting MS, while older individuals have a higher prevalence of secondary progressive MS.

Keywords: multiple sclerosis, 10-year age groups, age at diagnosis, clinical course.

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Lateral Ventricle Volume is associated with disease severity in Pediatric Multiple Sclerosis.

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Background. Although brain volume loss and its involvement in patient deterioration have been established, the effects of changes in the volume of the brain lateral ventricles in pediatric patients have yet to be thoroughly examined.

Aim. The purpose of this study was to examine changes in the lateral ventricular volume and its correlation with disease severity in POMS

Methods. Brain MRI performed at baseline and 3 years follow up were analyzed in POMS. The scans were segmented and quantified for volume using semiautomatic software. The POMS lateral ventricle volumes were matched to age and sex matched healthy subjects.

Results. Sixty six patients, (39 females) with mean ± SE age at onset 13.8 ± 0.4 years, baseline median Expanded Disability Status Scale (EDSS) score of 3.0 , disease duration of 8.1±0.5 years . After 3 years follow up the median EDSS were 1.0 (IQR 1.0-2.0) . At disease onset, the lower levels of lateral ventricle volume was associated with higher EDSS scores (p=0.05), that could be explained by more exudative inflammation in patients brains leading to reducing of ventricle volumes. In the opposite, after 3 years of the follow up, higher lateral ventricle volumes were now associated with higher EDSS scores (p=0.002), probably as it associated with initiation of neurodegeneration and neuronal loss.

Conclusion. Lateral ventricle volume in POMS associated with higher EDSS at onset and disease severity at 3 years follow up. This able as to follow patients deterioration and disease progression by conventional MRI observations, already in the onset and early disease progression.

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Tau in Multiple Sclerosis: Mediator or Bystander in Disease Progression?

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Introduction: Multiple Sclerosis (MS) is a neurological disorder characterized by inflammatory and neurodegenerative mechanisms. While disease-modifying therapies effectively control inflammation in relapsing-remitting MS, their limited impact on progressive MS highlights a critical gap in addressing neurodegeneration. Emerging evidence implicates tau, a protein traditionally associated with Alzheimer's disease, in MS. This raises the question: is tau merely a bystander in MS, or does it play an active role in driving neurodegeneration?
Methods: Utilizing specialized "biosensor" cell systems to detect and quantify tau seeds in brain tissues, we recently tested for and detected tau seeding in frozen brain tissue of 6/8 subjects with multiple sclerosis. Then, a critical review of literature was conducted, analyzing findings from rodent models, human brain tissue, cerebrospinal fluid studies, and PET imaging. The review explored the relationship between inflammation and degeneration in the context of tau pathology.
Results: Based on the review of existing studies, abnormal tau is present in MS brains, with insoluble tau aggregates emerging in progressed disease. Tau seeds have been identified in border zones of lesions, but their role in MS pathophysiology remains unclear. Tau may act as an acute-phase protein in early inflammation, undergoing post-translational modifications and aggregation, potentially driving neurodegeneration. Immunoprecipitation studies suggest tau aggregates in MS exhibit distinct conformations compared to Alzheimer's disease.
Conclusion: Evidence suggests tau as a mediator in MS progression - but challenges remain. These include the lack of reliable animal models, limited brain tissue access, and unvalidated biomarkers. Overcoming these barriers could enable novel therapeutic strategies targeting tau aggregation or modulating inflammatory pathways to mitigate neurodegeneration in progressive MS.

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Case report: Therapeutic controversy: patient with sudden onset of NMOSD treated with rtPA

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The case presents a 38-year-old patient who developed sudden massive paresis of the left limbs. Based on the dynamics of symptom development and the results of a head CT scan, an ischemic stroke was suspected and the patient was qualified for rtPA treatment (in the hospital where the patient was diagnosed, it was not possible to urgently perform an MRI). On the next day, the patient developed tetraparesis with persistent hiccups and nausea. MRI of the head and cervical spinal cord revealed a long-segment T2 hyperintense lesion from the level of the medulla oblongata to the level of C6 Gd(+) and with signs of spinal edema. Additionally, area postrema involvement was found. No AQP4-IgG or anti-MOG antibodies were detected, but visual evoked potential testing revealed bilateral demyelinating damage to the visual pathway. Treatment with methylprednisolone infusions was performed, 5 plasmaphereses were performed, followed by immunoglobulin infusions, resulting in clinical improvement and the diagnosis of AQP4-IgG-seronegative NMOSD was made.

Conclusions: The rtPA treatment used in a patient with acute onset of NMOSD did not lead to bleeding complications. The use of rtPA in the course of acute ischemic stroke in patients diagnosed with NMOSD may be a safe form of treatment. This is probably the first described case of a patient who was treated with rtPA in the course of NMOSD.

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Trigeminal neuralgia in multiple sclerosis – case series

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Introduction

Trigeminal neuralgia, characterized by intense, stabbing pain attacks, may result from demyelinating lesions in the pons or spinal trigeminal nucleus in MS. This study examines MS patients with trigeminal neuralgia, analyzing nuances to refine patient care strategies.

Methods

We retrospectively examined five cases of MS patients with trigeminal neuralgia. For each case, we reviewed medical records to determine the onset times of MS and trigeminal neuralgia, as well as the medications and interventions for trigeminal neuralgia. Brain MRI images were analyzed to identify demyelinating lesions near the trigeminal ganglion.

Results

Among the patients studied, four were female and one male, with ages ranging from 44 to 48 years. Three had relapsing-remitting MS (with EDSS scores between 1 and 2), while two had secondary progressive MS (both with EDSS = 6.5), with disease onset occurring between the ages of 29 and 37. Trigeminal neuralgia typically developed approximately 9.6 years after the onset of MS. Imaging revealed pontine lesions in three patients, vascular-nerve conflict in one, and no significant lesions in another. Initial drug treatments were attempted for all patients, but two showed no response. As a result, interventions such as Gasser ganglion ablation or microvascular decompression were performed, but these did not lead to substantial symptom improvement. One patient relapsed after 4 months, while the other showed no noticeable change.

Conclusions

In summary, this case series underscores the link between multiple sclerosis and trigeminal neuralgia, emphasizing diagnostic complexities and the need for a personalized, multidisciplinary approach.

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Lifestyle Interventions in Depressive People with Multiple Sclerosis: a Review

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Depression is considered to be one of the most common comorbidities in people with multiple sclerosis. It is connected to the reduction in the quality of life of people in multiple sclerosis, and an increase in health care expenses due to an increased health system usage.
We conducted a literature review in order to summarize the publications published in the last five years concerning lifestyle interventions that might be used to reduce depressive symptoms.
Regular physical activity shows a positive impact on depression levels in people with multiple sclerosis: home-based exercises as well as physiotherapy should be encouraged.
Ketogenic diet reduces depression levels, improves quality of life, cognitive and motor skills of people with multiple sclerosis, yet it should only be undertaken under medical supervision as it could possibly lead to unwanted side-effects after a longer period of time.
A reduction in depressive symptoms can also be achieved through psychological education, mindfulness-based programs, cognitive and dialectical behavior therapy.
Screening for depressive symptoms in people with multiple sclerosis should be made regularly. Next to undertaking further pharmacological steps upon eventual positive screening, neurologists should encourage people with multiple sclerosis in making lifestyle changes which could be helpful reducing depressive symptoms.

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Assessing Nutritional Knowledge and the Quality of Dietary Recommendations for Patients with Multiple Sclerosis in Ukraine: a Mixed-Methods Study

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Intro:
Nutrition knowledge is a potential tool for improving disease management in multiple sclerosis (MS). This study evaluates patient satisfaction with dietary advice and explores the need for tailored educational materials.
Methods:
A sequential explanatory mixed-methods design was used. Quantitative data were collected through structured online questionnaires from MS patients receiving treatment at Kyiv City Clinical Hospital №4 in Ukraine between November 2024 to January 2025, and descriptive statistics were calculated. Semi-structured interviews were then conducted until thematic saturation was reached.
Results:
A total of 59 patients were invited to participate in the survey, with 7 declining to participate. The median age was 36 (IQR: 29-42). The group included 38 (65,4%) inpatient and 14 (34,6%) outpatient participants, with 65,4% being female. Patients were categorized as having relapsing-remitting (86.5%), primary progressive (9.6%), secondary progressive (3.9%) forms of MS. A majority (70.6%) considered nutrition recommendations important, while 49% initiated the primary dialogue about nutrition with physicians, and 67.4% sought information online. Satisfaction with online resources averaged 3.7/5 (n=30), compared to 3.6/5 (n=23) for information provided by physicians. Interviews were conducted with seven patients. Three major themes were identified: insufficient evidence-based dietary recommendations, the need for personalized guidance and gaps between recommendations between different physicians.
Conclusion:
This study indicates moderate satisfaction with dietary information from online and physicians-provided sources, underscoring a necessity for improvement. Patients with MS value nutrition in disease management and express interest in receiving evidence-based guidance, highlighting the need for better educational materials.

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Why navigated transcranial magnetic stimulation is not used in clinical settings as an objective method for assessing motor disability in patients with multiple sclerosis?

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Although MRI has become the standard in diagnosing and monitoring patients with multiple sclerosis (MS), the evoked potentials (EP) (motor EP -MEP, somatosensory EP-SEP, and visual EP-VEP) for assessing functional integrity of motor and sensory pathways are unjustifiably considered less useful. MEP latency provides congruent information on the function of the corticospinal tract and is closely related to clinical EDSS score. A combination of two or all three EP modalities is significantly related to future EDSS scores over two to twenty years in CIS, RRMS, and PPMS. Recent studies point to MEP latency as the promising marker for an objective assessment and monitoring of motor disability in MS.

In the present study, navigated transcranial magnetic stimulator (nTMS) was used for mapping the corticospinal tract integrity for upper and lower extremity muscles as an additional tool to standard EDSS clinical assessment. The study will present several cases of PPMS and RRMS patients in whom nTMS was performed showing clear benefits in addition to standard EDSS evaluation. Ongoing clinical recommendations for MEP use in MS refer to the application of a magnetic stimulator connected to a standard EMG unit, and less to-line navigated TMS and electric-field navigated TMS implementations that could provide more precision in targeting and visualization of the primary motor cortices for single muscle representation.