To measure confounding, an E-value is calculated for the primary endpoint (time-to-first adjudicated on-trial relapse).
Given the serious impact of NMOSD attacks, eculizumab approval precluded the use of a concurrent comparator for ethical reasons, as it would require assigning patients to placebo when effective treatments exist. A non-inferiority efficacy trial was also considered but recruiting the very large sample size to adequately power the study was not feasible for this ultra-rare disease. Thus, a standard randomized clinical trial design was used. The trial enrolled 58 adults with EDSS score = 7 to receive an infusion of ravulizumab every 8 weeks after the loading dose. The primary treatment period will end when the last enrolled patient reaches week 50 unless a predefined number of patients have an adjudicated on-trial relapse by that time. The entire treatment period will last up to ~4.5 years.

Conclusions

ALXN1210-NMO-307 is an ongoing study evaluating the efficacy and safety of ravulizumab in patients with AQP4+ NMOSD. It is designed to be consistent with PREVENT, and robust statistical methods will address the potential impact of an external comparator.

Disclosure: Dr. Pittock has received personal compensation in the range of $5,000-$9,999 for serving as a Consultant for Genentech, Inc. Dr. Pittock has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Sage Therapeutics, Inc. The institution of Dr. Pittock has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Astellas. Dr. Pittock has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Prime Therapeutics. Dr. Pittock has received personal compensation in the range of $500-$4,999 for serving as a Consultant for UCB. Dr. Pittock has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Roche/Genentech. The institution of Dr. Pittock has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Alexion. The institution of Dr. Pittock has received personal compensation in the range of $500-$4,999 for serving as a Consultant for MedImmune/Viela Bio. Dr. Pittock has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for UCB, Inc. Dr. Pittock has received personal compensation in the range of $5,000-$9,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Hoffman/LaRoche AG. Dr. Pittock has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Genetech. Dr. Pittock has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for F. Hofman/LaRoche. The institution of Dr. Pittock has received personal compensation in the range of $5,000-$9,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Alexion. The institution of Dr. Pittock has received research support from Grifols. The institution of Dr. Pittock has received research support from NIH. The institution of Dr. Pittock has received research support from Viela Bio/MedImmune/Horizon. The institution of Dr. Pittock has received research support from Alexion Pharmaceuticals. The institution of Dr. Pittock has received research support from F. Hoffman/LaRoche/Genentech. Dr. Pittock has received intellectual property interests from a discovery or technology relating to health care. Dr. Pittock has received intellectual property interests from a discovery or technology relating to health care. Kerstin Allen has received personal compensation for serving as an employee of Alexion Pharmaceuticals. Kerstin Allen has stock in AstraZeneca. Kerstin Allen has stock in Alexion Pharmaceuticals. Dr. Mashhoon has received personal compensation for serving as an employee of Alexion, AstraZeneca Rare Disease. Dr. Mashhoon has stock in AstraZeneca. Dr. Yountz has received personal compensation for serving as an employee of Alexion, AstraZeneca Rare Disease. Dr. Yountz has stock in AstraZeneca.

Disease Characteristics of Seropositive Neuromyelitis Optica Spectrum Disorder in a Turkish Cohort

Samet Cam, Bade Gulec, Melih Tutuncu, Sabahattin Saip, Aksel Siva, Ugur Uygunoglu

Objective

To determine the clinical, demographic and imaging characteristics of a Turkish cohort with aquaporin-4-antibody positive (AQP4-IgG+) neuromyelitis optica spectrum disorder (NMOSD) from a single center.

Background

NA.

Design/Methods

35 patients seen between January-2008 and December-2020 with a diagnosis of AQP4-IgG+NMOSD who could be studied in detail were included in the study. Inclusion criteria for patients with NMOSD diagnosis was defined according to International Consensus Diagnostic Criteria (Wingerchuk et al.2015) and all patients were confirmed for AQP4-IgG positive serology at least once by Euroimmune transfected cells assay (EU90). Demographic, clinical and MRI data were obtained retrospectively.

Results

The female-to-male ratio was 16.5: 1. The mean age of disease onset was 26,16±10,96 years for patients with optic neuritis onset (n:12), and 43.17±11,95 for the subgroup that started with transverse myelitis (TM) (n:16), confirming a significant difference of age at onset according to the first attack type ($p < 0.001$). The mean age at onset in 5 patients with area postrema syndrome was 35,74±16,83. Half of the total attacks occurred within the first year of disease onset (98/196). The mean time to diagnosis was 2,98±5,78 years after the initial attack. Disease duration was 10,06±9,76 years. Cerebrospinal fluid oligoclonal bands were studied in 24 and were positive in 25%. An autoimmune rheumatologic disease comorbidity was present in 34.5% of the patients. In patients with MRI disclosing = 2 McDonald dissemination in space criteria (spinal included) was more common in TM group and correlated with a higher disability (EDSS) score.

Conclusions

Turkish AQP4-IgG+NMOSD patients whose disease start with optic neuritis have an earlier age of onset compared to the ones with TM onset. Half of the total attacks occur within the first year of disease onset. Patients with = 2 McDonald MRI dissemination in space criteria were more common in the TM group and had a higher disability (EDSS) score.

Disclosure: Samet Cam has nothing to disclose. Bade Gulec has nothing to disclose. Dr. Tutuncu has nothing to disclose. Sabahattin Saip has nothing to disclose. Dr. Siva has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Novartis. Dr. Siva has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Roche. Dr. Siva has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Sanofi-Genzyme. Dr. Siva has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Biogen - TR. Dr. Siva has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Roche. Dr. Siva has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Abdi Ibrahim Ilac - TR. Dr. Siva has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Biogen - TR. Dr. Siva has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Merck Serono. The institution of Dr. Siva has received research support from Turkish MS Society. The institution of Dr. Siva has received research support from The Scientific and Technological Research Council Of Turkey - Health Sciences Research Grants. Dr. Uygunoglu has nothing to disclose.

Nipocalimab's Selective Targeting of FcRn and IgG Clearance Preserves Key Immune Functions

Leona Ling, Steven Tyler, Christopher Beneduce, Faye Yu, Julia Brown, Sujatha Kumar, Rui Xu, Jay Duffner, William Avery

Objective

To characterize the effect of nipocalimab, a fully human, effectorless IgG1 anti-neonatal Fc receptor (FcRn) monoclonal antibody on immune function.

Background

Nipocalimab binds to FcRn with high affinity which prevents IgG recycling, leading to reduced serum levels of total IgGs, including pathogenic IgG autoantibodies. Rapid, sustained lowering of IgG was observed in the phase 2 VIVACITY study in generalized myasthenia gravis (gMG) and in phase 1 healthy volunteers. In gMG patients, nipocalimab induced rapid and sustained lowering of anti-AChR autoantibodies and MG-ADL scores, but no serious adverse events including clinically significant infections.

Design/Methods

Nipocalimab was evaluated extensively in vitro and in nonhuman primate-based chronic toxicology studies to evaluate selectivity, tolerability, safety and immunopharmacology. Safety, tolerability and immune-focused assessments in clinical phase 1 and Phase 2 MG studies were also completed (NCT02828046, NCT03772587).

Results

Nipocalimab binds specifically in vitro to FcRn without activation of effector function or inhibition of antigen presentation. In nonhuman primates administered up to 300 mg/kg nipocalimab QW for up to 6 months, sustained lowering of IgG was observed without adverse effects. Immunotoxicology identified no effect on immune cell phenotypes; CD8 T cell, NK or innate cell functions; T-dependent neoantigen IgM responses. Neoantigen IgG production was observed, but with lowered peak IgG titers consistent with the anticipated increase in IgG clearance with nipocalimab. In clinical studies, nipocalimab demonstrated a reproducible selective decrease in total serum IgG, including all subclasses of IgG, with no effect on IgM, IgA, IgE, CH50, C3, C4, inflammatory cytokines or acute phase proteins including, C-reactive protein (CRP).

Conclusions

These data suggest that nipocalimab can selectively lower IgG and IgG autoantibodies while preserving cellular immunity, complete IgM response and IgG production after neoantigen challenge. Overall, nipocalimab's selective effect on IgG recycling provides a mechanistic rationale for potentially decreased infection risk despite substantial IgG lowering.

Disclosure: Dr. Ling has received personal compensation for serving as an employee of Janssen Pharmaceuticals (Johnson&Johnson). Dr. Ling has stock in Janssen Pharmaceuticals (Johnson&Johnson). Dr. Ling has received intellectual property interests from a discovery or technology relating to health care. Dr. Ling has received intellectual property interests from a discovery or technology relating to health care. Mr. Tyler has received personal compensation for serving as an employee of AVROBIO, INC. Mr. Beneduce has received personal compensation for serving as an employee of Janssen Pharmaceuticals of Johnson and Johnson. Mr. Beneduce has received stock or an ownership interest from Janssen Pharmaceuticals of Johnson and Johnson. Mr. Beneduce has received intellectual property interests from a discovery or technology relating to health care. Ms. Yu has received personal compensation for serving as an employee of Janssen Pharmaceuticals. Ms. Yu has received personal compensation for serving as an employee of Momenta Pharmaceuticals. Ms. Yu has stock in Johnson and Johnson. Dr. Brown has received personal compensation for serving as an employee of Janssen Pharmaceuticals. Dr. Brown has received personal compensation for serving as an employee of Momenta Pharmaceuticals. Dr. Brown has received stock or an ownership interest from Janssen Pharmaceuticals. Dr. Brown has received stock or an ownership interest from Momenta Pharmaceuticals. Dr. Brown has received intellectual property interests from a discovery or technology relating to health care. Dr. Kumar has received personal compensation for serving as an employee of GlaxoSmithKline. Dr. Kumar has received personal compensation for serving as an employee of Checkmate Pharmaceuticals. Dr. Kumar has received stock or an ownership interest from GSK. Dr. Kumar has received stock or an ownership interest from Checkmate Pharmaceuticals. Dr. Xu has nothing to disclose. Dr. Duffner has received personal compensation for activities with Momenta Pharmaceuticals. Dr. Avery has received personal compensation for serving as an employee of Lyndra Therapeutics. Dr. Avery has received personal compensation for serving as an employee of Xilio Therapeutics. Dr. Avery has received personal compensation for serving as an employee of Kisbee Therapeutics. Dr. Avery has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Momenta Pharmaceutical. Dr. Avery has received stock or an ownership interest from Life Biosciences.

Validation of MATCH Score: A Predictive Tool for Identification of Patients With Kelch-Like Protein-11 Autoantibodies

M Bakri Hammami, Mohamed Rezk, Divyanshu Dubey

Objective

To validate performance of the MATCH score using an independent paraneoplastic neurological syndrome (PNS) cohort.

Background

Kelch-like protein 11 (KLHL11)-IgG is a high-risk paraneoplastic antibody associated with rhombencephalitis. MATCH score is a composite clinical model recently developed to predict KLHL11-IgG positivity

Design/Methods

Retrospective review of cases with definite or probable PNS who underwent neural specific autoantibody evaluation at Mayo Clinic Neuroimmunology laboratory between January 2001 and December 2021 was performed. MATCH score was calculated for all patients to assess the score's discriminative ability

Results

186 patients who met the definite or probable PNS criteria were identified. The MATCH score was = 4 in 31/36 patients who were KLHL11-IgG positive and in 17/150 patients who were KLHL11-IgG negative but positive for other high-risk autoantibodies including CRMP5, ANNA1, PCA1 and amphiphysin, among others, or seronegative to all antibodies. MATCH Score's sensitivity, specificity, positive and negative predictive value were 86%, 89%, 65% and 96%, respectively. The score showed an excellent discriminative ability with an AUC of 0.924 [95% CI 0.885-0.962].

Conclusions

MATCH score is a sensitive and specific tool to identify patients likely to be KLHL11-IgG positive. Utilization of MATCH score can improve pretest probability. However, some KLHL11-IgG cases with motor neuronopathy or limbic encephalitis presentation or those without a detectable testicular cancer at the time of initial assessment may potentially be missed.

Disclosure: Dr. Hammami has received intellectual property interests from a discovery or technology relating to health care. Dr. Rezk has nothing to disclose. The institution of Dr. Dubey has received personal compensation in the range of $500-$4,999 for serving as a Consultant for UCB. The institution of Dr. Dubey has received personal compensation in the range of $5,000-$9,999 for serving as a Consultant for Astellas. Dr. Dubey has received personal compensation in the range of $0-$499 for serving on a Speakers Bureau for AGRIMS. Dr. Dubey has received personal compensation in the range of $0-$499 for serving on a Speakers Bureau for Advances in Neurology. Dr. Dubey has received personal compensation in the range of $0-$499 for serving on a Speakers Bureau for Moffit Cancer Center. Dr. Dubey has received research support from Department of Defense. Dr. Dubey has received intellectual property interests from a discovery or technology relating to health care. Dr. Dubey has received intellectual property interests from a discovery or technology relating to health care. Dr. Dubey has received intellectual property interests from a discovery or technology relating to health care.

Caveolae-Associated Protein (cavin)-4 Autoantibodies in Immune Mediated Rippling Muscle Disease

M Bakri Hammami, Grayson Beecher, Andrew Knight, Teerin Liewluck, James Triplett, Abhigyan Datta, Surendra Dasari, Youwen Zhang, Matthew Roforth, Calvin Jerde, Stephen Murphy, William Litchy, Anthony Amato, Vanda Lennon, Andrew McKeon, John Mills, Sean Pittock, Margherita Milone, Divyanshu Dubey