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Phase 3 Trial Designs Evaluating Riliprubart, a C1s-Complement Inhibitor, in Chronic Inflammatory Demyelinating Polyneuropathy

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Introduction: Standard-of-care (SoC) therapies for chronic inflammatory demyelinating polyneuropathy (CIDP) have variable efficacy and side-effects. Riliprubart, a first-in-class, humanized, IgG4-monoclonal antibody, selectively inhibits activated-C1s, and has convenient weekly subcutaneous administration. Phase 2 (NCT04658472) results indicated promising clinical benefits on functional disability, reduced neurofilament light chain-levels, and a favorable benefit:risk profile.

Aim: To present two Phase 3 trial designs evaluating riliprubart in high unmet-need CIDP subpopulations: participants refractory to SoC therapies, and responders to intravenous immunoglobulins (IVIg) with residual disability.

Methods: MOBILIZE ((NCT06290128), is a placebo-controlled trial initiated in SoC-refractory participants; VITALIZE (NCT06290141), is a double-dummy trial targeting IVIg-treated participants with residual disability (i.e., persistent Inflammatory Neuropathy Cause and Treatment [INCAT] score ≥2). Each trial consists of 48-week period: 24-week double-blinded period (Part-A), followed by an additional 24-week open-label period (Part-B). In Part-A, participants are randomized (1:1) to receive riliprubart or placebo (MOBILIZE; N~140), and riliprubart plus IVIg-placebo or IVIg plus riliprubart-placebo (VITALIZE; N~160). Sample sizes will be re-estimated based on pre-defined interim analysis during Part-A. Eligible adults with CIDP diagnosed based on 2021 EAN/PNS guidelines with INCAT score 2-9 (score 2 exclusively from legs) can be included. Primary endpoint is %-participants responding, defined as ≥1-point decrease from baseline in adjusted INCAT score at Week-24 (Part-A). Key secondary endpoints include change from baseline in additional disability/impairment measures (Part-A) and long-term safety (Part-B).

Results: Recruitment is ongoing for both trials.

Conclusions: Phase 3 trials aim to demonstrate riliprubart's efficacy and safety for CIDP, including participants with residual disability/refractory disease despite SoC therapies.

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Phase 2 Efficacy and Safety of Riliprubart, a C1s-Complement Inhibitor, in Chronic Inflammatory Demyelinating Polyneuropathy

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Introduction: Riliprubart, a first-in-class humanized IgG4-monoclonal antibody, selectively inhibits activated-C1s within the classical complement pathway.

Aim: To report efficacy and safety of riliprubart in chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: Global, multicentre, Phase-2, open-label trial (NCT04658472) evaluating riliprubart across three groups of participants with CIDP: Standard-of-care (SOC)-Treated, SOC-Refractory, and SOC-Naïve. Participants undergo 24-week treatment (Part-A), and 52-week Part-B (optional). Part-A primary endpoint for SOC-Treated is %-participants with relapse (≥1-point increase in adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] disability score) after switching from SOC to riliprubart. For SOC-Refractory and SOC-Naïve, primary endpoint is %-participants with response (≥1-point decrease in adjusted INCAT score) from baseline up to 24-weeks. Part-B evaluates safety and efficacy durability based on % relapse-free participants (SOC-Treated) or with sustained-response (SOC-Refractory/Naïve). Exploratory endpoints include additional efficacy measures (INCAT, I-RODS, MRC-SS, grip-strength), change in total complement, and plasma neurofilament-light chain (NfL).

Results: As of May-2023, Part-A results from pre-specified interim-analysis show that 88% (N=22/25) SOC-Treated participants improved or remained stable (44%; N=11/25 improved), and 12% relapsed (N=3/25). For SOC-Refractory participants, 50% (N=9/18) responded to riliprubart. Clinically meaningful improvements were observed across secondary efficacy measures. Sustained inhibition of complement activity and reduction in NfL levels were observed. Treatment-emergent adverse events occurred in 60% (N=15/25) and 72% (N=13/18) of SOC-Treated and SOC-Refractory participants, respectively. Most frequent TEAEs were headache, fatigue, and nasopharyngitis. Available Part-A and Part-B data for all groups will be presented at the meeting.

Conclusions: Preliminary results demonstrate a favourable benefit:risk profile, supporting further investigation of riliprubart in Phase-3.

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Efficacy and Safety of Efgartigimod PH20 Subcutaneous in Chronic Inflammatory Demyelinating Polyneuropathy: Results of ADHERE/ADHERE+

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Introduction: Efgartigimod, a human immunoglobulin G (IgG)1 antibody Fc fragment, blocks the neonatal Fc receptor, decreasing IgG recycling and reducing pathogenic IgG autoantibody levels. This study aims to assess the efficacy and safety of efgartigimod PH20 subcutaneous (SC; coformulated with recombinant human hyaluronidase PH20) in chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: Participants with active CIDP (off treatment or on standard treatments withdrawn during run-in) enrolled in the multi-stage, double-blinded, placebo-controlled ADHERE trial (NCT04281472) and received once weekly (QW) efgartigimod PH20 SC 1000mg (stage A). Responders were randomized (1:1) to QW efgartigimod PH20 SC 1000mg or placebo (stage B). Participants with clinical deterioration in stage B or those who completed ADHERE could enter the ongoing, open-label extension ADHERE+ trial (NCT04280718; QW efgartigimod PH20 SC 1000mg). Primary outcomes were confirmed evidence of clinical improvement (ECI; stage A), relapse risk (stage B), and safety (ADHERE+).

Results: In stage A, 214/322 (66.5%) participants demonstrated confirmed ECI. In stage B, efgartigimod significantly reduced relapse risk (HR: 0.394 [95% CI 0.253–0.614]) vs placebo (P=0.00004); this reduction was observed regardless of prior CIDP therapy. 99% of eligible participants entered ADHERE+. The safety profile of efgartigimod was consistent over 137.42 total patient-years of follow-up for ADHERE+. Most treatment-emergent adverse events were mild/moderate; the incidence/severity did not increase in ADHERE+.

Conclusion: ADHERE demonstrated effectiveness of efgartigimod PH20 SC in reducing relapse risk in CIDP. The safety profile of efgartigimod PH20 SC was similar between ADHERE and ADHERE+ and was consistent with the previously demonstrated safety profile of efgartigimod.

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Distal weakness and paresthesia with facial diplegia: An uncommon variant of Guillain-Barre syndrome

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Background: Bilateral facial weakness with distal paresthesia (BFWdp) occurs in less than 1% of Guillain-Barré syndrome (GBS) cases. GBS can present as a distal acute demyelinating polyradiculoneuropathy, characterized by severe distal demyelination without radiculitis. We report a 63-year-old male with distal weakness, paresthesia, and facial diplegia. Case: A previously healthy 63-year-old male developed distal weakness, facial diplegia, and severe distal paresthesia, consistent with acute distal demyelinating sensorimotor polyneuropathy. Examination revealed bilateral facial paralysis, left partial oculomotor nerve palsy, reduced sensation in both distal limbs, and distal weakness. Proximal strength was minimally reduced. Cerebrospinal fluid showed albuminocytological dissociation, and ganglioside and anti-MAG antibodies were negative. Ultrasound revealed swelling of the median and ulnar nerves, while the sural, vagus, and brachial roots were normal. After intravenous immunoglobulin treatment, the patient improved. Two years later, the patient still had tingling in the hands and feet, but there was no recurrence or progression on NCS. Discussion: The clinical and NCS findings suggest a mixed GBS phenotype, characterized by BFWdp and a distal phenotype. GBS can present with various manifestations and electrodiagnostic features, requiring serial NCS and clinical follow-up for a definitive diagnosis.

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Achievement of Minimal Symptom Expression in Participants Treated With Efgartigimod in ADAPT+ and ADAPT-SC+

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Introduction: Efgartigimod, a human immunoglobulin G (IgG1) antibody Fc-fragment, reduces IgG levels through neonatal Fc receptor blockade. Efgartigimod treatment has been investigated in generalized myasthenia gravis (gMG) via intravenous (IV) and subcutaneous (SC, coformulated with recombinant human hyaluronidase PH20) administration in ADAPT/ADAPT+ and ADAPT-SC/ADAPT-SC+ studies, respectively. Minimal symptom expression (MSE), defined as a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of 0 or 1, is explored as a novel proposed treatment target in gMG.

Methods: The proportion of acetylcholine receptor antibody positive (AChR-Ab+) participants in ADAPT+ (n=111) and ADAPT-SC+ (n=141) achieving MSE was assessed.

Results: In ADAPT, MSE was achieved in 44.6% of efgartigimod-treated participants vs 10.9% of placebo-treated participants at any time point up to 3 cycles. In ADAPT+, the number of participants achieving MSE at any time in up to 19 cycles was 40.5%. Eighty-one percent of efgartigimod-treated participants who achieved MSE in ADAPT also achieved MSE during ADAPT+; 23% who had not achieved MSE in ADAPT did so in ADAPT+. In ADAPT-SC, 45.5% and 41.3% of participants receiving efgartigimod PH20 SC or efgartigimod IV achieved MSE at any time in cycle 1, respectively. In ADAPT-SC+, the number of participants achieving MSE at any time in up to 9 cycles was 54.6%. Clinical improvements may not have been fully captured in OLEs (ADAPT+/ADAPT-SC+) due to the limited number of assessment timepoints.

Conclusion: Achievement of MSE was consistently seen across cycles in AChR-Ab+ participants of both ADAPT+ and ADAPT-SC+, similar to results demonstrated in ADAPT and ADAPT-SC.

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Fucoxanthin prevents Aβ-induced cognitive dysfunction *via* RAGE-dependent NF-κB signaling pathway

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Background: Alzheimer's disease (AD) is characterized by memory loss and cognitive dysfunction caused by neuronal cell death. The accumulation of β-amyloid (Aβ) is considered to be the major neurotoxin that triggers microglial activation, which drives the inflammatory cascade leading to synaptic dysfunction and apoptosis. Recently, the receptor for advanced glycation end-products (RAGE) has been identified as a novel mediator of nuclear factor-κB (NF-κB) pathway for neuroinflammatory response in AD. The present study investigated the neuroprotective effects of fucoxanthin, the most abundant marine carotenoid, against Aβ-induced microglial activation and cognitive impairment *via* inhibiting the RAGE/NF-κB signaling pathway in AD mouse model.

Methods: Passive avoidance test, Y-maze test, and Morris water maze test were used for behavioral test. Aβ accumulation, microglial activation, synaptic loss, RAGE and NF-κB regulated inflammatory proteins were determined by immunohistochemistry and western blotting.

Results: Oral administration of fucoxanthin (100 or 200 mg/kg) significantly improved Aβ-induced spatial learning and cognitive dysfunction *via* upregulating hippocampal post synaptic density protein (PSD-95). It showed a significant inhibitory effect on periplaque microglial activation by suppressing Aβ accumulation. Moreover, the compound suppressed NF-κB-mediated pro-inflammatory cytokines and their upstream enzymes by ameliorating RAGE, suggesting the inflammatory response is directly related to the RAGE/NF-κB signaling pathway.

Conclusions: Overall, the present results demonstrated that fucoxanthin ameliorated Aβ-induced microglia activation and cognitive dysfunction by targeting RAGE/NF-κB pathway-mediated inflammatory process. These findings provide a better understanding of the critical role of fucoxanthin in the prevention of AD and its potential as a promising candidate for anti-AD agents.

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Real-world reduction in oral corticosteroid utilization at 1-year following efgartigimod initiation

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Aim: To evaluate oral corticosteroid (OCS) usage at 1 year following efgartigimod (EFG) initiation.

Methods: Patients with generalized myasthenia gravis (gMG) using OCS pre-EFG initiation were identified from a United States medical and pharmacy claims database (based on information licensed from IQVIA: Longitudinal Access and Adjudication Data [LAAD] for the period April 2016−December 2023, reflecting estimates of real-world activity [all rights reserved]). Mean (standard deviation [SD]) average daily dose (ADD) of OCS was evaluated during the 3 months prior to, and at 6 and 12 months post-EFG initiation. To assess outcomes, de-identified Myasthenia Gravis Activities of Daily Living (MG-ADL) data collected in the "My VYVGART Path" patient support program were tokenized and integrated into the primary dataset.

Results: A total of 169 adults (aged ≥18 years) who were using chronic OCS pre-EFG initiation initiated EFG by December 31, 2022, and continued EFG for at least 12 months were included in the analysis. At 6 and 12 months post-EFG, respectively, 31 (18%) and 45 (27%) patients had no OCS usage. Overall mean (SD) OCS ADD was significantly reduced at 6 months (13.2 [13.9] mg/day, P0.001), and at 12 months (10.2 [12.1] mg/day, P0.001) post-EFG initiation compared with baseline (17.2 [13.7] mg/day). Among a subset of 72 patients (43%) who had both pre- and post-EFG MG-ADL scores available, best follow-up mean (SD) MG-ADL was significantly improved (from 8.3 [3.7] to 3.4 [2.8], P0.001).

Conclusion: The significant reduction of OCS usage observed at 6 months post-EFG initiation was retained at 12 months, while demonstrating MG-ADL response expected from EFG treatment.

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Optimizing Infliximab Dosing for Paradoxical Neurotuberculosis: A Case Report on Treatment Challenges and Decision-Making

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Introduction: Neurotuberculosis is a severe central nervous system infection. Paradoxical reactions can complicate its management, causing disease progression despite appropriate anti-TB treatment.This case report highlights the challenges in treating paradoxical reactions and the role of infliximab therapy.

Case Report: A 21-year-old HIV-negative female with disseminated tuberculosis (TB) and positive CSF(cerebro spinal fuild) TB PCR (polymerase chain reaction) was treated with a Category-1 regimen of anti-TB drugs.Initial imaging revealed right pleural effusion,multiple tuberculomas in the cerebellum and cerebral hemispheres, and meningeal thickening.Seven months into treatment,during the continuation phase she developed gradual right visual loss with temporal field deficit. MRI(magnestic resonance image) showed progression of suprasellar tuberculoma, with mass effect on the cavernous sinus, optic chiasm, pituitary stalk and hypothalamus. Despite normal pituitary function and negative CSF studies, her vision worsened. She was treated with high-dose IV (intravenous) Dexamethasone for 6-weeks, but vision deterioration continued. Subsequently, IV infliximab 6mg/kg was initiated at 0,2,6,12 weeks intervals along with anti-TB therapy for 18-months. Continuation phase included isoniazid, pyrazinamide and rifampicin.After 3-months of infliximab vision gradually improved with regression of tuberculoma.

Conclusion: This case underscores the challenges in managing paradoxical tuberculosis,especialy when the first-line treatment with high dose staeroids fail. Second-line treatments are thalidomide and infliximab, both TNF-alpha inhibitors, can be considered in such cases. In this case, infliximab was preferred due to the risk of thrombosis with thalidomide. The dose of infliximab was selected based on previous experience of inadequate response with lower doses.However, optimal dosing strategies and long term outcome require further investigations.

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How could diagnose MOGAD without MRI?

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BACKGROUND. Establishing the role of HLA in diagnosis of MOGAD among patients with characteristic clinical manifestations, MOGAD IgG antibodies and contraindication for MRI.

METHODS. We propose a case report of a 23 years old woman who presented with ocular pain succeeded by right monocular vision loss without recovery. One month later, she presented with progressive right hemiparesis. She have a history of idiopatic lumbar scoliosis which required surgical intervention with ZODIAC implant, being incompatible with MRI scan.

RESULTS. According to hers symptoms, she performed a normal brain CT scan. In our clinic, we rule out MS, NMOSD and other diseases of the CNS based on clinical signs, brain CT and laboratory tests (infectious, immunologic, etc.). AQP4 IgG antibodies were negative, but IgG antibodies anti-MOG were present. In addition, the HLA testing were concludent for MOGAD (HLA-DRB1 *15:02:01). Based on MOGAD diagnostic criteria and despite the contraindication of performing an MRI scan, we still consider MOGAD diagnosis, due to clinical, immunological and genetic testing.

CONCLUSION. In particular cases, typing HLA profile could substitute MRI scan when it’s not available or it’s contraindicated. In conclusion, we need future studies on large cohorts of pacients to make a clear differential diagnosis between demyelinating disorders.

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Study of levels of oxidative stress and inflammation in rat brain tissue during Escherichia coli lipopolysaccharide-induced endotoxemia: modulatory effect of lycopene

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Introduction: Lipopolysaccharide (LPS) is an integral part of the cell walls of gram-negative bacteria, so during septic conditions, it leads to brain tissue damage. Lipopolysaccharide-induced endotoxemia produces excessive proinflammatory cytokines and reactive oxygen species in brain tissue. Lycopene (LYC) is a powerful antioxidant in the carotenoid plant pigments family (found in papaya, watermelon, grapefruit, apricot, and rosehip).

The Aim: The objective of this research was to analyze the effect of lycopene in the prevention of brain damage caused by Escherichia coli lipopolysaccharide, by monitoring the level of oxidative stress (concentration of malondialdehyde-MDA, carbonyl groups-PCC, and reduced glutathione-GSH) and inflammation parameters (NF-kB, IL-6 and TNF-a), as well as the effects of lycopene supplementation on the investigated parameters.

Material and Methods: Twenty-eight Wistar Albino rats were randomly divided into four groups (n=7): Control group, LYC group (50 mg/kg), LPS group (10 mg/kg), and LPS+LYC group.

Results: In the brains of rats treated with LPS, the concentrations of MDA, PCC, and GSH were significantly increased(p0.01), while the administration of LYC led to a decrease in the level of these parameters(p0.01). Administration of Lycopene in animals with endotoxemia(LPS+LYC group) significantly normalized the high levels of NF-kB, IL-6, and TNF-a in the brain tissue, compared to the LPS group(p0.05).

Conclusion: This study showed a significant therapeutic effect of lycopene, by exhibiting antioxidant and anti-inflammatory effects in brain tissue during endotoxemia. This work was supported by the project funded by the Ministry of Science of the Republic of Serbia(451-03-66/2024-03/200113).

Keywords: Lipopolysaccharide, Lycopene, Oxidative stress, Inflammation, Brain

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Guillain-Barré syndrome with five long-interval episodes and scoping review on recurrent Guillain-Barré syndrome

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Recurrent Guillain-Barré syndrome (RGBS) is a rare neurological condition occurring in approximately 2-6% of Guillain-Barré syndrome (GBS) patients. Due to its rarity, the clinical features and pathophysiology of RGBS remain to be elucidated. We present a unique case of RGBS with five recurrences at long intervals and scoping review of RGBS.
An eighty-one year old woman presented to our department with both leg weakness and paresthesia, the fourth relapse of GBS (mean interval between relapses 71 months) with stereotypical symptoms (distal leg weakness and paresthesia), IgM anti-GM1 antibody positivity and demyelinating neuropathy pattern. In addition, the patient recovered rapidly after intravenous immunoglobulin treatment in all attacks.
Our scoping review focused on RGBS such as our case using a specific criterion: clinically definite relapses with an interval of at least one year, objectively diagnosed GBS by nerve conduction studies or anti-ganglioside antibody assays, and three or more definite relapses. The analysis identified nine cases of GBS with 42 relapses since 1990 using the above criteria.
The results revealed a distinct subtype of RGBS with long intervals characterised by: 1) Stereotypical clinical manifestations across attacks 2) Positive presence of anti-ganglioside antibodies 3) Rapid response to intravenous immunoglobulin (IVIG) treatment.
This study suggests that anti-ganglioside antibodies or other immunological attacks play an important role in causing symptoms. This may be due to the existence of specific vulnerable sites in the peripheral nervous system that are susceptible to repeated antibody-mediated attacks. This comprehensive review provides insights into the complex immunological mechanisms of RGBS.

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Viral polyneuropathy in an immunocompromised person: A case report

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Viral infections are associated with a wide range of nervous system complications. Upper and lower cranial nerve polyneuropathies have been reported from VZV infections. Chronic progressive polyneuropathies are observed in immunocompromised patients due to overlapping viral infections. A 76-year-old woman, with a past medical history of breast cancer three years ago followed by chemo and radiotherapy, was admitted to our hospital with complaints of dysphagia, dysphonia, left sided facial asymmetry, and progressive difficulty walking. Five months before she experienced a vesicular rash overlying the lumbar region and one week later left peripheral facial paralysis, difficulty swallowing, dysphonia and dysarthria. Two months before hospitalization, complained of febrile episodes with cough, followed by worsening of dysphagia and a progressive difficulty in controlling limbs. Neurological examination revealed hoarse voice, mild dysarthria, left sided peripheral facial asymmetry, decreased gag reflex, flaccid tetraparesis with inferior predominance, and hypoesthesia of the limbs. Laboratory findings: leukopenia and + anti-VZV. CSF indicated only elevated protein and pleocytosis. Brain+cervical MRI was unrevealing. Pulmonary scan showed bilateral viral pneumonia, not present before. Corticotherapy and Acyclovir were started. The electrophysiological study is suggestive for a demyelinating neuropathy with secondary axonal degeneration. We started IV immunoglobulin therapy. Unfortunately, her condition deteriorated leading to respiratory failure and subsequent death within a week of ICU admission. With our case, we emphasize the importance of recognizing and managing viral infections in immunocompromised patients as soon as possible. The rapid progression of her condition underscores the need for early recognition and intervention in similar clinical scenarios.

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Challenges in diagnosis and treatment of autoimmune encephalitis with anti-GAD antibodies – analysis of case series with clinical and MRI characteristics.

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INTRODUCTION:

Autoimmune encephalitis with anti-glutamic acid decarboxylase antibodies (anti-GAD AE) is a rare but potentially life threatening condition. It is linked with many neurological syndromes such as stiff-person syndrome (SPS), cerebellar ataxia or limbic encephalitis. However, the clinical presentation may include several atypical features. The MRI analysis may show certain characteristic abnormalities but frequently has no diagnostic value.

CASE PRESENTATION:

1: A 59-year-old male admitted with tonic-clonic seizures. Initially treated with steroids later with intravenous immunoglobulin (IVIg) with good control of the symptoms.

2: A 23-year-old male with diplopia, impaired coordination and balance. Patient also presented mild cognitive impairment. The initial therapy was IVIg and azathioprine.

3: A 54-year-old male on admission presented clinical features typical for SPS. Following methylprednisolone treatment mofetil mycofenolate was administrated with significant clinical improvement.

In all cases laboratory tests confirmed the presence of anti-GAD antibodies in the serum. Only in the first patient, brain MRI revealed pathologies.

CONCLUSIONS:

Our work shows variability of clinical and radiological presentation of anti-GAD AE. Our findings are only partially consistent with presentation described in the literature. None of the patients presented psychosis, but cognitive impairment and seizure occurred. We detected no malignancies, one patient had other autoimmune disorder. Interestingly, all of our patients were males, whilst the literature indicates the disease being more frequent among women. Brain MRI was moderately supportive for diagnosis. Immunosuppression mitigated symptoms in all cases. Our report can be of use for creating clear guidelines for anti-GAD AE diagnosis and management.

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Rituximab in AChR Positive Myasthenia Gravis Patients – A Highly Controversial Topic

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Before the introduction of new drugs since 2017, rituximab was one of the few therapeutic options available for patients with refractory generalized myasthenia gravis (gMG) who did not respond to conventional treatment. Rituximab is an anti-CD20 therapy that is used off-label for all neurological indications. Its effectiveness in MuSK-positive patients is well-established, but its efficacy in AChR-positive patients is less clear. There is a lack of consensus not only on its administration but also on the dosing regimen.

Our center administers this treatment in 33 cases (21 men and 12 women). The initial impetus was the clear neurological improvement observed in an MG patient who received rituximab for a hematological indication in 2009. Although rituximab is the drug of choice for patients with active MG, our patient cohort is relatively small, with all patients receiving at least two pulses. Among these, 23 achieved excellent results with minimal disease manifestation (relapse reduction $p \leq 0.0001$, QMGS decrease 10 IQR (3-10) $p \leq 0.0001$), and in 24 cases was possible to reduce chronic oral immunosuppressive therapy (especially corticosteroids 5 mg IQR (0-12.5), $p \leq 0.0001$), but also discontinuation of intravenous immunoglobulins. The greatest effect is seen in repeatedly hospitalized MG patients who cannot be stabilized despite repeated IVIG therapy and plasmapheresis. When initiating treatment, we are aware of the increased risk of infections, but so far, we have not observed significant adverse effects. This may be partly due to the rapid extension of the treatment interval between doses. In our cohort, the median interval between applications is 10 months (IQR 7-13.75) and the treatment duration is 4 years (IQR 1.5-10).

Rituximab is not intended for the treatment of all patients with active gMG. It is necessary to assess the risks of infectious complications and other comorbidities. Especially in patients with high disease activity and frequent exacerbations, this treatment is worth considering.