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Late-breaking Abstracts

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Longitudinal evolution of white matter damage in Parkinson's disease

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Background and objective: No strong MRI biomarkers were identified to define the Parkinson's Disease (PD) progression. We aimed to investigate the longitudinal evolution of cerebral white matter (WM) micro- and macrostructural damage and its relationship with clinical picture.
Methods: 154 PD patients and 114 healthy control (HC) subjects underwent clinical assessment, cognitive evaluation and MRI scan (including T2-weighted and diffusion tensor [DT] MRI sequences) once a year over a follow-up of 48 months. White matter lesions (WML) were identified on T2-weighted scans and the total WML volume was calculated and excluded to define normal appearing white matter (NAWM). Applying tract-based spatial statistics, mean fractional anisotropy (FA), mean (MD), axial (axD) and radial (radD) diffusivity values of the total WM and NAWM skeleton were extracted. Regression and partial correlation models between MRI and clinical/cognitive data were performed, corrected for age, sex, years of education and disease duration.
Results: MMSE, UPDRS-III, UPDRS-total score and DTI metrics varied significantly longitudinally, both in WM than NAWM. DTI metrics differed significantly between total and NAWM ($p \leq 0.001$). The same metrics differed significantly also between PD and HC ($p<0.001$), while WML burden did not. Longitudinal evolution of WML values significantly correlated with UPDRS-III and UPDRS total score, while MD, raD and axD of both WM and NAWM significantly correlated with the presence of visuospatial deficit and with tremor items of UPDRS-III.
Conclusions: Our study showed that the NAWM presents a global microstructural damage in PD that is associated to deficit in the visuospatial functions. The WML burden is not significantly higher in PD compared to HC, even though it is associated to motor impairment. The DT-MRI and the WML evaluation might provide a biomarker of disease prognosis and progression.
Funding: Ministry of Education and Science Republic of Serbia (Grant #175090).

LB1

Long-Term Safety and Efficacy of Patisiran: Global Open-label Extension 24-month Data in Patients with Hereditary Transthyretin-mediated Amyloidosis

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Introduction: Hereditary transthyretin-mediated (hATTR) amyloidosis is a progressive, life-threatening disease; most patients develop a mixed phenotype including polyneuropathy and cardiomyopathy.
Patisiran's safety/efficacy have been demonstrated in Phase 2 and 3 studies in patients with hATTR amyloidosis with polyneuropathy. Interim 24-month efficacy/safety analyses of the ongoing Global openlabel extension (OLE) study are described.
Methods: Multicentre, international, safety and efficacy study (NCT02510261) in eligible patients who completed parent studies, including patients in the Phase 3 APOLLO randomized to placebo (APOLLO/placebo, n=49) or patisiran (APOLLO/patisiran, n=137) over 18 months and patients in the Phase 2 OLE (n=25) receiving patisiran over 24 months.
Results: 178/211 patients had ≥24 months of exposure as of 07/10/2019. Safety profile remained consistent with previous studies. After 24 months of additional patisiran treatment in the Global OLE, durable improvement was seen for modified Neuropathy Impairment Score+7 (mNIS+7) (mean change [SEM]) in APOLLO/patisiran (-4.9 [2.1]) and Phase 2 OLE (-5.9 [2.1]) groups compared to parent study baselines. Norfolk quality of life-diabetic neuropathy (QOL-DN) continued to show durable improvement in APOLLO/patisiran patients (-2.4 [2.4]) following additional 24-month treatment. APOLLO/placebo patients experienced halting of disease progression and QOL improvement compared to Global OLE baseline after 24 months of patisiran in the OLE (mNIS+7: +0.1 [3.3], Norfolk QOL-DN: -4.1 [3.3]),

although they had progressed relative to APOLLO baseline (mNIS+7: +26.3 [5.0], Norfolk QOL-DN: +15.8 [4.5]) given the progression while on placebo.
Conclusion: Patients with long-term exposure to patisiran continue to demonstrate durability of efficacy and patisiran demonstrates a positive benefit:risk profile. Topic: Neurological manifestations of systemic diseases

LB3

MnSOD Ala16Val Polymorphism in Cognitive Dysfunction in Epilepsy Patients: a Relationship with Inflammatory Markers

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Introduction: To evaluate the neurocognitive profile and its relation with Ala16ValMnSOD (manganese-dependent superoxide dismutase) polymorphism in the epilepsy, and if these clinical parameters are linked to inflammatory markers.
Methods: Epileptic patients (n=31) and healthy subjects (n=42) were recruited to participate in this study. Neuropsychological evaluation was performed in both groups through a battery of cognitive tests. Inflammatory markers, apoptotic factors, and DNA damage were measured in blood samples.
Results: Statistical analyses showed the association MnSOD Ala16Val polymorphism with cognitive impairment, including praxes, perception, attention, language, executive functions, long-term semantic memory, short-term visual memory, and total memory in epilepsy patients with VV (valine homozygous) genotype compared to the control group. Compared to the controls and epilepsy patients with AA (alanine homozygous) and AV (alanine-valine) genotype, epilepsy patients with VV genotype exhibited higher levels of TNF-alfa, IL-1 beta, IL-6 as well as higher activation of caspases 1 and 3 (CASP -1 and -3), and DNA damage. Our findings also showed higher SOD and acetylcholinesterase (AChE) activities in epilepsy patients with VV genotype.
Conclusion: This study supports the evidence of a distinct neuropsychological profile in epileptic patients, mainly with VV genotype. Furthermore, our findings suggest that inflammatory pathway may be associated with genetic polymorphism and cognitive dysfunction in epilepsy patients.

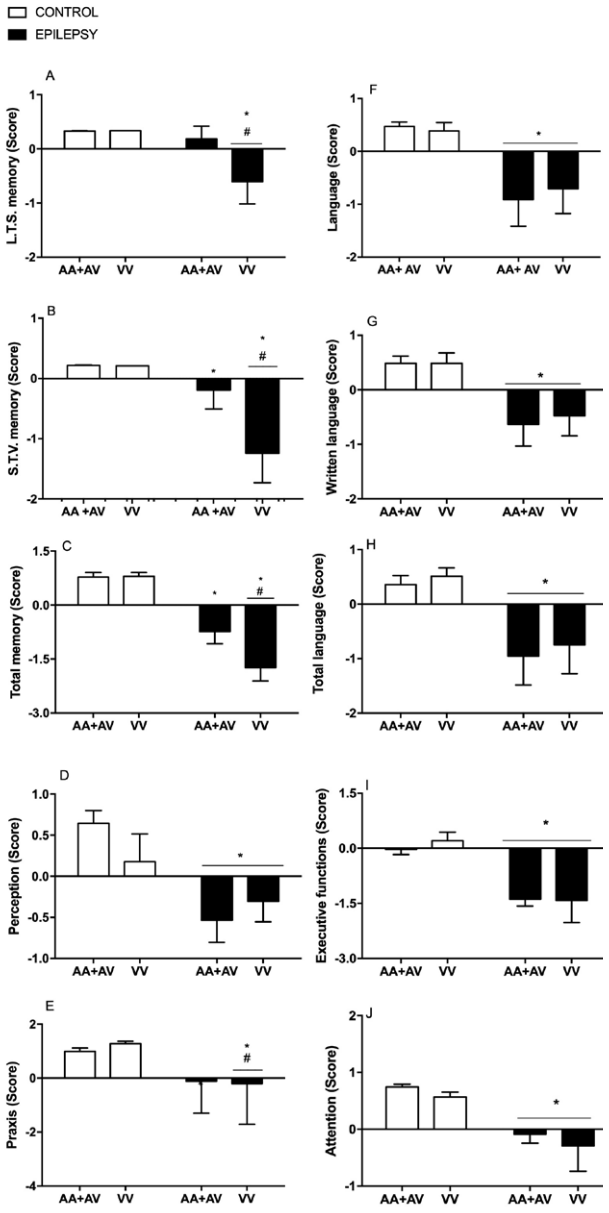

Figure 1: Relation of Ala16ValMnSOD polymorphism with Long-Term Semantic Memory (A), Short-Term Visual Memory (B), Total Memory (C), Perception (D), Praxis (E), Oral Language (F), Written Language (G), Total Language (H), Executive Functions (I), and Attention (J). Statistical analysis was significant if *p<0.05 when epilepsy group was compared to respective control group. Statistical analysis was significant if *p<0.05 when VV and AA+AV epilepsy groups were compared to respective control group and #p<0.05 when VV epilepsy group was compared to AA+ AV epilepsy group.

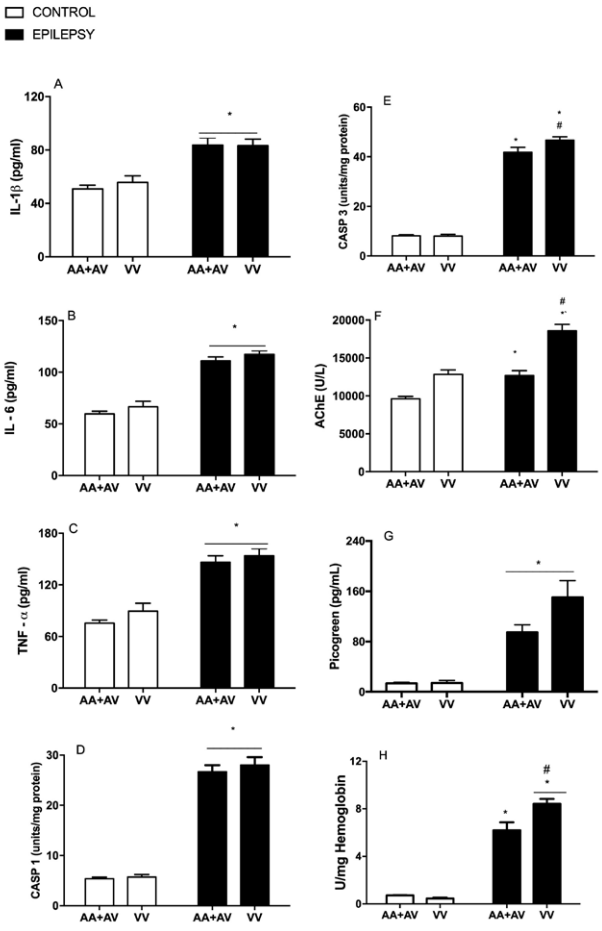

Figure 2: Relation of Ala16ValMnSOD polymorphism with, IL-1 beta (A), IL-6 (B), TNF-alfa (C), CASP-1 (D), CASP-3 (E), AChE activity (F), Picogreen (G), and SOD activity (H). Statistical analysis was significant if *p<0.05 when VV and AA+AV epilepsy groups were compared to respective control group and #p<0.05 when VV epilepsy group was compared to AA+ AV epilepsy group.

Table 1. Characteristics of epilepsy of control groups

CHARACTERISTICS	EPILEPSY (n=31)	CONTROL (n=42)	χ^2	P
Sex (%)				
Male	15 (48.4%)	22 (52.4%)	0.11	0.73
Female	16 (51.6%)	20 (47.6%)		
Mean age (Years)				
Male	32.1	21.1	1.44	0.22
Female	31.2	32.2		
Mean of crisis (min)	6.1	0		
AEDs use (%)				
None kind	0	42 (100%)		
One kind	12 (38.7%)	0		
≥Two kinds	19 (61.3%)	0		

AED= Antiepileptic drug. Data are expressed as percentage.

LB12

Viral encephalitis in Brazil: hospitalization and mortality in 2019

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Background and aims: Encephalitis is an inflammation of the brain parenchyma. Viruses are the most common agents associated with acute encephalitis. The most important agents worldwide are the herpes viruses and arboviruses, being the same in Brazil.
Methods: The data were obtained from the Hospital Information System of the Unified Health System. The evaluated information includes the number of hospitalizations and deaths - by age group and gender - as a result of viral encephalitis in Brazil, in 2019.
Results: There were 18,894 hospitalizations in Brazil in 2019 due to viral encephalitis. Regarding gender, females had 9,875 (52,26%) hospitalizations and males 9,019 (47,73%). About the age group, the highest prevalence of this pathology was in individuals between 0 and 4 years old, with 4,665 (26,4%) hospitalizations. In contrast, the elderly over 80 years old had only 142 hospitalizations (0,75%). There were 324 deaths due to viral encephalitis in 2019, 152 (46,9%) of whom were female and 172 (53,08%) were male. Regarding the age group, the highest number of deaths was found between 0 and 4 years, with a number of 190 (58,64%). In comparison, the lowest number of deaths were observed in individuals between 15 and 19 years, who had 4 (1,23%) deaths in the 2019.
Conclusion: Viral encephalitis still being a pathology with high incidence in the brazilian territory, presenting worse morbidity and mortality in the child age group.

LB15

1 Year Data from First in Human Study of Pegzilarginase for the Treatment of Arginase 1 Deficiency (ARG1-D)

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Background: Arginase 1 deficiency (ARG1-D) is a debilitating, progressive, inherited, metabolic disease associated with the accumulation of arginine and metabolites. ARG1-D typically manifests in early childhood with progressive spastic diplegia, developmental delay, intellectual disability, and seizures, in addition to hyperammonaemia, which may not be prominent, leading to delays in diagnosis. Current treatment (severe protein restriction, amino acid supplements and ammonia scavengers) does not adequately control arginine (target<200 μM) or the progression of symptoms in the majority of patients, often leading to early mortality
Methods: Pegzilarginase is a cobalt substituted, pegylated human recombinant arginase 1 enzyme therapy. Here, we report the safety and efficacy of pegzilarginase in the treatment of 13 adult and paediatric ARG1-D patients who reached at least 56 weeks of follow-up in a Phase 1/2 study.
Results: Baseline median plasma Arginine (pARG) was 390 μM (normal range 40-115 μM). pARG reduction was significant with median levels of 112μM during follow up with 8/13 patients in the normal range. Clinically there were improvements in 6MWT (mean change 46m) and in measures of neuromuscular function (GMFM-D and E). The most common treatment related SAEs were hypersensitivity, which was manageable and decreased over time, and hyperammonaemia, which is a known feature of ARG1-D.
Conclusions: Pegzilarginase was effective in lowering pARG levels with an accompanying clinical response in patients with ARG1-D, with sustained effects seen after 1 year of therapy. These improvements occurred on a background of standard treatment and suggest that significant benefit could be gained from the addition of pegzilarginase.

LB16

Modafinil effects on long-term brain dysfunction in sepsis

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Introduction: Modafinil (MD) is a psychostimulant drug indicated for the management of sleep disorders that cause excessive sleepiness. MD is also used off-label as an adjunctive treatment for neuropsychiatric disorders due to its positive effect in cognitive and executive function. The objective of this study was to evaluate the effect of MD in the memory impairment and neurochemical parameters of rats submitted to sepsis by cecal ligation and perforation (CLP).
Methods: Male Wistar rats (250-350g) were submitted to CLP, or sham as control, and divided into the groups sham+water, sham+MD (300mg/kg), CLP+water and CLP+MD (300mg/kg). Ten days after administration of MD and CLP, the rats were submitted to passive avoidance test before being sacrificed.
Results: The nitrite and nitrate (N/N) concentration, myeloperoxidase (MPO) and catalase (CAT) activity, lipid and protein oxidative damage, and brainderived neurotrophic factor (BDNF) levels were measured in their prefrontal cortex and hippocampus. Results revealed decreased N/N concentration and MPO activity in the prefrontal cortex of rats submitted to CLP and MD, as well as reduced lipid and protein oxidative damage in hippocampus, which was accompanied by increased CAT activity and BDNF levels. The behavioral test, was verified an increase of the latency time in the groups sham+water and CLP+MD.
Conclusion: Collectively, our data indicates the role of Modafinil in the attenuation of oxidative stress parameters, as well as the alteration of BDNF and an improvement in memory impairment in rats 10 days after induction of sepsis.

LB21

The epidemiological profile in ceará in diagnostic patients with meningitis associated with social determinants

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Presentation preference: poster
Presenter: Carlos Victor Chaves de Lima
Introduction: In the last ten years, despite the reduction in meningitis cases observed in Brazil, the state of Ceara showed an increase of 70,12%. The situation is worrisome considering the clinical repercussions that the disease brings. In this manner, the current study has the objective to link the data with social, economical, and ethical/racial factors.
Methods: This work is a descriptive epidemiological study, carried out from the analysis of data from Sistema de Informação de Agravos e Notificação (SINAN), in Brazil Health Ministry, and from the Boletim Epidemiologico da Meningite, from State of Ceara Health Department. The data was tabulated in Excel and analyzed using descriptive statistics.
Results: From 2010 to 2019 there was non-linear increase of 100,80% of meningitis cases among browns, while there was a 34,78% reduction among whites. In addition, there was a 133,33% increase among individuals with no middle school degree from 5th and 8th grades, and a 50% increase among those with incomplete High School degree. In the same period, the number of male patients represented 61,755% against 38,218% of female patients.
Conclusion: The discussion raised here is evidence that the epidemiological profile in Ceara is male, brown and poorly educated. In this manner, mitigating public policies are pressing considering the social reality, as well as a more action in social economical matters regarding this scenario. Therefore, more studies are needed to achieve more concrete conclusions.

LB24

Pembrolizumab for progressive multifocal leukoencephalopathy in a patient with myelodysplasia and graft-versus-host disease

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Introduction: Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system caused by the John Cunningham virus (JCV). Recently, there has been interest in pembrolizumab for the treatment of PML.[1,2] A 52-year-old male with a history of myelodysplasia and graft-versus-host-disease (GVHD) was diagnosed with PML. Treatment with pembrolizumab was tried despite concerns of exacerbating his GVHD or causing immune-related adverse events.[3]
Methods: The patient was taking mycophenolate mofetil (MM) and prednisone for GVHD. MM was discontinued. Prednisone was continued due to adrenal insufficiency. He received pembrolizumab 2 mg/kg intravenously. Serial exams, lumbar punctures (LPs), and magnetic resonance imaging (MRI) were performed. Although he was scheduled for three doses of pembrolizumab at four week intervals, the patient was palliated after the first dose.
Results: After one dose of pembrolizumab, he declined neurologically. His modified Rankin score increased from 2 to 5 over four weeks. MRI revealed progressive white matter lesions. LPs revealed persistent positive cerebrospinal fluid (CSF) JCV polymerase chain reaction (PCR). Serial quantitative CSF JCV PCR was not obtained due to issues with sample processing. His GVHD remained stable despite cessation of MM and administration of one dose of pembrolizumab.
Conclusion: Pembrolizumab was not helpful in treating this patient's PML, but it also did not exacerbate his GVHD. Given that he only received a single dose of pembrolizumab, our interpretation of this is limited. Appropriate caution should be taken in patients with complex immune profiles, as the risks and benefits of pembrolizumab to treat PML remain uncertain.

[1]Cortese I, Muranski P, Enose-Akahata Y, et al. Pembrolizumab Treatment for Progressive Multifocal Leukoencephalopathy. N Engl J Med 2019; 380(17): 1597-1605. [2]Rauer S, Marks R, Urbach H, et al. Treatment of Progressive Multifocal Leukoencephalopathy with Pembrolizumab. N Engl J Med 2019; 380(17). [3]Abdel-Wahab N, Shah M, Lopez-Olivo MA, et al. Use of Immune Checkpoint Inhibitors in the Treatment of Patients with Cancer and Preexisting Autoimmune Disease: A Systematic Review. Ann Intern Med 2018; 168(2): 121-130.

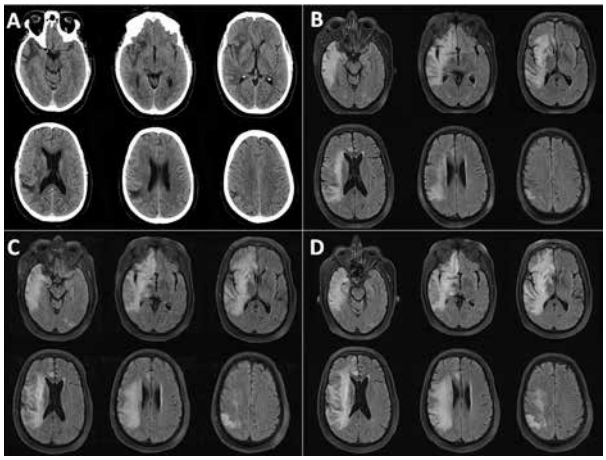

Figure 1. Serial neuroimaging done on presentation and following treatment with pembrolizumab, showing radiographic progression correlating with clinical deterioration.

A) Axial CT head with contrast done on presentation revealed hypoattenuation throughout the white matter of the right temporal, frontal, and parietal lobes. The cortex was spared. There was mild mass effect, with approximately 4 mm of midline shift to the left. There was no enhancement.
B) Initial axial T2 FLAIR MRI of the brain showed confluent T2 hyperintensity throughout the white matter of the right temporal, frontal, and parietal lobes. There was mild edema and mass effect, with 3.5 mm of midline shift. There were no areas of gadolinium enhancement (not shown).
C) Repeat axial T2 FLAIR MRI done 10 days after pembrolizumab was limited by movement artifact. However, it clearly revealed interval increase in non-enhancing, confluent right temporal, frontal, and parietal white matter T2 hyperintensity. Involvement of the right basal ganglia and precentral gyrus increased, and there was new involvement of the right caudate head, right thalamus, and right cerebral peduncle. There was a leading edge of restricted diffusion, but no pathological enhancement (not shown).
D) Final axial T2 FLAIR MRI done 17 days after pembrolizumab showed ongoing progression in the same areas as prior, with stable mass effect and midline shift.

LB32

NLRP3 inflammasome contributes to microglial activation and cognitive impairment in sepsis-surviving rats

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Introduction: Sepsis survivors present acute and long-term cognitive impairment and the pathophysiology of neurological dysfunction in sepsis involves microglial activation. Recently, the involvement of cytosolic receptors capable of forming protein complexes called inflammasomes have been demonstrated to perpetuate neuroinflammation. Thus, we investigated the involvement of the NLRP3 inflammasome activation on early and late brain changes in experimental sepsis.
Methods: Two-month-old male Wistar rats were submitted to the sepsis model by cecal ligation and perforation (CLP group) or laparotomy only (sham group). Immediately after surgery the animals received saline or NLRP3 inflammasome formation inhibitor (MCC950, 140 ng/kg) intracerebroventricularly. Prefrontal cortex and hippocampus were isolated for cytokine analysis, microglial and astrocyte activation, oxidative stress measurements, nitric oxide formation, and mitochondrial respiratory chain activity at 24 h after CLP. A subset of animals was followed for 10 days for survival assessment, and then behavioral tests were performed.
Results: The administration of MCC950 prevented the elevation of IL-1β, TNF-α, IL-6 and IL-10 cytokine levels in the hippocampus. NLRP3 receptor levels increased in the prefrontal cortex and hippocampus at 24 h after sepsis, associated with microglial, but not astrocyte, activation. MCC950 prevented oxidative damage to lipids and proteins as well as preserved the activity of the enzyme SOD in the hippocampus. Mitochondrial respiratory chain activity presented variations in both structures studied.
Conclusion: MCC950 reduced microglial activation, decreasing acute biochemical and behavioral damage and increased survival after experimental sepsis.

LB34

Sleep quality and circadian rhythm phase preferences among institutionalised and non-institutionalised groups of elderly people in Fortaleza, Brazil.

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Introduction: Although a sleep-wake consolidation reduction might occur among the elderly, its quality should not necessarily worsen. The Pittsburgh Sleep Quality Index (PSQI) evaluates sleep quality during one-month. It consists of questions answered by the person evaluated and their roommate. The Morningness-Eveningness Questionnaire (MEQ), available as a circadian phase test based on the respondent's responses, characterized as „morning" or „afternoon" types. This study aims to compare sleep quality and circadian rhythm phase preferences from elderly people residing in a Long-Stay Care Facility (LCSF) to those who do not.
Methodology: This is a cross-sectional, observational study, conducted between july/2018 and july/2019 in Fortaleza, Brazil, with 189 elderly people living in a LSCF or not. Both PSQI and MEQ were applied.
Results: The data obtained from the PSQI application in 88 institutionalised elderly people revealed that 36 had good sleep quality, 37 reported poor quality and 15 referred some sleep disorder. Among 101 non-institutionalised seniors, 35 presented good sleep, 43 had poor quality and 22 showed sleep disorder.The MEQ results from 101 non-institutionalised people evaluated indicates that 83 classified as morning types, whereas the rest of them matched to an intermediate level. Results from those in LSCF varied among intermediate, moderately and definitely morning types. None of the seniors assessed had been classified as "evening types".
Conclusion: After the application of questionnaires, all seniors were classified as "morning types", as well as non-institutionalised seniors reported poorer sleep quality than those in LSCF.

LB35

Is transient hyperCKemia a new feature of neuromyelitis optica spectrum disorders? A retrospective study in 439 patients

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Objective: To investigate the incidence of hyper CKemia in patients with neuromyelitis optica spectrum disorders (NMOSD) and the clinical characteristics of these patients.
Method: A series of 439 NMOSD patients were retrospectively observed and followed. Records of patients with hyperCKemia were analyzed.
Results: 19 patients had elevated CK levels, absolutely occurred in the acute phase of the disease. No CK elevation was observed in positive MOG antibody patients or negative AQP4 antibody patients. All the 19 patients were positive for AQP4 antibodies. 4/19 cases showed classic NMO manifestations, 4/19 cases showed optic neuritis only, 3/19 cases showed myelitis only, area postrema syndrome was present in 8/19 cases. CK levels were reduced to the normal range after treated with tapering methylprednisolone. 18/439 patients were conducted muscle MRI, 4 patients presented with myositis changes, and all of them were positive for AQP4.
Conclusions: Muscle involvement can only be seen in seropositive AQP4 NMOSD patients and mostly occured in the acute phase of the disease. The MRI findings were mainly described as inflammatory changes, which did not consistent with CK levels or clinical symptoms. The ictus treatment of large dose methylprednisolone can reduce CK levels to normal. Transient hyperCKemia might be a new feature of NMOSD, more attention are recommended to this phenomenon.
Keywords: NMOSD; Muscle damage; HyperCKemia; Magnatic resonance imaging

LB36

The effect of canabidiol on cerebral dysfunction in experimental sepsis: pparγ receptor involvement

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Introduction: Neuroinflammation and oxidative stress are pathophysiological mechanisms involved in Sepsis-Associated Encephalopathy, which is related to brain and memory damage. The immunomodulatory effect of cannabidiol (CBD) is well known and the objective was to verify whether CBD exerts a neuroprotective effect on experimental sepsis dependent on the PPARγ activation using a receptor antagonist.
Methods: Wistar rats were submitted to sepsis by cecal ligation and puncture (CLP) model. The groups were divided into SHAM (control)+vehicle, CLP+vehicle, CLP+CBD (10mg / kg), CLP+PPARγ antagonist GW9662 (1mg / kg), CLP+CBD (10mg / kg) + GW9662. Ten days after CLP and CBD treatments, the Passive Avoidance Behavioral Test was performed and subsequently the prefrontal cortex and hippocampus were removed for biochemical analyzes (Myeloperoxidase (MPO), Nitrite Nitrate (N / N), Catalase (CAT), Substances Reactive to Thiobarbituric Acid (TBARS), Carbonyl protein).
Results: CBD was able to reduce MPO activity in the CLP+CBD group when compared to CLP+vehicle. Treatment with the PPARy inhibitor isolated or in association was not able to attenuate MPO activity. There was a reduction in the N / N concentration, lipid peroxidation and oxidative damage in proteins in the group treated with CBD. In the Passive Avoidance Behavioral Test, the SHAM+vehicle and CLP+CBD groups had an increase in the latency when compared training to the test 24h after.
Conclusion: CBD was effective in improving the parameters of oxidative stress, neuroinflammation and the performance of animals aversive memory depending on the activation of the PPARγ receptor.
Palavras-chave 4-6: Sepse, Canabidiol, estresse oxidativo, PPARy.

LB37

lipoic acid and fish oil association potentiates neuroinflammation and oxidative stress regulation and prevents cognitive decline of rats after sepsis

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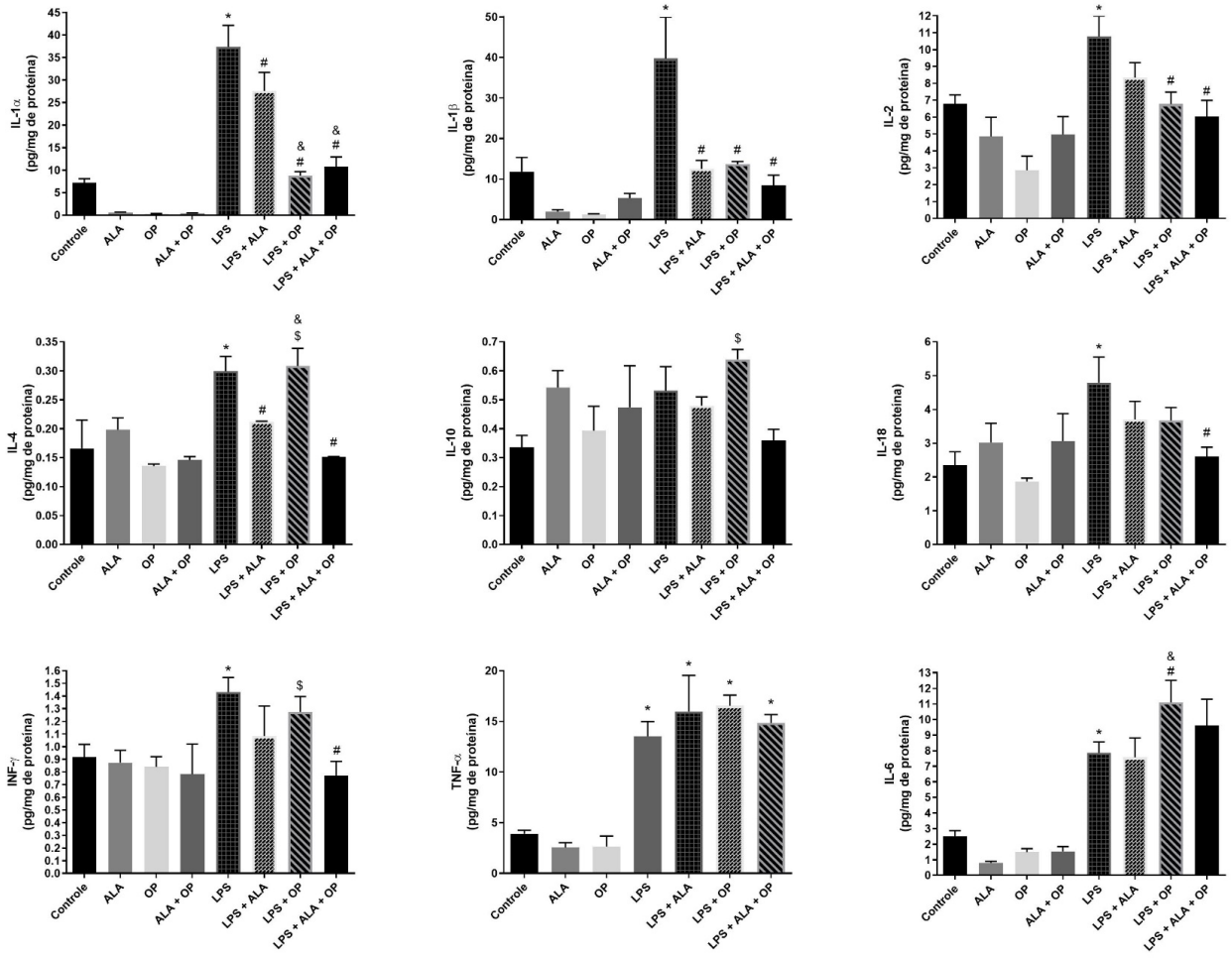
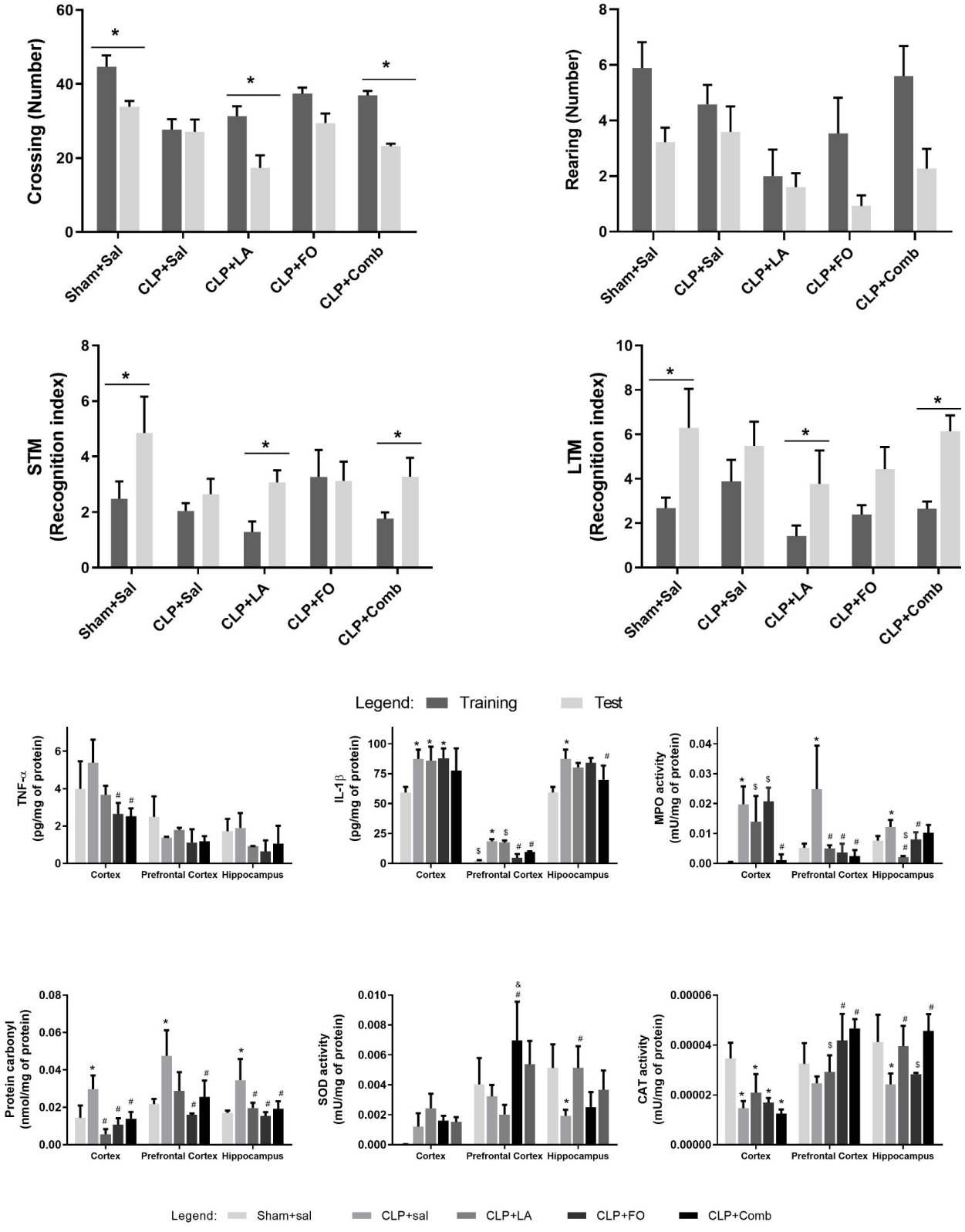
Introduction: sepsis causes organ dysfunction due to an infection and it may impact the central nervous system. Neuroinflammation and oxidative stress are related to brain dysfunction after sepsis. Both processes affect microglia activation, neurotrophin production and long-term cognition. Fish oil (FO) is an anti-inflammatory compound, and lipoic acid (LA) is a universal antioxidant substance. They exert neuroprotective roles when administered isolated. We aimed at determining the effect of FO + LA association on microglia activation and on brain dysfunction after sepsis.
Methods: microglia cells from neonatal pups were co-treated with lipopolysaccharide (LPS), FO or LA, isolated or combined, for 24 hours. Cytokine levels were measured. Wistar rats were subjected to sepsis by cecal ligation and perforation (CLP) or sham (control) and treated orally with FO, LA, or FO+LA. At 24 h after surgery, the hippocampus, prefrontal cortex, and total cortex were obtained and assayed for levels of cytokines, myeloperoxidase (MPO) activity, protein carbonyls, superoxide dismutase and catalase activity. At 10 d after surgery, brain-derived neurotrophic factor (BDNF) levels were determined and behavioral tests were performed.

Results: the association diminished in vitro levels of pro-inflammatory cytokines. The association reduced TNF-alfa in the cortex, IL-1beta in the prefrontal cortex, as well as MPO activity, and decreased protein carbonyls formation in all structures. The association enhanced catalase activity in the prefrontal cortex and hippocampus, elevated BDNF levels in all structures and prevented behavioral impairment.

Conclusion: the association was effective in preventing cognitive damage by reducing neuroinflammation and oxidative stress and increasing BDNF levels.

in vitro evaluations




Crossing (Number)
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STM (Recognition index)
LTM (Recognition index)
Sham+Sal
CLP+Sal
CLP+LA
CLP+FO
CLP+Comb
Legend: Training Test
TNF-α (pg/mg of protein)
IL-1β (pg/mg of protein)
MPO activity (mU/mg of protein)
Protein carbonyl (nmol/mg of protein)
SOD activity (mU/mg of protein)
CAT activity (mU/mg of protein)
Cortex
Prefrontal Cortex
Hippocampus
Hipoocampus
Legend: Sham+sal CLP+sal CLP+LA CLP+FO CLP+Comb

LB38

Ageing influences in the blood-brain barrier permeability and cerebral oxidative stress in sepsis

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Introduction: Sepsis compromises cellular homeostasis and can result in dysfunction of the central nervous system. The elderly had a higher risk of developing sepsis than the younger ones. Under the influence of inflammatory mediators and oxidizing agents released in the periphery as result of the infectious stimulus, changes occur in the bloodbrain barrier(BBB) permeability, with neutrophil infiltration, passage of toxic compounds, activation of microglia and production of reactive species that results in potentiation of neuroimmune response, with progression of neuronal damage and neuroinflammation. The permeability of BBB and the development of oxidative stress was compared in the hippocampus and prefrontal córtex(PFC) of young and old rats submitted to the induction of severe polymicrobial sepsis.

Methods: Male Wistar rats grouped into: adult(60d) and old(210d) sham, adult and old cecal ligation and puncture(-CLP) that was induced severe sepsis(n =16 per experimental group). Hippocampus and PFC were collected 24h after sepsis induction for analysis.

Results: The concentration of nitrite/nitrate, the myeloperoxidase activity(MPO) and the damage to lipids and proteins in the structures were increased in the CLP groups. Only hippocampus in MPO had an increase in the CLP 210d group compared to the 60d group and for lipid peroxidation there was a difference between the PFC and CLP groups. Catalase activity(CAT) in hippocampus was decreased in CLP groups and in the CLP 210d group compared to the CLP 60d group.

Conclusion: The findings indicated that ageing potentiated BBB permeability in sepsis, which possibly caused an increase in neutrophil infiltration and oxidative stress.

LB39

Mysterious Ataxia and Refractory Epilepsy, or Maybe not? Report of a Case of an Opsoclonus-Myoclonus Syndrome

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Background: Opsoclonus-Myoclonus Syndrome (OMS) is a rare disorder characterized by opsoclonus, myoclonus, ataxia, behavioural and sleep disturbances. It is presumed to be an autoimmune disorder (paraneoplastic or postinfectious). Onset is usually abrupt. In a sustained number of cases, a full recovery could be seen, especially in the setting of early immunotherapy. We present a case of OMS, which was unrecognized during 25 years of paediatric and neurological follow-up and considered as refractory epilepsy and ataxia of unknown cause.

Case presentation: 27-year-old woman was referred to our Centre as pharmacoresistant epilepsy. She had normal development until the age of 2 when she experienced eyelid myoclonic status. She was diagnosed with epilepsy and introduced valproate and clonazepam. She continued taking antiepileptic drugs during the next 25 years while presenting with progressive ataxia and pharmacoresistant multifocal myoclonus. A myriad of diagnostic tests was performed with no clue for the diagnosis. At the time of admission to our Centre patient had severe opsoclonus, dysarthria and ataxia (ambulatory only with the help of another person). After a detailed review of patient‘s medical reports, we noticed a viral prodrome 20 days before the myoclonic status. The patient was diagnosed as chronic postinfectious OMS. After administered immunotherapy we have observed a significant recovery, most notably in reduction of opsoclonus and ataxia (now ambulatory without assistance).

Conclusion: We reported an extreme case of a misdiagnosed OMS, treated as refractory epilepsy during 25 years in which, despite the duration, we observed significant recovery after immunotherapy.

LB41

An unusual Case of simultaneous presentation of POTS and APS with hematologic resistance to anti-coagulative therapy

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Introduction: Postural tachycardia syndrome (POTS) is a debilitating disorder often caused by a dysregulation of the peripheral autonomic nervous system. Mostly occurring in young women it affects approximately 1% of the population. Patients experience symptoms of orthostatic intolerance and non-orthostatic neurologic symptoms with significant impairment of daily life. The occurrence of anti-alpha-adrenergic-autoantibodies suggest an autoimmune etiology in some patients. Antiphospholipid syndrome (APS) is a hypercoagulative autoimmune disorder associated with anti-phospholipid-antibodies that causes arterial and venous thrombosis.
Methods and Results: Here we report a 28-year-old female that presented with palpitations, vertigo and vasovagal syncopes upon standing, as well as marked heat and exercise intolerance. She fulfilled the criteria of POTS showing a clinically symptomatic heart rate (HR) increase of 53-beats-perminute (bpm) and an increase in HR to 121 bpm within 10 min of standing as well as in headup tilt (HUT), in absence of orthostatic hypotension. The thermoregulatory sweat test revealed a severe patchy anhidrosis. Serologically anti-alpha-1-adrenergic autoantibodies were found and we could not detect elevated norepinephrine levels. Thus we could confirm the neuropathic subtype of POTS. During the disease course she developed APS that was hematologically unresponsive to several anti-coagulative treatments.
Conclusion: To our knowledge, this is the first report of POTS and APS presenting one after the other. We discuss the specific pitfalls of the diagnosis and treatment in this case, and speculate of possible driving etiologies. Furthermore, the resistance to various anti-coagulative agents for treatment of the APS is highly unusual and might reflect the complexity of the pathogenesis.

LB42

Is thrombolytic treatment with Tenecteplase a new trend in the management of the acute phase of ischemic stroke?

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Autorship: *All authors have made substantial contributions to all of the following: the conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted.*

Background and aims: Thrombolytic treatment with Alteplase recombinant tissue plasminogen activator is the established standard therapeutic strategy, whose benefit has already been proven[1], for the management of Ischemic Stroke in the acute phase. However, some evidences indicate that this drug also has negative effects on cerebral ischemia[2], including cytotoxicity and increased blood-brain barrier permeability, which contributes to cerebral edema[3–6]. Thus, Tenecteplase emerges as an alternative therapy that can minimize such effects. This study aims to compare the efficacy of Alteplase with Tenecteplase in the treatment of the acute phase of ischemic stroke.
Methods: A search for scientific articles published between the 2001 and 2017 was carried out in the PUBMED database. The descriptors "Alteplase", "Tenecteplase" and "Acute Ischemic Stroke" were used, resulting in the following research formula: "((alteplase) AND tenecteplase) AND acute ischemic stroke)".
Results: In one study – a randomized, open label, phase IIb clinical trial[7] – there was considerable benefit in relation to the use of Tenecteplase for the primary outcomes „greater reperfusion within 24 hours after treatment" and „clinical improvement within 24 hours". In a randomized, open label, phase III clinical trial[8], Tenecteplase did not demonstrate superiority in relation to Alteplase for the primary outcome "score between 0-1 on the modified Rankin scale in three months".
Conclusion: Although Tenecteplase is more easily administered as a single bolus and has a higher recanalization rate than Alteplase, randomized, double-blind, phase III clinical trials need to be conducted to prove efficacy and safety of its use in clinical practice.

Disclosures:
Conflict of interest: The study is not receiving funding/assistance from any commercial organizations.
Originality: All authors declare that neither this study nor one with substantially similar content, has been submitted, accepted or published elsewhere.
Copyrights: This is a study carried out exclusively by the aforementioned authors, which did not receive support from other institutions.Bibliographic references were duly registered, guaranteeing the integrity of this research.

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LB44

Evaluation of the masticatory activity influence on numerical estimate of astrocytes in CA1 and CA3 layers of hippocampus in murine model

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Introduction: Evidences indicate that reduction in masticatory activity works in detrimental to memory. To measure possible influences of masticatory changes on the astrocyte population of hippocampus in murine model we imposed one of three diets regimens on different experimental groups, from the 21st postnatal days onward until 6 months, when the animals were, then, sacrificed. To that end the control groups with normal, reduced and rehabilitated masticatory activity received, respectively, a pellet-type hard diet (HD), a pellet diet followed by a powdered diet (HD/SD) and pelletized diet followed by powder and pellet again (HD/SD/HD). The changing intervals were proportionally divided.
Methods: After 21 days, experimental groups were arranged according to changes in masticatory activity. After six months, we conducted anti-GFAP immunohistochemistry for stereological procedures, to access the laminar distribution in the hippocampus (Ammon's Horn 1 - CA1 and 3 – CA3).
Results: The analysis of *oriens* layers, from CA1 and CA3, revealed difference between HD groups (Figure 1). In *radiatum*-CA1, HD showed greater number of astrocytes, when compared to HD/SD (Figure 2). The comparison between layers on the same region showed no significant difference (Table 1).
Conclusion: Reduction of masticatory activity in mice decreased numerical astrocyte population in CA1 *(radiatum)* and masticatory activity rehabilitation seems to recover these losses. In addition, the analysis of hippocampal layers may show differences in astrocytes number in different regions and the change in masticatory activity influences the number of cells in these layers.

LB45

The epidemiological profile of patients diagnosed with leprosy, in the state of ceara between 2014 and 2018, that have social determinants as aggravating factors

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Introduction: Leprosy is an infectious disease of a chronic nature that causes neural lesions capable of damaging the body's functioning. In Brazil, between 2014 and 2018, were 172,627 new cases were notified, 8,536 of them in the state of Ceará. Therefore, the objective is to evaluate the epidemiological profile, in the state of Ceará between 2014 and 2018, of leprosy patients who have social determinants as aggravating factors.
Methods: This is an analysis quantitative based on leprosy indicators. Secondary data from the Brazilian Ministry of Health's Aggravated Notification Information System (SINAN), as well as the epidemiological bulletin of Leprosy, of the Secretary of Health of Ceará.
Results: In the state of Ceará, leprosy reached predominantly males (57.4%) between 2014 and 2018. Moreover, the average detection rate, taking into account the age range, was higher in the population over 60 (55.7/100,000 inhabitants) and in all age groups there was a rate reduction, the most significant being in individuals under 15 years of age, with a reduction of 60% of new cases. Furthermore, the brown-skinned population was mostly affected, representing 65.61% of the cases detected. Also, during this period the population with incomplete primary education represented the majority of new cases with 38.54%.
Conclusion: Considering the results exposed, health education is necessary as a form of prevention of this disease. Can be used active methodologies such as: culture wheels and theatres. In this way, we will decrease the number of new cases of leprosy.

LB47

Scientific integrity of adaptive randomized clinical trials in neurology: a call for critical scientific consumption.

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Centre for Evidence Based Medicine of Bahiana School of Medicine and Public Health

Introduction: Randomized clinical trials (RCTs) are recognized as the best design for testing interventions. Adaptive RCTs aim to decrease the cost and completion time from changes during the study after registration of the protocol. Our study aims to describe the pattern of scientific integrity of adaptive clinical trials in Neurology.
Methods: We searched on PubMed using descriptors for adaptive studies without data filter. Among the phase II and III studies, those in the area of neurology were identified and its references were searched for more articles. Data extracted included, type of adaptation, a priori protocol registration within clinicaltrials.gov, presence of an Independent Monitoring Committee (IMC) and its blinding for data analysis. An evidence quality analysis was also performed. More than one reviewer performed data extraction and review.
Results: We analyzed 10 phase II or III adaptive RCTs in Neurology. The subjects were stroke, migraine, peripheral neuropathic pain and spinal surgery failure syndrome. Within the stroke studies, 4 were published in the New England Journal of Medicine and 1 in the American Stroke Association. Overall, conclusions were positive in 70%. 100% of the negatives had spin. 60% not pre-defined adaptation in the study protocol. 70% had IMC, but 86% of those were not blinded to assess interim analyzes. 60% were sponsored by the pharmaceutical industry.
Conclusions: The level of scientific integrity in adaptive clinical trials in the field of neurology is unsatisfactory.

LB48

The interference of sleep-wake cycle in alzheimer's progression.

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Introduction: Losses in sleep architecture, already present in elderly, are often found together with the disruptive behavioral symptoms of Alzheimer's dementia, sleep impairments can have a substantial impact on cognitive activity. Interference in the sleep-wake cycle, given by the fragmentation of sleep, suggest a deficit of cognitive functions and possible demential progression.
Methods: This is a retrospective analytical study with a descriptive approach. It was conducted by applying a questionnaire based on the Neuropsychiatric Inventory, covering questions about sleep pattern in patients with Alzheimer's disease retrospectively.
Results: The study analysis include 17 participants. The age range varies from 60 to 92 years. Most patients had an average daily sleep time of 6 to 8 hours. 38.4% of those interviewed had symptoms of nocturnal psychomotor agitation, with frequent interruptions at night. Research data show the high prevalence of sleep-deprivation-related disorders, which affect approximately 41% of patients. As for the quality of sleep, only 35.2% of patients reported not having a peaceful and deep sleep all night. Of these, approximately 23.5% reported difficulties in initiating sleep, and around 29.4% of respondents reported having difficulty maintaining sleep for a satisfactory period of time. Of those who had sleep disorders, only 29.4% of this appeared in the past and 41%, appeared after the diagnosis of Alzheimer's dementia. Regarding the relationship of disorders with Alzheimer's progression, 47% of patients had shown a worsening of sleep deprivation disorders after diagnosis.
Conclusion: This study evidences a probable involvement between sleep impairment, mainly sleep disruption, and the Alzheimer's dementia.
Keywords: Alzheimer. Dementia. Sleep disturbance. Sleep deprivation

LB49

The pathophysiology of glucocerebrosidase and parkinson's disease: a review

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Introduction: The Mutations of the gene GBA1 has a importante relevance leading to a deficiency of lysosomal enzyme glucocerebrosidase (GBA), associated to lysosomal storage disorder, Gaucher disease. This mutations are the most common genetic risk factors for the development of diverse Parkinsonism phenotypes, including Parkinson's Disease (PD). Thus, knowning the interactions between this disorders could lead to a increased quality of life of this patients and better treatment.
Methods: This is na integrative literature review study, presenting na analysis of articles published in the period from 2019 to 2020, available in the databases SciencDirect and Pubmed.
Results: The incidence of GBA mutations is significantly higher among PD patients, associated with earlier age onset, rapid progression and a more pronounced deficit of cognitive functions. However, just a small portion of GBA carriers will develop PD, due to his reduced penetration.
The glucocerebrosidase is part of the endolysosomal pathway, crucial to the pathogenesis of the Parkinson Disease. The mechanism of this association are not totally understud. The main hypotesis leads to an inverse relationship between glucocerebrosidase and alpha-synuclein levels. Moreover Parkinson disease has decreased glucocerebrosidase levels that could contribute to the pathogenesis of the disease by disrupting lysosomal homeostasis, enhancing endoplasmic reticulum stress or contributing to mitochondrial impairment. Furthermore, the accumulation of alpha-synuclein in the dopaminergic neurons is one of the hallmarks of PD.
Conclusion: The knowledge of the association between mutations of GBA gene and PD, contribute to the understanting of the pathophysiology. Thus, therapies that make approaches that enhance glucocerebrosidase levels could prove efficacious in the treatment of forms of parkinsonism.

LB51

Nocturnal pruritus: an experimental study in humans in response to histamine-evoked itch

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Introduction: Nocturnal pruritus, is a common symptom with a negative impact on quality of life. The pathophysiological mechanisms are still unclear; however, a disruption in circadian rhythm of prostaglandins (PGs) has been proposed. We investigated features of nocturnal pruritus by applying a surrogate model of itch.
Methods: A histamine (1%) provocation test was utilized on volar forearm of healthy volunteers (20-30 years) to examine itch characteristics in daytime and night. Itch intensity was assessed for 15 min on a visual analogue scale. Participants drew their perceived itch area and dispersion of wheal and flare areas were marked. Saliva samples were collected 10 min before and 30 min after the itch induction and analysed by ELISA for PGD2. SPSS statistics (v. 25) was used with a p value <0.05 as significant.
Results: Eight participants (4 men and 4 women; mean age± standard deviation: 23.75±2.38 years) were enrolled. No significant difference was found in the average itch intensity between day and night ($p>0.05$). No sex-related differences was found ($p>0.05$). Pearson's correlational analysis did not show any correlation between the size of flare area and itch intensity (R2: 0.023), itch intensity and itch area (R2: 0.002), or flare and itch area (R2: 0.168). No alteration was found in salivary levels of PGD2 ($p>0.05$).
Conclusion: Some trends was evident towards higher itch intensity and longer duration at night, with an influence of sex, but no statistically significant differences were found. Further investigation in a larger population or testing non-histaminergic cowhage itch model is proposed.

LB52

Salivary levels of opiorphin in response to acute short-lasting pain: an experimental study in humans

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Introduction: Endogenous opiorphin prevents degradation of enkephalin, leading to a longer analgesic effect. Opiorphin has therefore captured attention as a potential candidate for treatment of pain. We investigated baseline opiorphin level in human saliva and whether it would show any changes after induction of acute pain in heathy men and women.
Methods: Healthy volunteers (18-30 years) were tested prior and post induction of cold pressor test. Pain intensity was rated on a visual analogue scale and salivary samples were collected before, 15, and 30 minutes after the experimental model of pain. The samples were analysed using a competitive ELISA. Data were presented as median and interquartile. IBMSPSS (v. 24.0) was used for statistical analysis and $p<0.05$ was considered significant.
Results: Eight participants (4 men and 4 women; mean age± standard deviation: 24.88 ± 3.00 years) were enrolled after obtaining consent forms. Peak of pain intensity was 7.80 (5.48,9.08), with no sex-related difference. Salivary concentrations of opiorphin (ng/ml) were 1.38 (1.05, 3.50) at baseline, 1.59 (1.31, 8.46) at 15 min, and 1.43 (1.14, 5.86) at 30 min post cold pain induction. No significant difference was found on Friedman test between the 3 time-points. Spearman's correlation showed no correlation between salivary concentrations and pain intensity.
Conclusion: No significant difference was found in salivary opiorphin levels, when participants were exposed to the cold pressor test. Salivary opiorphin and pain intensity were not correlated. Lack of detectable alterations in circulating opiorphin might be a result of selected time points or acute short- lasting pain.

LB53

Tattoo and somatosensation: investigation of tactile sensitivity by two-point discrimination

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Introduction: There is a growing number of tattoos made with tattoo machines, where needles penetrate epidermis and insert inks into dermis. The perforation of tattoo needle and composition of applied ink, leave a question as if this procedure could alter somatosensation. Literature is limited and controversial about a potential link between tattooing and alterations in cutaneous sensation. Hence, we investigated tactile perception in response to two-point discrimination (TPD) on tattooed and non-tattooed skin.

Methods: In a randomized self-controlled study (Nov-Dec 2019), Danish healthy men (20-30 years) were tested for TPD with an aesthesiometer (Baseline®, 1 mm accuracy). Demographic information and consent forms were obtained and participants were tested twice in a random ascending-descending order on both tattooed and non-tattooed (mirror control) skin. Threshold values (mm) of TPD were recorded. Tattoos location were restricted to upper and forearms (>5 months and <8 years). Data were checked for normality and t-test was applied. The study consisted of one session (60 min). SPSS (v.26) was used for statistical analysis and $p<0.05$ was considered significant.

Results: Twenty-one participants were enrolled, where one was excluded due to a dermatological disease (N=20, average age ± standard deviation: 24.10 ± 3.23 years). No significant difference was fond between the tattooed and non-tattooed arms ($p> 0.05$).

Conclusion: Tactile sensitivity was not altered with a gain or loss of sensitivity when tattooed arms compared with non-tattooed control arms. However, results must be cautiously interpreted due to the small sample size and application of a handheld aesthesiometer.

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LB54

Open-label Study of Patisiran in Patients with Hereditary Transthyretin-mediated Amyloidosis with Polyneuropathy Post-orthotopic Liver Transplant

Introduction: Hereditary transthyretin-mediated (hATTR) amyloidosis is a progressive, life-threatening disease. Orthotopic liver transplant (OLT) has been used in early stage hATTR amyloidosis but is associated with disease progression from wild-type amyloid fibril deposition. Patisiran significantly suppresses liver production of mutant and wild-type transthyretin (TTR) and demonstrated halting or reversal of polyneuropathy and improvement of quality of life in the Phase 3 APOLLO study. Patisiran is approved in certain countries globally for the treatment of hATTR amyloidosis with polyneuropathy.
Methods: A Phase 3b open-label study was designed to evaluate the safety, efficacy, and pharmacokinetics of patisiran in patients with hATTR amyloidosis with polyneuropathy with disease progression post-OLT (NCT03862807). Baseline demographics, reduction in serum TTR levels following 3 weeks of patisiran treatment, and 3-month interim safety were summarised.
Results: 23 patients enroled and received patisiran. Median age was 58.0 years, 13 (56.5%) were males, and 15 (65.2%) had V30M mutation. At baseline, 1 (4.3%) patient was Polyneuropathy Disability (PND) I, 9 (39.1%) were PND II, and 13 (56.5%) were PND IIIA/B. At 3 weeks after first dose of patisiran, the mean percentage reduction from baseline in serum TTR levels was 81.9%. Twenty-one (91.3%) patients experienced an adverse event (AE); majority of AEs were mild or moderate in severity and the most common AEs were consistent with those reported in APOLLO.
Conclusion: This study will continue to investigate the efficacy, safety, and pharmacokinetics of patisiran with the potential to address an unmet need in hATTR amyloidosis with polyneuropathy patients with disease progression post-OLT.

LB55

Aspects of the use of steroids in patients with Duchenne muscular dystrophy: data from the Neuromuscular Disorders Unit of Northern Greece

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Introduction: Steroids remain the gold standard therapy for Duchenne dystrophy, especially in settings with poor resources. Our aim is to present our experience about the use of steroids in patients with Duchenne.
Methods: Our study included 60 patients with Duchenne being under follow-up in our unit since 2009. The age at which treatment with steroids was recommended was baseline time.
Results: Totally 30 patients were treated with steroids (prednisolone: 14 patients, deflazacort: 7, methylprednisolone: 7, $\geq$ 1 different steroids were used by 3). Administration regimens included daily (10 patients), alternate days (6) and 10 days per month (11). A change in the administration regimen took place in 3 patients. The mean duration of treatment was 2 years. Baseline age was the same (7.5y) for both groups (steroids, non-steroids). After 3 years of follow-up the proportion of boys being still ambulant was 68.9% in the steroid group and 50% in the non-steroid ($p=0.18$). % predicted values of pulmonary function tests did not differ significantly between two groups at baseline, 1 and 3 years later. Patients receiving steroids had their annual flu vaccination at a higher rate compared to the other group (53% VS 42%, $p<0.05$). The commonest causes of treatment discontinuation were ineffectiveness and adverse events. The most frequent adverse event was osteoporosis (8/30).
Conclusion: A clear beneficial effect of steroids use was not apparent in our cohort. Age at steroids onset or treatment duration may have played a role. Patients with Duchenne should be timely informed about any new treatments.

LB56

Microglial activation role at sickness behavior and cognitive damage in sepsis animal model.

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Introduction: Cognitive damage is observed in sepsis patients. Microglia activation plays an important role in neuroinflammation leading to sickness behavior and long-term cognitive damage. Here we evaluated the influence of microglial activation in sickness behavior and long-term cognitive damage in sepsis animal model.
Methods: Forty-eight male Wistar rats aged 2 months were submitted to sepsis model by cecal ligation and puncture/ CLP (sepsis group; n = 18), submitted to sepsis model and microglia inactivation by 50mg/kg minociclin i.p. (mino group; n=18) or only median laparotomy (control / sham group; n = 12). Sickness behavior was accessed by the sickness behavior score (SBS) proposed by Goldim et al (2020) daily during 8 days. And after cognitive damage was accessed by memory aversive test.
Results: Mortality rate in mino group was 94% and sepsis group was 78%. All animals presented high SBS during 4 days after sepsis induction. But minociclin animals recover faster than sepsis group to healthy behavior, being revover at day 5 instead of at day 8 (p=0,001). Animals with higher SBS (indicating more sickness behavior) had worst performance at memory aversive test (Spearman correlation, r=0,610 and p=0,0009).
Conclusion: Sickness behavior is observed in septic animals, and minociclin, as an inhibitor of microglial activation, administration showed modulate its behavior during sickness and at long-term.

LB57

Treatment of Complex Regional Pain Syndrome in patients seen at the Chronic

Pain Clinic of a University Hospital
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Introduction: Complex Regional Pain Syndrome (CRPS) is a chronic pain condition composed of autonomic and inflammatory characteristics. It occurs acutely in about 7% of patients who have limb fractures, limb surgery or other injuries. Its treatment is multidisciplinary. The present study aims to describe how a Chronic Pain Ambulatory conducts the treatment of CRPS.
Methods: The subjects of this study were 23 patients diagnosed with complex regional pain syndrome and neuropathic pain symptomatology, followed up at a Chronic Pain Clinic, whose last consultation took place between August 2017 and January 2020. The data were collected from the institution‘s medical records and the variables evaluated were: location and intensity of pain, associated symptoms, previous pharmacological and non-pharmacological treatment, prescribed treatment, response to medication and adherence to instituted therapy.
Results: Of the 23 patients studied, 20 had a treatment segment, of these 12 showed partial improvement or improvement, and 8 without improvement. Among the pharmacological therapies used by patients there are: Gabapentin (52.2%), Amitriptyline (36.7%), Pregabalin (30.4%), Tramadol (26.7%), Methadone (4.3%), Carbamazepine (4.3%) and Amato (8.7%). Among the non-pharmacological ones there was physical therapy, blockades, hydrotherapy and acupuncture. The patients who performed the treatments faithfully for both intervention obtained better results, especially in the treatments associating anticonvulsants and tricyclic antidepressants to physical therapy.
Conclusion: The results of this study demonstrated that fidelity to the integral treatment of CRPS, in the pharmacological and non-pharmacological áreas, is associated with partial or effective pain.

LB58

Cenobamate management and outcomes in focal refractory epilepsy: a long-term experience in one single center

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Objective: To review our experience regarding effectiveness, adverse effects (AE) and drug adjustments that optimized cenobamate therapy for long-term.
Background: Cenobamate is a novel antiepileptic drug that has shown an extraordinary efficacy for focal refractory epilepsy (FRE) in recent clinical trials. However, available data involving long-term effectiveness and management are scarce so far.
Methods: An exploratory post-hoc analysis of our local samples from two international multicenter clinical trials was undertaken. Adult patients with FRE (NCT0186611= focal seizures ≥4/month; NCT02535091= FRE with any number of seizures, designed to search for idiosyncratic AE) despite treatment with stable doses of 1-3 antiepileptic drugs were enrolled.
Results: Forty-two patients, mean 40 yo (19-66), followed up from 2015 (NCT01866111, open label-extension beginning; n=8) and 2017 (NCT02535091; n=34) until 2020. A significant clinical response was obtained in 73.8% with a 1-year remission rate of 21.4%. The seizure frequency evolution with cenobamate (pre vs post) for focal impaired awareness seizures was: daily (31.0% vs 7.1%), weekly (50.0% vs 21.4%), monthly (14.3% vs 38.1%), sporadic (4.8% vs 19%), seizure-free (0% vs 14.3%). Focal to bilateral tonic–clonic seizures were present pre and post cenobamate treatment in a 45.2% vs 11.9%. Cenobamate introduction allowed the withdrawal of 0, 1 or 2 adjuvant AED in 11.9%, 42.9%, 45.2%, respectively. Main AE consisted of somnolence, dizziness and instability, which globally caused a cease of treatment in 8 patients (50% within first 6 months); and were mild-transient in 22 patients. No biochemical, hematic or idiosyncratic disorders were found. In 2020, 57.1% of the total continued cenobamate treatment with benefit, achieving optimal seizure control (11.9% 1-year terminal remission) with a median daily dose of 200 (100-300) mg/d.
Conclusion: Beyond 3 years, cenobamate treatment continues to be safe and very effective for FRE, involving a 1-year remission rate of 21.4% (1-year terminal in 11.9%) and adjuvant AED reduction in 88.1%.
Keywords: cenobamate; focal refractory epilepsy; anti-epileptic drugs (AEDs); long-term efficacy; drug interactions.

LB59

Meningitis in Brazil: epidemiological profile from 2015 to 2019

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Introduction: Meningitis consists in the inflammation of the meninges that is caused by different agents and can be fatal. It is a compulsory notification disease in Brazil. Thus, this study analyzes the epidemiological profile of meningitis in the brazilian population.
Methodology: Retrospective analytical work carried out in April/2020, with confirmed cases of meningitis in Brazil, between 2015 and 2019. The data was obtained on the website of the Departamento de Informática do Sistema Único de Saúde (DATASUS), with the variables: sex, region, age, evolution and etiology. Ignored or blank data were excluded.
Results: A total of 81,892 cases were found, 58% male and 42% female, with approximately 16 thousand cases per year. Analyzing by region, 54% were from the Southeast, 22% from the South, 14% from the Northeast, 5.6% from the North and 4.4% from the Midwest. The most affected groups were patients under 4 years old (34,38%) between 20 and 39 years old (19.58%) and between 40 and 59 (14.79%). Regarding the evolution, 74,738 cases were registered, where 85.37% were discharged, 10.07% died from meningitis and 4.56% died from other causes. In addition, 38,939 cases were viral, 13,196 bacterial and 12,733 unspecified.
Conclusion: Thus, meningitis has a high prevalence in Brazil, especially in male children under 4 years old in more developed region. Furthermore, there is a considerable difficulty in identifying the etiological agent, demonstrating the obstacle in the conduct of patients and reducing deaths.

LB61

The reality of the acute treatment for ischemic stroke in a Brazilian reference hospital

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Introduction: The use of endovenous *alteplase* in the acute treatment of ischemic stroke (IS) is well established (NINDS, 1995; ECASS, 1995-2008) regarding an *endovenous treatment* in the therapeutic window of 4.5 hours since the begging of the ischemic symptoms. The *Hospital da Restauração (HR)* is a public reference hospital located in the Northeast region of Brazil, the largest reference centre in the city, which attends an average of 4,500 patients with stroke per year. This paper aims to determinate the time between the IS ictus and the clinical evaluation by a neurologist in the HR and quantify the number of endovenous thrombolysis performed.

Methods: Observational, cross-sectional, retrospective and analytical study, with 492 patients diagnosed with a stroke, treated between November and December 2017.

Results: The IS group (n=274) had an ictus-neurologist interval time of 40.6 ± 59.1 hours (95% CI 33.5-47.6, median 24 hours) versus hemorrhagic stroke (n = 49) with 31.4 ± 39.2 hours (95% CI 22.1-42.6, median 16 hours) (p = 0.1430; Mann-Whitney test). Thirty-four IS patients were classified as „wake-up stroke“ and 19 as transient ischemic attacks. 116/492 (23.6%) of the patients did not have a defined ictus-neurologist time. Only 27/396 (6.8%) patients with IS arrived in the therapeutic window, and only 7/27 (26%) received thrombolytic therapy.

Conclusion: In the most majority of the cases, the time interval between the ictus and the first neurological evaluation was too long for an adequate acute endovenous treatment of the ischemic stroke.

LB62

Ofatumumab vs Teriflunomide in Relapsing Multiple Sclerosis: Analysis of No Evidence of Disease Activity (NEDA-3) from ASCLEPIOS I and II Trials

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Introduction: Ofatumumab, the first fully human anti-CD20 monoclonal antibody, demonstrated superior efficacy over teriflunomide in the Phase 3 ASCLEPIOS I/II relapsing multiple sclerosis (RMS) trials. We evaluated the effect of subcutaneous ofatumumab 20 mg (monthly) versus oral teriflunomide 14 mg (once daily) in achieving no evidence of disease activity (NEDA-3) and separately assessed the annualised relapse rate (ARR) and gadolinium-enhancing (Gd+) T1 lesions from the ASCLEPIOS I/II trials.

Methods: Data were pooled from ASCLEPIOS I (n=927) and II (n=955) trials. Outcomes included NEDA-3 (defined as composite of absence of 6-month confirmed disability worsening [6mCDW], confirmed MS relapse, new/enlarging T2 lesions and Gd+ T1 lesions) and its individual components (logistic regression model), ARR by time-interval and Gd+ T1 lesions (negative binomial model for both).

Results: The odds of achieving NEDA-3 with ofatumumab versus teriflunomide was >3-fold higher at Month (M) 0–12 (47.0% vs 24.5% patients; odds ratio [95% confidence interval (CI)]: 3.36 [2.67–4.21], p<0.001) and >8-fold higher at M12–24 (87.8% vs 48.2% patients; 8.09 [6.26–10.45], p<0.001). Over 2 years, a higher proportion of ofatumumab- than teriflunomide-treated patients were free from 6mCDW (91.9% vs 88.9%), relapses (82.3% vs 69.2%) and lesion activity (54.1% vs 27.5%). Ofatumumab significantly reduced

ARR versus teriflunomide at all cumulative time-intervals: M0–3 (p=0.011) and subsequent M0–27 (p<0.001). Ofatumumab significantly reduced the number of Gd+T1 lesions per scan by 95.9% versus teriflunomide (mean [95% CI]: 0.02 [0.01; 0.03] vs 0.50 [0.42; 0.59]; p<0.001).
Conclusions: Ofatumumab increased the probability of achieving NEDA-3 and demonstrated superior efficacy versus teriflunomide in RMS patients.
Disclosure: This study was funded by Novartis Pharma AG, Basel, Switzerland.

LB66

Employment status and associated outcomes in patients with CIS treated with interferon beta-1b from the 15-year follow-up of the BENEFIT trial

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Introduction: Multiple sclerosis (MS) may affect patients' ability to work. Employment status of patients followed for 15 years after first disease manifestation and treated early with interferon beta-1b was examined to identify associated factors.
Methods: Prospective follow-up of patients continued to Year 5 in the BENEFIT trial. Employment status was assessed 11 years after the first clinical event and at Year 15 grouped as working >=20 hours/week, <20 hours/week, or non-working. Other assessments included Expanded Disability Status Scale (EDSS), Paced Auditory Serial Addition Test (PASAT-3), Center for Epidemiologic Studies Depression (CES-D) scale, Fatigue Scale for Motor and Cognitive Functions (FSMC), EuroQol-5D Health-Related Quality of Life (EQ-5D HRQoL), Functional Assessment of Multiple Sclerosis (FAMS), Symbol Digit Modality Test (SDMT) and normalized brain volume (NBV) stratified to employment status.
Results: Of the originally randomized 468 patients, 261 (55.8%) participated in BENEFIT 15; employment status was available for 257/261 (98.5%). At Year 15, 173 (66.3%) were employed compared to 200 (76.6%) at disease onset. Employed patients had lower EDSS, fatigue, depression and better QoL than non-employed patients. Patients becoming non-employed between Years 11 and 15 showed significantly higher EDSS, FSMC, and CES-D, but not lower PASAT or NBV at Year 11 (Table 3).
Conclusion: At 15 years, employment status between original randomization arms was similar. Greater levels of disability, cognitive impairment, depression, fatigue, and lower HRQoL were associated with reduced working hours and non-employment. Becoming non-employed between Years 11 and 15 was predicted by higher disability, fatigue and depression, but not by cognitive impairment at Year 11.

Disclosures:

- Ludwig Kappos's institution (University Hospital Basel) received in the last 3 years and used exclusively for research support: steering committee/consulting fees from Actelion, Addex, Bayer HealthCare, Biogen, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono, Pfizer, Receptos, Sanofi-Aventis, Santhera, Siemens, Teva, UCB, and Xenoport; speaker fees from Bayer HealthCare, Biogen, Merck, Novartis, Sanofi-Aventis, and Teva; support of educational activities from Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi-Aventis, and Teva; license fees for Neurostatus products; grants from Bayer HealthCare, Biogen, the European Union, Merck, Novartis, Roche, Roche Research Foundations, the Swiss Multiple Sclerosis Society, Innoswiss and the Swiss National Research Foundation.
- Mark S. Freedman has received compensation from Bayer HealthCare, Biogen Idec, EMD Canada, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, and Teva Canada Innovation for consulting services. He also participates in a Genzyme-sponsored speakers bureau.
- Gilles Edan has received honoraria for consulting from Biogen, Merck, Novartis, Sanofi, Roche, LFB and has received personal compensation for serving on the BENEFIT scientific advisory board and for speaking from Bayer AG. His institution has also received research support from Novartis, Sanofi, Merck, Biogen, Roche and Teva.
- Xavier Montalbán has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, Excemed, MSIF and NMSS.
- Hans-Peter Hartung has received honoraria for consulting and speaking at symposia from Bayer AG, Biogen, Merck, Novartis, Roche, Sanofi Genzyme, TG Therapeutics with approval by the rector of Heinrich-Heine University.
- Frederick Barkhof has received compensation for consultancy from Bayer, Biogen-IDEC, Merck, Novartis, Sanofi, Roche, Teva, and IXICO, and has received research support from the Dutch Foundation for MS research and the EU (FP7 and IMI).
- Ralf Koelbach is a salaried employee of PAREXEL International GmbH.
- Eva-Maria Wicklein is a salaried employee of Bayer AG.

Table 1. Employment information of patients at baseline and BENEFIT 15[a]

	Number of patients, n (%)
Employed at baseline and Year 15	165 (63.2%)
Non-employed at baseline and Year 15	51 (19.5%)
Employed at baseline, but non-employed at Year 15	33 (12.6%)
Non-employed at baseline, but employed at Year 15	8 (3.1%)

[a]*Employment status analysis included categorisation of non-employed, homemaker, retired, early retired, long-term disability and other as "non-employed" with a total of 60 patients at baseline and 84 patients at Year 15 and a categorisation of working >=20 hours/week, <20 hours/week and student as "employed" with 200 patients at baseline and 173 patients at year 15.*

Table 2. Outcome measures by working ability at Year 15

	Employed, working >=20 hours per week (n=143)	Employed, working <20 hours per week (n=30)	Non-employed[a] (n=56)	Overall (n=229)
EDSS, mean (SD)[b] Correlation Rho: 0.471 (*p*-value <0.0001)	1.8 (1.3)	3.1 (1.4)	3.9 (2.1)	2.5 (1.8)
CES-D, mean (SD) Correlation Rho: 0.416 (*p*-value <0.0001)	9.5 (8.9)	15.3 (13.2)	21.5 (11.3)	13.2 (11.3)
FSMC, mean (SD) Correlation Rho: 0.506 (*p*-value <0.0001)	40.6 (19.0)	56.2 (19.8)	68.0 (17.1)	49.3 (22.0)
EQ-5D HRQoL[c] Correlation Rho: -0.431 (*p*-value <0.0001)	0.86 (0.16)	0.73 (0.26)	0.62 (0.27)	0.78 (0.23)
FAMS, mean (SD) Correlation Rho: -0.501 (*p*-value <0.0001)	119.7 (21.5)	101.9 (28.7)	84.5 (25.0)	108.8 (27.8)

[a]*Categorisation as "non-employed": non-employed, early retired and long-term disability (patients in the categories homemaker, retired and other were not included).*

[b]*The number of non-employed patients was 57, and overall number of patients was 230.*

[c]*The number of employed patients was 142, and overall number of patients was 228.*

Table 3. Outcome measures at Year 11 by change of employment status using factors measured from Year 11 to 15[a]

	Employed at Year 11 and Year 15	Employed at Year 11 but not employed at Year 15	Overall
EDSS, mean (SD) *p*-value 0.02	n=132	n=15	n=147
	1.7 (1.2)	2.8 (2.0)	1.9 (1.3)
CES-D, mean (SD) *p*-value <0.02	n=131	n=15	n=146
	10.2 (10.8)	15.5 (10.2)	10.8 (10.9)
FSMC, mean (SD) *p*-value <0.01	n=129	n=15	n=144
	42.8 (20.1)	57.5 (20.6)	44.3 (20.5)
FAMS, mean (SD) *p*-value <0.01	n=130	n=15	n=145
	118.3 (23.2)	100.9 (23.8)	116.5 (23.7)
PASAT-3, mean (SD) *p*-value = 0.12	n=110	n=14	n=124
	54.2 (7.0)	49.6 (10.9)	53.7 (7.6)
NBV, mean cm^3 (SD) *p*-value = 0.65	n=90	n=13	n=103
	1484.7 (133.7)	1485.4 (153.2)	1484.8 (135.5)
SDMT (90s), mean (SD) *p*-value = 0.08	n=114	n=15	n=129
	53.9 (12.9)	46.7 (13.8)	53.1 (13.1)

[a]*Only patients with assessments at Year 11 and Year 15, who were not categorized as homemaker, retired or other were included.*

LB67

Understanding the Stone of Madness and it's philosophical impact on the ethics of neurology.

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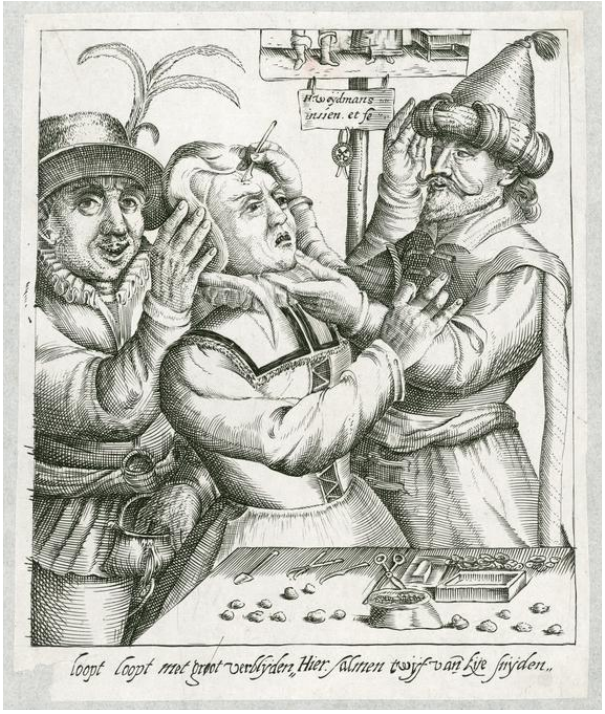
Introduction: The Stone of Madness was a hypothetical stone located in the patient's head, thought to be the cause of madness, idiocy or dementia. Hieronymus Bosch and other early Renaissance artists explored the trephination procedure, which consisted of surgically drilling a hole into the patient's head. The study intended to link the artistic relevance of the paintings with philosophical matters related to the historic evolution of the ethics on how patients with neurological disorders are treated.
Methods: The present work was carried out from a narrative bibliographic research. In this way, scientific articles, books, and paintings were used to contextualize the study using the phenomenology method.
Results: Analyzing Massay's 'An Allegory of Folly', Bosch's 'Extracting the Stone of Madness', Weydman's 'Operation for stones in the head', it's inscriptions, symbols, and literature from the Renaissance period, the study explored correlations with the popular view of physicians, patients and neurological conditions. The study discussed how it affects modern-day ethics of neurology using Hegel's philosophical approach and art's metaphysics.
Conclusion: The study has various interpretations of the paintings. The symbols are purposefully constructed to represent the moment's anguish, on the perspective of the painter's phenomenology. Physicians are often portrayed as charlatans, which contributed to the modern myths on how the neurology practitioner may be viewed. Ethical implications apply as they question the passive narrative that the patient held, being restrained with chains and forced against their will.



LB68

Deaths from malignant neoplasia of the brain in the brazilian state of pará: a proposed intervention to reduce cases

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Introduction: In Brazil, it is estimated that more than eleven thousand new cases of Malignant brain tumors (MBT) occur each year. New therapies treating MBT can reduce the disease's death toll. This research aims to evaluate the number of deaths caused by MBT in the state of Pará, in Brazil, and to propose an intervention that allows the reduction of deaths caused by the disease in the state.
Methodology: Epidemiological retrospective research, with data from the Information System for Notifiable Diseases (SINAN), a platform that records deaths in Brazil. Deaths by MBT in Pará between 1996 and 2018 were analyzed. With the Chi-Square Test, the statistical difference between the number of deaths by NME and the categories of years with an interval established between 1996 and 2018 was calculated. A narrative literature review supported the elaboration of the intervention proposal.
Results: In 2002, MBT's mortality in the state was 0.44. This index grew to 2.76, increasing 527%, in 2018 ($p < 0.05$). As an intervention proposal, the literature review indicated that expanding access to methylation identification of the methylguanine methyltransferase (MGMT) promoter gene can reduce deaths from MBT.
Conclusion: The number of deaths caused by MBT has risen considerably in the state of Pará, which may cause a significant impact on Brazil's public healthcare system. Our study proposes the expansion of the access to the exam that identifies the MGMT promoter methylation as an intervention to improve MBT care, and thus reduce its death toll.

LB71

Tranexamic Acid can reduce the risk of rebleeding in ruptured intracranial aneurysms

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Introduction: Tranexamic acid (TXA) is used to reduce re-bleeding which is a major complication in rupture of intracranial aneurysms occurring between 10% and 22% of the affected patients. This study analyses the effectivity and risks of using TXA in ruptured intracranial aneurysm.
Methods: We selected articles, published from 1976 to 2019, on the PubMed and EMBASE using the keywords: „Tranexamic Acid", „brain aneurysm" and „subarachnoid haemorrhage (SAH)".
Results: In a Cochrane review published in 2013 comprising 10 randomised controlled trials regarding the effects of antifibrinolytics agents on haemorrhage the overall mortality rate was unaffected. In a meta-analysis performed with 2872 individuals, 1380 patients received antifibrinolytics agents for the management of SAH. It showed that TXA-treatment was may be beneficial for diminishing rebleeding rate in the short term, i.e. less than 3 days. Hillman et al. analysed the use of TXA in patients after the diagnosis of SAH within 48 hours before first hospitalisation. A 1-g dose of TXA was administered intravenously followed by 1 g every 6 hours until the aneurysm was occluded, not exceeding 72 hours of treatment. The results showed a reduction in rebleeding rate, ranging from 10.8% to 2.4%, and reduced mortality rate due to rebleeding by 80%, with no increase in drug-related ischemic and vasospasm events.
Conclusion: The TXA can considerably reduce the risk of rebleeding, but there is weak evidence regarding its influence on mortality reduction. More studies on the subject are needed in order to establish unified guidelines.

LB72

Stanniocalcin-1 decreases the hipocampal oxidative stress and memory impairment after experimental sepsis in rats

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Introduction: The brain damage in sepsis is associated with changes that occur due to oxidative stress. In this study is was verified the effect of Staniocalcine-1 (STC-1) under oxidative stress and long-term memory damage in animals submitted to sepsis by binding and cecal perforation (CLP).
Methods: Male Wistar rats (250-350g) were submitted to sepsis by CLP. The first experiment was divided into sham+saline, CLP+saline and CLP+rhSTC-1 (20, 50 and 100ng/Kg via icv). In the second experiment, they were divided into sham+saline, sham+rhSTC-1 100ng/Kg, CLP+saline and CLP+rhSTC-1 100ng/Kg. Hippocampus was removed 24h after CLP to analyse nitrite/nitrate (N/N), oxidative damage in lipids, proteins and superoxide dysmitase (SOD) and catalase (CAT) activity. The inhibitory avoidance test was performed 10 days after sepsis induction.
Results: There was an increase in N/N concentration in relation to sham+saline in the CLP+saline group and all rhSTC-1 doses decreased such levels. For lipid damage there was also increase in CLP+saline and CLP+rhSTC-1 20ng/Kg and no rhSTC-1 dose was effective. For protein damage there was increase in CLP+saline and decrease in to CLP+rhSTC-1 100ng/kg. SOD activity was decreased in CLP+saline and reestablished levels in CLP+rhSTC-1 100ng/kg and for CAT activity there was decrease in CLP+saline and none of the groups with rhSTC-1 treatment was effective. In the memory test, there was improvement in the performance of rats in the CLP+rhSTC-1 100ng/rat group in relation to CLP+saline.
Conclusions: STC-1 attenuates hippocampal oxidative stress in rats submitted to polymicrobial sepsis and improves the memory 10 days after sepsis induction.
Keywords: sepsis, hippocampus, oxidative stress, memory.

LB76

The clinical characteristics of children with congenital Zika syndrome: a case series

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Introduction: The congenital Zika syndrome involves structural brain changes, including ventriculomegaly, thin cerebral cortices, abnormal gyral pattern, cortical malformations, and microcephaly in newborns. Objective: To describe the clinical characteristics of children with congenital Zika syndrome; to compare the outcomes of infants infected in the first (1T, n=20) and second trimesters of pregnancy (2T, n=11); to investigate correlations between birth weight, birth and follow-up head circumference, birth gestational age, and gross motor scores.
Methods: Participants were evaluated with Alberta Infant Motor Scale (AIMS) and part A of the Gross Motor Function Measure (GMFM-A).
Results: ANOVA showed differences in birth and follow-up head circumferences. Head circumference was smaller in 1T, compared to 2T. Motor performance was classified as below the fifth percentile in AIMS in all children and 1T showed lower scores in prone, sitting, and total AIMS score, compared to 2T. Children ranged from 8 to 78% on GMFM-A and there was a poorer motor performance of 1T. Nineteen children showed hypertonia, six showed normal tone and six

showed hypotonia. Birth head circumference was correlated with AIMS prone postural control. Follow-up head circumference was correlated to prone, supine and total AIMS scores. Smaller head circumference at birth and follow-up denoted poorer postural control.
Conclusion: Children with congenital Zika syndrome showed microcephaly at birth and follow-up. Smaller head circumferences and poorer motor outcomes were observed in 1T. Infants showed poor visual and motor outcomes. Moderate positive correlations between birth and follow-up head circumference and gross motor function were found.
Keywords: Zika Virus; Microcephaly; Child.

LB82

Effect of Ofatumumab on Serum Immunoglobulin Levels and Infection Risk in Relapsing Multiple Sclerosis Patients from the Phase 3 ASCLEPIOS I and II Trials

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Introduction: Ofatumumab, the first fully human anti-CD20 monoclonal antibody, demonstrated superior efficacy versus teriflunomide in relapsing multiple sclerosis (RMS) patients in the ASCLEPIOS I/II trials. This study investigated serum immunoglobulin (Ig)G and IgM levels, and their associations with risk of infections in ofatumumab-treated patients.
Methods: Patients received subcutaneous ofatumumab 20 mg on Days 1, 7, and 14, Week 4, and every 4 weeks thereafter or oral teriflunomide 14 mg once-daily for up to 30 months (average follow-up: 18 months). Serum IgG/IgM levels were monitored at baseline, Weeks 4 and 12, and every 12 weeks thereafter (ofatumumab, n=946; teriflunomide, n=936). We assessed the proportion of patients with IgG/IgM levels <50% of lower limit of normal (LLN [g/L]; IgG [3.5], IgM [0.2]), and association between low IgG/IgM levels and infection rates.
Results: At Week 120, no patients reached IgG levels <50%LLN with ofatumumab (ASCLEPIOS I and II, median[g/L]: 10.57 and 9.57, respectively) or teriflunomide (10.01 and 9.65). Proportion of patients with IgM levels <50%LLN was 2.1% (n=20/944) for ofatumumab (median[g/L]: 0.91 and 0.59) and 0.6% (n=6/933) for teriflunomide (0.84 and 0.92) at Week 120. Of these, five ofatumumab-treated patients experienced infections, mostly non-serious (Grade-1/2), except one recurrent urinary tract infection (Grade-3); all infections were resolved. One patient on teriflunomide who experienced nasopharyngitis had not recovered at the time of last follow-up.

Conclusions: No reduction in serum IgG levels <50% LLN was observed with either treatment, while IgM levels decreased with both treatments; there was no apparent association with increased rate of serious/non-serious infections in RMS patients.
Disclosure: This study was funded by Novartis Pharma AG, Basel, Switzerland. A detailed disclosure from each author will be included in the oral/poster presentation.
Submission requirements:
Abstract Category: Oral presentation
Topic of Choice: MS and related disorders

LB83

Efficacy and Safety of the Bruton's Tyrosine Kinase Inhibitor (BTKI) Evobrutinib in Relapsing Multiple Sclerosis Over 108 weeks: Open-label Extension to a Phase II Study

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Introduction: In a Phase II randomised controlled trial (RCT; NCT02975349) in patients with relapsing MS, evobrutinib 75mg twice-daily (BID) reduced total T1 Gd+ lesions (primary endpoint) and annualized relapse rate (ARR) over 24 weeks versus placebo, with efficacy maintained through Week 48. We report long-term efficacy and safety from the study's open-label extension (OLE).
Methods: In the 48-week double-blind period, patients received evobrutinib 25mg once-daily (QD) or 75mg QD, 75mg BID, open-label dimethyl fumarate (240mg BID) or placebo for the first 24 weeks; all arms continued with the original treatment assignment until 48 weeks, except placebo patients who were switched to evobrutinib 25mg QD. At Week 48, all patients could enter the OLE, where treatment was initially evobrutinib 75mg QD (for approximately 48 weeks, median) before switching to 75mg BID. The OLE assessed long-term efficacy (0–108 weeks) and safety (60-week OLE) of evobrutinib.
Results: Of 267 randomised patients, 213 (80%) completed 108 weeks of treatment (48 weeks in main study and 60 weeks in OLE). For patients receiving 75mg BID in the main study, the annualised relapse rate (ARR) was 0.11 (95% CI 0.04–0.25) at Week 48, and 0.12 (0.06–0.22) for the 108-week period. Evobrutinib was generally well-tolerated, with the safety profile maintained during the 60-week OLE. Transient elevated liver aminotransferases, reported in the 48-week double-blind period, were not observed in the OLE.
Conclusions: Efficacy and safety were maintained long-term. Two Phase III RCTs evaluating efficacy and safety of evobrutinib in relapsing MS patients commence in 2020.

Disclosures:

Xavier Montalban
Has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, Genzyme, Immunic, Medday, Merck, Mylan, Nervgen, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.

Douglas Arnold
Reports consultant fees and/or grants from Acorda, Adelphi, Alkermes, Biogen, Celgene, Frequency Therapeutics, Genentech, Genzyme, F. Hoffmann-La Roche, Immune Tolerance Network, Immunotec, MedDay Pharmaceuticals, Merck Serono, Novartis, Pfizer, Receptos, Sanofi-Aventis, and an equity interest in NeuroRx Research.

Martin Weber
Has received travel funding and/or speaker honoraria from Biogen-Idec, Merck Serono, Novartis, F. Hoffmann-La Roche, TEVA, Bayer, and Genzyme.

Ivan Staikov
Has received travel funding, registration fees and/or speaker honoraria from Sanofi-Genzyme, Ewopharma-Biogen, Shire, Gedeon-Richter, TEVA, Boehringer Ingelheim, Pfizer, Bayer, F. Hoffmann-La Roche, Mylan, Polpharma, Penumbra, Adapt, and Merck Serono.

Karolina Piasecka-Stryczynska
Has received travel funding and/or speaker honoraria from Merck Serono, Sanofi-Aventis, Biogen Idec, TEVA, F. Hoffmann-La Roche, and has served on scientific advisory boards for Sanofi-Aventis and Biogen Idec.

Jerry Wolinsky
Has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Acorda Therapeutics, Actelion, Alkermes, Brainstorm Cell Therapeutics, Celgene, EMD Serono, GeNeuro, GW Pharma Ltd, MedDay Pharmaceuticals, NervGen Pharma Corp, Novartis, Otsuka, PTC Therapeutics, Roche/Genentech, and Sanofi-Genzyme. Royalties have been received for out-licensed monoclonal antibodies through UTHealth from Millipore Corporation, and a patent (US 2018/0243270 A1) issued to Board of Regents of the University of Texas System.

Emily Martin, Matthew Mandel, Victor Ona, and Fernando Dangond

Employed by EMD Serono (a business of Merck KGaA, Darmstadt, Germany).

LB90

Clinical benefits of eculizumab monotherapy in neuromyelitis optica spectrum disorder: findings from the phase 3 PREVENT study

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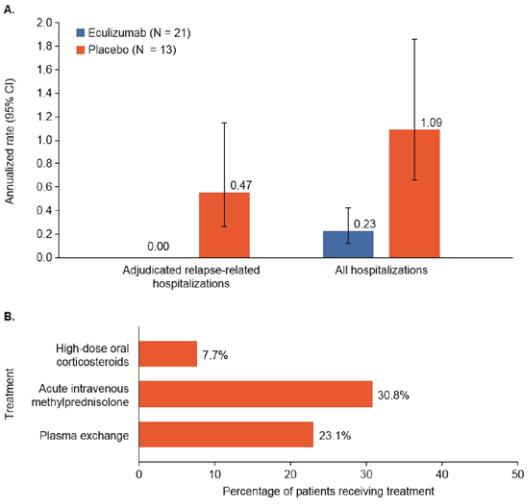
Introduction: In the phase 3 PREVENT trial (NCT01892345), eculizumab was well tolerated and significantly reduced relapse risk versus placebo. The relapse time course in a pre-specified subgroup of patients who did not receive concomitant immunosuppressive therapy (IST) suggested a treatment effect consistent with the overall population.
Methods: Adults with AQP4-IgG+ NMOSD received eculizumab (maintenance dose, 1200 mg/2 weeks) or placebo with/without concomitant IST. A post hoc analysis was performed of the following outcomes, using data from patients receiving eculizumab monotherapy or placebo without concomitant IST during PREVENT: relapses; hospitalizations; acute relapse treatment; and worsening of Expanded Disability Status Scale (EDSS) and Hauser Ambulation Index (HAI) scores.
Results: Of 34 patients in the no IST subgroup: 10 had never received IST; 14 previously received rituximab (eculizumab monotherapy, 7/21; placebo, 7/13). Adjudicated relapses occurred in 0/21 patients receiving eculizumab monotherapy and 7/13 (53.8%) receiving placebo ($p < 0.0001$; post hoc analysis). In the placebo group, 6/13 patients (46.2%) were hospitalized for adjudicated relapses and received treatment. Monotherapy subgroup hospitalization rates and adjudicated relapse treatment use in the placebo group are report-

ed (Figure A, B). EDSS and HAI each worsened in 1/21 patients (4.8%) receiving eculizumab monotherapy, and in 5/13 (38.5%) and 4/13 (30.8%), respectively, receiving placebo (Table).

Conclusions: These data support the efficacy of eculizumab monotherapy in reducing relapse risk in AQP4-IgG+ NMOSD. Patients receiving eculizumab monotherapy were spared relapse-associated hospitalizations and acute treatments, and the majority (95%) did not experience disability worsening. Long-term results from PREVENT's open-label extension will be analysed.

Disclosure: Funded by Alexion Pharmaceuticals.

Figure. A. Annualized hospitalization rates in the monotherapy (no IST) subgroup. **B.** Treatment received for adjudicated relapses by the patients in the placebo group.



Annualized hospitalization rates calculated as the total number of events requiring hospitalization during the study period for all patients, divided by the total number of patient-years in the study period. CIs based on a Poisson regression with treatment group covariate.
CI, confidence interval; IST, immunosuppressive therapy.

Table. Additional efficacy outcomes for the monotherapy (no IST) subgroup and overall PREVENT population.

	Monotherapy (no IST) subgroup		Overall	
	Eculizumab (N = 21)	Placebo (N = 13)	Eculizumab (N = 96)	Placebo (N = 47)
ARR[a] (95% CI)	0.00 (0–NE)	0.63 (0.31–1.25)	0.02 (0.01–0.05)	0.35 (0.20–0.62)
Change in score from baseline to study end, mean (SD)				
EDSS	–0.36 (0.79)	0.42 (1.04)	–0.18 (0.81)	0.12 (0.95)
mRS	–0.4 (0.92)	–0.2 (0.90)	–0.2 (0.72)	0.1 (0.75)
HAI	–0.4 (1.20)	0.6 (1.50)	–0.4 (1.08)	0.5 (1.61)
EQ-5D-3L visual analogue scale	5.9 (22.47)	2.3 (15.69)	5.4 (18.53)	0.6 (16.39)
EQ-5D-3L index	0.07 (0.19)	–0.002 (0.18)	0.05 (0.18)	–0.04 (0.21)
Patients with EDSS worsening,[b] n (%)	1 (4.8)	5 (38.5)	11 (11.5)	11 (23.4)
Patients with HAI worsening,[c] n (%)	1 (4.8)	4 (30.8)	8 (8.3)	11 (23.4)

[a]Adjudicated relapses; for monotherapy subgroup, based on Poisson regression with treatment group covariate. [b]Worsening of EDSS score was defined as an increase of >= 2 from a baseline score of 0, >= 1 from a baseline score of 1.0–5.0, or >= 0.5 from a baseline score of >= 5.5. [c]Worsening of HAI score was defined as an increase of >= 2 from a baseline score of 0, or >= 1 from a baseline score of >= 1.
ARR, annualized relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; HAI, Hauser Ambulation Index; IST, immunosuppressive therapy; mRS, modified Rankin scale; NE, not estimable; SD, standard deviation.

LB94

Sustained efficacy and safety of erenumab in episodic migraine patients failing 2–4 prior preventive treatments: 2-year interim results of the LIBERTY open-label extension study

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Aim: To assess the efficacy and safety of erenumab at Week 112 of the 3-year open-label treatment phase (OLTP) of the LIBERTY study (NCT03096834).

Methods: Patients completing the 12-week double-blind treatment phase (DBTP) of the LIBERTY study (N=240) initially randomised to placebo and erenumab 140mg (1:1) were enrolled into the OLTP to receive monthly erenumab 140mg for 3 years. Outcomes measured included proportion of patients who achieved >=50%/>=75%/100% reduction from the DBTP baseline in monthly migraine days (MMD), change from the DBTP baseline in MMD, Headache Impact Test total score, Migraine Physical Function Impact Diary (Everyday Activities and Physical Impairment) scores and safety.

Results: Both patients: on continuous erenumab and those who initiated erenumab in the OLTP, demonstrated improvement through 2 years of treatment (Table 1) similar to that reported at 1 year. The responder rates refer to a cross sectional interindividual observation and not a longitudinal intraindividual responder rate. The change in MMD from DBTP baseline in the overall group sustained over 2 years (1 year [52 weeks]:−3.7[4.1]; 2 year [112 weeks]:−4.2[5.0]). The median erenumab exposure (during OLTP) was 106 weeks. Nearly 86.3% (overall group), 82.2% (continuing erenumab) and 90.2% (initiating erenumab) of patients reported adverse events (AEs) in OLTP. The most frequently reported AEs/100 patient-years during OLTP were nasopharyngitis (33.9), influenza (10.3), and back pain (6.6).

Conclusions: Efficacy of erenumab was sustained over long-term treatment in EM patients with 2–4 PPTF both in patients continuously treated with erenumab and those initiating erenumab during the OLTP. Erenumab was well tolerated with no new safety signals.

Table 1. Efficacy outcome measures at the end of the second year of the OLTP, Observed (Open-Label Analysis Set)

Outcomes	Values at Week 112 of OLTP					
	Patients on erenumab 140 mg continued on erenumab 140 mg in the OLTP, N=118		Patients on placebo who initiated erenumab 140 mg in the OLTP, N=122		Overall population, N=240	
	n		n		n	
>=50% reduction in MMD	88	47 (53.4%)	85	52 (61.2%)	173	99 (57.2%)
>=75% reduction in MMD	88	26 (29.5%)	85	27 (31.8%)	173	53 (30.6%)
100% reduction in MMD	88	13 (14.8%)	85	15 (17.6%)	173	28 (16.2%)
Change from the DBTP baseline in MMD	88	−3.9 (5.5)	85	−4.6 (4.6)	173	−4.2 (5.0)
Change from the DBTP baseline in HIT-6™	91	−8.5 (8.0)	90	−10.4 (9.3)	181	−9.5 (8.7)
Change from the DBTP baseline in MPFID-PI	88	−4.1 (9.1)	86	−5.0 (11.4)	174	−4.5 (10.3)
Change from the DBTP baseline in MPFID-EA	88	−4.9 (9.7)	86	−6.0 (10.9)	174	−5.4 (10.3)

Data are mean (SD) or n (%) of the patients with non-missing value at Week 112; data for HIT-6 reported at Week 108; n=number of patients with a value at both baseline and that time point.
Change from baseline = post-baseline−baseline. The baseline period is defined as the period between Week-4 visit and the day prior to first dose
DBTP, double-blind treatment phase; HIT-6, Headache Impact Test; MMD, monthly migraine days; MPFID-EA; Migraine Physical Function Impact Diary-everyday activities; MPFID-PI, Migraine Physical Function Impact Diary-physical impairment; N, number of subjects included in the analysis set; OLTP, open-label treatment phase; SD, standard deviation

Conflicts of interest: The study was funded by Novartis Pharma AG, Basel, Switzerland. Erenumab is co-developed by Novartis and Amgen.
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LB111

Stem cells derived neural tissue with SCN2A mutation, comparative analysis of migration and growth.

Introduction: The Autistic spectrum disorder (ASD) have genetic and environmental factors causality, with the SCN2A and RELN genes being the most prominent associated to ASD. Hence, this study aims to investigate the role of SCN2A and RELN genes at ASD phenotype expression.
Methods: Previously produced induced pluripotent stem cells (iPS) lineages from healthy donors (EA1, EB4), SCN2A gene knockout (EB4CRISPR) and autistic patient (iM5) with this mutation proceed to cerebral organoids and neurospheres generation. Following maturation, their immunofluorescence analysis were performed. For statistical assay were used One-way ANOVA test with Tukey's post-test for multiple comparisons.
Results: iM5 embryoid bodies didn't develop cerebral organoids, in contrast to EB4 and EA1. All NSCs were cell-type validated with Q-PCR, indicating higher iM5 differentiation. iM5 neurospheres had atypical morphology and smaller neuronal extensions when compared with others at immunofluorescence. Also, knockout clone kept migrating and growing more than iM5 one – this clone also had a mutation at genes like RELN. At last, iM5 cultivated with conditioned medium from knockout clone showed better growing and migration, compared with healthy cells conditioned or basal mediums iM5 cultures
Conclusion: Normal migration of knockout clone when compared with impaired one from iM5, improoved with conditionated medium, indicates that SCN2A doesn't have a main role at neuronal migration and leads to hypothesys that RELN is related to neuronal migration and growth. More experiments are needed to confirm this results.

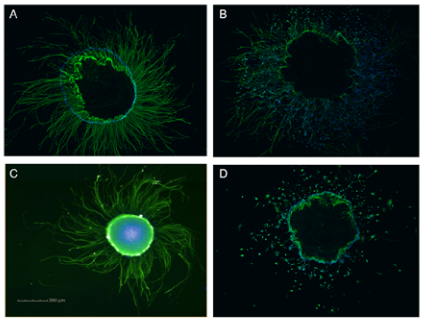

Figure 2. Immunofluorescence analysis of neurospheres. With analysis through Operetta HCS (PerkinElmer) it was possible to verify the presence of neuronal extensions (TUJ1⁺) in green. (A) EB4 neurosphere emitting long axonal extensions. (B) Neurosphere EA1 and its extensions, however, here stands out the presence of a series of neuron nuclei outside the neurosphere, evidenced by DAPI marking. (C) EB4CRISPR neurosphere with typical migration and morphology. (D) iM5 Neurosphere, it's noticed that there is a substantially lower emission of prolongations compared to the neurospheres generated by other clones.

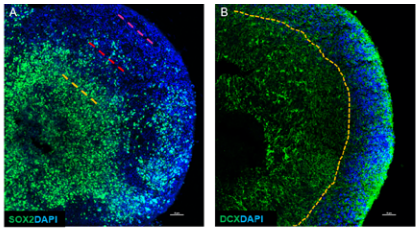

Figure 1. Characterization by immunofluorescence of cerebral organoids generated from EA1 cells. With confocal microscopy it was possible to observe the presence of pluripotent stem cell markers. (A) A highlight for the structural segmentation already evidenced previously in the literature, closer to the center (yellow line) we have strong SOX2 marking, followed by an intermediate marking region (red line), so that, finally, in the outermost region, it is possible to observe the very low presence of this marker (pink line). (B) Another section of a cerebral organoid showing the presence of immature neurons (DCX⁺) closer to the center of the structure (yellow line).

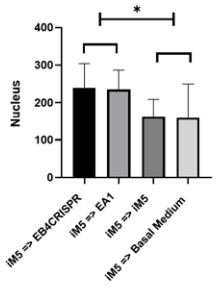

Figure 3. Representative graph of the migration of the nuclei of the iM5 neurosphere with different media conditioned by the well. This graph was generated through data obtained by immunofluorescence. It is possible to verify that there is no statistically significant difference between the iM5 neurospheres using the conditioned medium of EB4CRISPR and EA1. A similar fact occurs between the iM5 neurospheres using the conditioned medium of iM5 and the basal medium for neurospheres. However, the neurospheres of the first group migrated more across the plate than those of the second group. This demonstrates that possibly some component in the middle of the EB4CRISPR and EA1 neurospheres influences neuronal migration.

LB125

Ocrelizumab Phase IIIb Efficacy: 2-Year NEDA Rates With MRI Re-Baselining From the CASTING Study in Relapsing-Remitting MS Patients With a Suboptimal Response to Prior DMTs

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Introduction: Patients with relapsing-remitting multiple sclerosis (RRMS) often experience disease activity despite receiving a disease-modifying therapy (DMT). CASTING (NCT02861014) is a Phase IIIb study evaluating the efficacy/safety of ocrelizumab in patients with RRMS who suboptimally respond to one or two prior DMTs. We report the primary endpoint (2-year no evidence of disease activity [NEDA] rates) with MRI re-baselining) from CASTING.

Methods: Patients (Expanded Disability Status Scale score ≤4.0; discontinued prior DMT of ≥6 months' duration due to suboptimal disease control) received intravenous ocrelizumab 600 mg every 24 weeks for 96 weeks. The primary endpoint of NEDA (with prespecified MRI re-baselining at Week 8) was defined as absence of: protocol-defined relapses (PDRs), 24-week confirmed disability progression (24W-CDP), T1 gadolinium-enhancing and new/enlarging T2 lesions over 2 years.

Results: In total, 680 patients (female, 64.1%; mean [SD] baseline EDSS, 2.1 [1.1]; pretreated with one/two DMT(s) including orals/injectables, n=411 [60.4%]/n=269 [39.6%]; fewer than 5% of patients discontinued from the study) were evaluated. Most patients (74.8% [n/N=492/658]) reached NEDA between Weeks 8–96; the NEDA rate by epoch Weeks 0–48 was 82.6% (n/N=549/665) and by Weeks 48–96 was 87.0% (n/N=571/656). NEDA calculated without MRI re-baselining was achieved by 52.0% of patients (n/N=346/665). Most patients were free of PDR (89.8%), 24W-CDP (87.5%), T1 gadolinium-enhancing (97.7%; re-baselined) and new/enlarging T2 (91.5%; re-baselined) lesions. The adjusted annualised relapse rate (0.03) was low. Safety results were consistent with prior studies.

Conclusion: In CASTING, the NEDA rate with MRI re-baselining was high (74.8%). No new safety signals were observed.

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LB129

Effect of Subcutaneous Ofatumumab on Lymphocyte Subsets in Patients with RMS: Analysis from the APLIOS Study

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Introduction: Ofatumumab, the first fully human anti-CD20 monoclonal antibody, binds to two distinct non-continuous regions of CD20, resulting in potent B-cell depletion and reduced B- and T-cell interactions. Ofatumumab demonstrated superior efficacy versus teriflunomide in the Phase 3 ASCLEPIOS I/II trials in RMS; its effect on B- and T-cell subsets warrants further investigation.
We evaluated the effect of ofatumumab 20 mg subcutaneous (s.c.) dosing regimen on B- and T-cell subsets in relapsing multiple sclerosis (RMS) patients.
Methods: APLIOS was a 12-week, open-label, Phase 2 bioequivalence study. Patients received ofatumumab 20 mg (0.4 mL) s.c. loading doses on Days 1, 7, and 14, and maintenance doses every 4 weeks from Week 4 via a prefilled syringe or an autoinjector pen (SensoReady®). Changes in B- and T-cell subsets were analysed longitudinally in blood samples using fluorescence-activated cell sorting.
Results: Ofatumumab treatment showed rapid and sustained depletion in total B-cells (CD19+CD45+) measured on Day 4 until Day 84 versus baseline. The median total B-cell levels decreased to =<5 cells/μL by Day 7 through Day 14 of the loading regimen and was maintained until the study end. An effective depletion of memory B-cells (CD19+CD45+CD27+) along with decrease in naïve B-cells (CD19+CD45+IgD+CD27-CD38dim) was observed. Interestingly, a specific subset of T-cells (CD20+CD3+CD8+ T-cells), well-known to exhibit an activated phenotype, were also rapidly depleted, consistent with the previous findings from a primate study. By contrast, CD3+ T-cells were largely unaffected.
Conclusions: Ofatumumab 20 mg s.c. led to rapid and sustained depletion of both CD20+ B- and CD20+ T-cells in RMS patients.

This study was supported by Novartis Pharma AG, Basel, Switzerland.

LB130

Phase 1 study of the safety and efficacy of ATA188, an off-the-shelf, allogeneic Epstein-Barr virus-targeted T-cell immunotherapy to treat progressive forms of multiple sclerosis

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Introduction: Epstein-Barr virus (EBV) infection is associated with multiple sclerosis (MS) pathogenesis. Early experience with autologous EBV-specific T-cell adoptive immunotherapy proved safe and may offer clinical benefit [Pender M.P. JCI Insight. 2018]. This phase 1 study evaluates the safety and potential efficacy of off-the-shelf, allogeneic EBV-specific T-cell therapy (ATA188) in adults with progressive forms of MS (PMS; NCT03283826).

Methods: In part-1 of this study, four cohorts of PMS patients received escalating doses of ATA188 to determine the part-2 dose. Safety was assessed, as well as clinical responses through two composite scales. The first, an a priori classification of outcomes, was developed to detect early efficacy signals through validated MS clinical scales, and the second focuses on measuring sustained disability improvement (SDI; Table 1).

Results: As of April 2020, 25 patients receiving >=1 dose of ATA188 were available for analyses. Two treatment-emergent serious adverse events were reported: muscle spasticity and MS relapse. There was a dose-related increase in number of patients with SDI – a composite of improvement in EDSS or T25FW at consecutive time points (3 and 6 months, 6 and 12 months; Table 1). All patients showing SDI at 6 months maintained it through 12 months (Table 2).

Conclusions: Preliminary data indicate ATA188 immunotherapy is well tolerated. A trend of a higher proportion of patients showing favourable clinical improvement and sustained disability improvement with increasing ATA188 dose suggests a potential therapeutic response. Based on these data, part-2 of the study (randomised placebo-controlled portion) has been initiated using the cohort 3 dose.

Table 2. Clinical outcomes and composite scale of sustained disability improvement in patients receiving all six doses of ATA188 for cohorts 1–4 at 6 months (n=24) and cohorts 1–3 at 12 months (n=17)

	Cohort 1		Cohort 2		Cohort 3		Cohort 4
Outcome	6 m (N=6)	12 m (N=6)	6 m (N=6)	12 m (N=6)	6 m (N=6)	12 m (N=5*)	6 m (N=6**)
Composite Scale 1:* *A Priori* Clinical Outcome Classification**							
CD	4	5	1	1	2	2	2
S	0	0	0	0	1	0	0
pCI	1	0	3	2	0	0	4
CI	1	1	2	3	3	3	0
Composite Scale 2:* Sustained Disability Improvement**							
SDI	1	1	1	1	2	3	2

*One patient who has clinically declined has withdrawn, moved out of the country, and is lost to follow-up; **Seven patients were enrolled in cohort 4. One patient who had treatment-related MS relapse 7 days after dosing in the setting of ongoing upper respiratory infection symptoms and possible dental infection was replaced and not included in the above composite scale analyses; ***These analyses were not prespecified. CD = clinical decline; CI = clinical improvement; m = months; pCI = partial clinical improvement; S = stable; SDI = sustained disability improvement.

Table 1. Multiple sclerosis clinical outcome criteria

Outcome	Definition
Composite Scale 1: *A Priori* Clinical Outcome Classification, for early efficacy signal detection*	
Clinical decline	• Clinically significant decline in >= 2 scales at >= 1 time point • Clinical decline takes precedence over improvement
Stable	• Does not fulfil criteria for decline or improvement
Partial clinical improvement	• Minimal clinically significant improvement or greater on >= 2 clinical scales compared with baseline at >= 1 post-baseline time point
Clinical improvement	• Minimal clinically significant improvement or greater on two clinical scales compared with baseline sustained over >= 2 consecutive time points compared with baseline**
Composite Scale 2: Sustained Disability Improvement	
Sustained disability improvement (SDI)	• Disability improvement (DI) o Improvement in EDSS (>=1-point decrease compared with baseline <=5, or >=0.5-point decrease compared with baseline >5); or o Improvement in 25-foot walk time (>=20% decrease compared with baseline) • SDI at 6 months = DI at 3 months and confirmed at 6 months • SDI at 12 months = DI at 6 months and confirmed at 12 months

*Composite Scale 1 includes the following clinical scales: Fatigue Severity Score, MS Impact Scale-29 (physical), T25FW, 9-Hole Peg Test, 12-Item Multiple Sclerosis Walking Scale, EDSS, visual acuity (logMAR); **12-month response must include 12-month time point. EDSS = Expanded Disability Status Scale; logMAR = logarithm of the minimum angle of resolution; T25FW = Timed 25-Foot Walk.

Author disclosures: Phase 1 study of the safety and efficacy of ATA188, an off-the-shelf, allogeneic Epstein-Barr virus-targeted T-cell immunotherapy to treat progressive forms of multiple sclerosis

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LB131

Tiger Milk Mushroom has Neuroprotective and Neuroregenerative Properties in Human Neuroblastoma Cell Line

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Introduction: Tiger Milk Mushroom (TMM), belonging to the Polyporaceae family, has been used in Asian ethnomedicine for a variety of illnesses, including neurological problems. Recent development of laboratory culture of these naturally rare mushrooms have garnered interest in these purported properties. Previous studies conducted in rat in vitro models have shown that TMM has promising effects. However, the neuroprotective and neuroregenerative effects of TMM are not well-described in human-derived in vitro models.
Methods: Two different preparations of TMM were used: Subcritical CO2 fluid extraction (SFE) and aqueous extraction (AQ); on human-derived SH-SY5Y (neuroblastoma) cell lines. These preparations were assayed for cytotoxicity, neurite outgrowth induction, hydrogen peroxide-based oxidative stress rescue and amyloid beta-based neurotoxicity rescue at concentrations of 0.03mg/ml to 1.5mg/ml in 24hr assays.
Results: Both TMM preparations were well-tolerated by SH-SY5Y, with AQ having no cytotoxic effect on SH-SY5Y cells, even at the highest concentration applied. Neurite outgrowth induced by AQ were also observed to be comparable to that of nerve growth factor (NGF) as the positive control. Both SFE and AQ also exhibited varying neuroprotective effects in pre-, co-, and post-challenge oxidative stress models. However, the preparations were not effective in mitigating amyloid beta-induced neurotoxicity.
Conclusion: We conclude that the traditional use of TMM is scientifically sound as the TMM preparations here exhibited properties of neurological benefit, albeit not for amyloid beta-induced neurodegeneration. Specific studies on different models of neurotoxicity and disease states are warranted to determine the mechanistic pathways of TMM neuroprotection and neuroregeneration.
246 words

C2

RESidents' Initiative to STudy Headache During Coronavirus (COVID-19) Epidemic: the RESIST-HeaDaChE

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Introduction: Headache is a prominent disabling symptom of COVID-19. Headache attributed to viral infection has been scarcely studied, especially its pathophysiological mechanisms that may reflect the reason why some patients have it while others do not. Objective: To describe headache characteristics in COVID-19 patients

Methods: This is a prospective observational study, held in a Spanish tertiary hospital, where Neurology residents working as general physicians at the emergency room recruited consecutive patients with COVID-19 symptoms. We analyzed headache characteristics and compared patients with and without headache, including data from routine blood tests with inflammatory markers, performed at admission.

Results: From 133 patients, 99 (74.4%) had headache. From these, 58.6% were female, mean age was 50.4±15.2 years old, pain was mild-moderate in 75.8%, severe in 24.2%. 19.2% had history of migraine. Patients with severe headache had a migraine-like phenotype: female gender, throbbing pain and associated symptoms such as nausea and vomiting ($p<0.05$). Presence of headache was associated with loss of smell and taste ($p<0.001$). Comparing age-matched patients with and without headache, we observed that the headache group had higher proportions of women and lower inflammatory markers ($p<0.05$).

Conclusions: Headache attributed to COVID-19 could be mild or, less frequently, resemble to migraine, being the latter suggestive of the activation of the trigeminovascular system. Other COVID19 symptoms such as loss of smell and taste are significantly associated with the presence of headache, suggesting a potential direct role of SARS-CoV-2 in headache pathophysiology. The role of systemic inflammation is controversial and needs further evaluation.

C3

Innovation and transformation in a time of crisis; A National Rehabilitation Hospitals response to COVID-19

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Introduction and objective: The advent of COVID-19 has necessitated a radical transformation in how healthcare is organised and delivered. Rehabilitation Medicine has also responded to the crisis to ensure the ongoing delivery of specialist rehabilitation services.

The National Rehabilitation Hospital in Dublin, a complex specialist rehabilitation facility, has transformed how outpatient services are delivered in the space of 3 weeks. This paper describes the transformation and initial results.

Methods: An observational study of a period of rapid transformation during the COVID-19 pandemic.

Results: Prior to COVID-19, telehealth played a minor role in the provision of rehabilitation services with such provision being ad hoc with the vast majority of services being delivered face to face.

In the absence of any National guidance, interdisciplinary colleagues took immediate steps to maintain the continuity of care for patients during the COVID-19 pandemic and endeavoured to continue to deliver some form of treatment remotely. A WhatsApp Consultant group facilitated rapid exchange of information about telemedicine possibilities and experience and a responsive and agile OPD programme manager and information technology (IT) manager facilitated the testing of possible solutions. Microsoft teams was used for videoconferencing.

Table 1: Telehealth contacts in a Rehabilitation Hospital

Type of Telehealth Contact	Modality	Number booked Telehealth patient attendances
Medical – Consultant Only Brain Injury and Spinal Cord Injury Review Clinics		
Review	Phone	45
Consultant Led Interdisciplinary Clinics		
Adult Consultant Led Neurobehavioural Interdisciplinary Clinic	Videoconference	18
Paediatric IDT Brain Injury and Spinal Cord Injury Consultant Led Interdisciplinary Clinics	Videoconference	20
HSCP Led Clinics		
Individual Therapy Sessions	Phone	61
Interdisciplinary Assessment	Videoconference	4
Meet and teach Groups (OT/SALT)	Videoconference	48
Continuing Rehab sessions (e.g. OT/SALT)	Videoconference	4
Continuing Rehab Pilates Class (PT)	Videoconference	16
IDT Rehab sessions (e.g. SLT/MSW)	Videoconference	4
Continuing Neuropsychology	Videoconference	2
Total		**222**

Conclusion: Telehealth has become the predominant means of OPD provision in the space of 3 weeks. IDT colleagues and patients and their families have shown great innovation and agility and have embraced the technology with a resulting good patient and staff experience and plans are underway to expand our virtual rehabilitation offerings in partnership with the Health Services Executive.

C6

Anosmia and ageusia as the early signs in patients with laboratory confirmed COVID-19 infection

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Aim of our study was to examine the presentation and characteristics of olfactory and taste impairment in patients with laboratory-confirmed COVID-19.
Methods: 41 patients with laboratory confirmed COVID-19. Average age was 39.7±9.3 years (range 27-46 years). We used a questionnaire with questions about the smell and taste disturbances.
Results: We found that violation of smell and taste was observed in 27 (65,9%) and 24 (58.5%) patients, respectively. Both symptoms were seen in 23 patients (56,1%) cases. It`s important to note that in 5 (12,2%) patients, hyposmia manifested itself at the onset of the disease earlier than other symptoms of COVID-19 4 (9,8%) patients reported anosmia along with headache and fever at the onset of the disease. All patients with impaired smell and taste had a mild or moderate course of the COVID-19.
Conclusion: Anosmia, hyposmia, and ageusia appear to be early signs of a possible COVID-19. Screening for these symptoms in patients with minimal or no infectious disease symptoms and patients with negative COVID-19 will help to prevent further spread of infection.
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C7

Complementary reporting by patients and clinicians offers a more thorough picture of the impact of COVID-19 on people with multiple sclerosis

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All authors have consented to provide their data.
Introduction: The Coronavirus disease 2019 (COVID-19) pandemic has created uncertainties about different aspects of the lives of people with multiple sclerosis (PwMS). We intend to understand the impact of the virus and the risks of the infection in PwMS.
Methods: The study was launched on 17 March 2020 as part of the United Kingdom (UK) MS Register (UKMSR), a research project with 13,916 PwMS registered as of 22 April 2020 which holds longitudinal data about patients' demographics, MS related and other medical information, and patient-reported outcome measures since 2011. All patients on the UKMSR were asked to participate in the study by completing COVID-19 related questionnaires fortnightly. Telephone interviews by a neurologist confirmed the suspected diagnosis of COVID-19 based on symptoms. We also asked healthcare professionals to provide anonymised data on MS patients with COVID-19 using a separate questionnaire.
Results: As of 22 April 2020, 3,702 PwMS participated in the study and recruitment is on-going. A total of 196 (5.29%) participants reported that they had suspected COVID-19 out of which 41 (20.92%) reported having been diagnosed by a healthcare professional. Only three (1.53%) of the patients with suspected COVID-19 required hospitalisation.
On the contrary, out of the 26 suspected COVID-19 cases reported by clinicians, 21 have positive polymerase chain reaction tests and 3 have died.
Conclusion: These contrasting results emphasise the need to supplement clinician-reported outcomes with community-based studies to understand the true impact of COVID-19 in PwMS.

C10

Sphingosine 1-Phosphate Receptor Modulators as a Potential Treatment Option in COVID-19 Induced Acute Respiratory Distress Syndrome: Mechanistic Insights and Benefit-Risk Assessment

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Introduction: Coronavirus disease 2019 (COVID-19) is a viral infection caused by a newly emergent coronavirus, SARS-CoV-2, primarily affecting the respiratory tract. Maladjusted immune responses, e.g. cytokine release syndrome, may result in immunopathology and acute respiratory distress syndrome (ARDS). Sphingosine-1-phosphate (S1P), a bioactive lipid mediator, is crucial in maintaining endothelial cell chemotaxis and barrier integrity (Table 1). An industry-independent clinical study is currently underway in China investigating the efficacy of oral fingolimod 0.5 mg (a non selective S1P receptor modulator) taken once-daily, for three consecutive days in patients with COVID-19.

Methods: Here we review the potential mechanisms by which fingolimod may regulate the inflammatory response to SARS-CoV-2 and assess the potential benefit-risk of short-term treatment with fingolimod in patients with COVID-19 experiencing ARDS.

Results: The key hypotheses through which beneficial effects manifest are (1) attenuation of cytokine release via activation of serine/threonine protein phosphatase 2A (PP2A); (2) inhibition of Th17-mediated pathway; and (3) enhancement of the pulmonary endothelial barrier via c-Abl tyrosine kinase pathway (Table 2).

The short-term intervention with fingolimod might rapidly attenuate maladjusted immune responses while sparing memory immune responses and thus has relatively low risk of infections. Any potential effects on heart rate and cardiac rhythm could be managed under the intensive care treatment setting. Furthermore, simulations from a PKPD model of lymphocyte count data with short-term fingolimod treatment will be presented.

Conclusions: S1P receptor modulators, such as fingolimod, may represent a potential treatment option to ameliorate immune responses against SARS-CoV-2 and merit further investigation following careful benefit-risk evaluation in this setting.

Table 1. Role of sphingolipids in hyperinflammatory sequence of events in ARDS

Mediator	Neutrophil chemotaxis	Endothelial permeability	Neutrophil Apoptosis	Epithelial permeability
NSMase*	↑		↓	
ASMase*		↑		↓
S1P	↓		↓	
S1P1R		↓		↓
S1P2R				↑
S1P3R				↑
S1P4R	Unknown			

[*]catalyses the breakdown of sphingomyelin to ceramide and phosphorylcholine

ARDS, acute respiratory distress syndrome; ASMase, acid sphingomyelinase; NSMase, neutral sphingomyelinase; S1P, sphingosine-1-phosphate; S1P1-4R, type 1-4 S1P receptors

Table 2. Potential mechanisms of S1P receptor modulators

	Chemotaxis/immune response	Endothelial permeability
S1P receptor- modulated effects		
Reduction in Th-17 cell	Reduced tissue infiltration and release of IL-17 and downstream proinflammatory cytokines and chemokines	
Enrichment of T_{regs} and B_{regs} (*via* sparing of this subpopulation)	Shift towards anti-inflammatory response	
Innate immune cells	Reduced pro-inflammatory cytokines	
S1P1-mediated modulation of the endothelial barriers		Barrier enhancement
Non S1P receptor- modulated effects		
Increased PP2A	Suppresses IL-6 and IL-8 cytokine secretion in human alveolar epithelial cell lines	
	Decreases downstream CXCL1 and CXCL2 release	
Inhibition of c-Abl tyrosine kinase		Barrier enhancement by increased transendothelial electrical resistance

IL, interleukin; PP2A, protein phosphatase 2A

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C17

Developing a national notification strategy for COVID-19 infections using the Scottish MS register

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Introduction: COVID-19 may be particularly detrimental for people with MS (pwMS). Disease modifying therapies (DMT) alters immune function with an unknown effect on response to COVID-19. More disabled pwMS may be at increased risk of death from COVID-19. We have attempted to link data from the Scottish Multiple Sclerosis Register (SMSR) with COVID-19 test result data to develop a mechanism to inform neurologists across Scotland of pwMS who catch COVID-19.

Methods: The SMSR is an incidence register which aims to record all new diagnoses of multiple sclerosis in Scotland since 2010. This anonymised dataset is held within Public Health Scotland. COVID-19 test results are recorded by Health Protection Scotland. These datasets will be linked and a weekly report will be generated. Positive cases will be investigated by regional neurologists. Additional cases in pwMS diagnosed pre-2010 will be collected if reported by specialist teams.

Results: The SMSR holds data on more than 4256 pwMS. As of 22/3/20 1616 people in Scotland are known to have died with a COVID-19 infection with 9038 positive cases from a total of 43,309 tests. As of today we know of 6 pwMS with positive tests in Scotland. More data will be presented.

Conclusion: Data linkage using existing national datasets may give a better picture of the spread of COVID-19 amongst people with MS in Scotland. This may help inform future 'shielding' strategies to protect those most at risk of death from the COVID-19 and also may help us understand the interaction of DMT with COVID-19.

C20

COVID-19 related mortality in patients with cognitive impairment: a hospital-based retrospective cohort study.

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Objective: to analyse the frequency of cognitive impairment and other neurological comorbidities in deceased COVID-19 patients, during the outbreak of the pandemic in Madrid, Spain.

Methods: retrospective, single-center, hospital-based study. We included adults that died after admission from March 1 to March 31, 2020, at Hospital Universitario 12 de Octubre. Clinical and demographic data were extracted from electronic medical records.

Results: 477 cases: 58 with probable COVID-19, 281 confirmed COVID-19, and 138 who died of other causes. Comparing the latter two groups, median age (81.4 years vs. 78.1 years; $p<0.01$) and the proportion of males (62.3% vs. 49.3%, $p<0.01$) were higher in the confirmed COVID-19 group. The number of comorbidities was high and similar in both groups, and cognitive impairment was common (29.9%; 21.1% dementia; 8.9% mild cognitive impairment) in confirmed COVID-19. In this group group, subjects with cognitive impairment were older (median 85.8 years vs. 79.0 years, $p<0.0001$), more lived in nursing homes and had slightly shorter times from symptom onset to death than those without cognitive impairment. COVID-19 patients with cognitive impairment were rarely admitted to the ICU, and fewer received non-invasive mechanical ventilation (7.1% vs. 25.4%, <0.0001). Palliative care was provided in more subjects with cognitive impairment (79.2% vs. 66.3%, $p=0.038$).

Conclusions: in our study, dead patients with confirmed COVID-19 were older and had more comorbidities than those reported in the Asian population. Cognitive impairment is a frequent comorbidity in COVID-19 deceased patients. The burden of COVID-19 in the dementia community will be high.