Contemporary Issues in Practice, Education, & Research:

The Clinical Trial Landscape in Autoimmune Encephalitis: Challenges and Opportunities

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Key words: autoimmune encephalitis, NMDAR-antibody encephalitis, LGI1-antibody encephalitis, clinical trial, inebilizumab, rozanolixizumab, satralizumab, bortezomib

Word count: 4135

Number of tables: 2

Number of figures: 3

Number of references: 40

Abstract:

Autoimmune encephalitis is an important cause of neurological morbidity and mortality. Treatment algorithms are based on observational, primarily retrospective studies, plus expert opinion. Despite clinical improvement with empiric therapy, recovery is often incomplete with a substantial burden of residual neurological deficits and recurring symptoms. There is a pressing need for higher-quality evidence-based therapies. However, designing and conducting clinical trials for patients with rare diseases like autoimmune encephalitis has specific challenges, including slow recruitment, suboptimal outcome measures, and inclusivity versus exclusivity of the various disease subtypes. The anticipated knowledge gained from autoimmune encephalitis clinical trials emphasizes the need to overcome these challenges and support the development of the next generation of clinical trials. Yet, given these challenges, alternative approaches may be required. In this article, we review past and present clinical trials in autoimmune encephalitis with a focus on studies enrolling patients with neural surface antibodies. We discuss the potential challenges and opportunities inherent to clinical trials in rare diseases and provide an outlook for the field.

Introduction

In the last two decades, autoimmune encephalitis (AE) has emerged as a major cause of neurological morbidity with at least a similar prevalence to viral encephalitis.[1 2] Observational studies suggest that AE subtypes mediated by neural surface antibodies are more responsive to immunotherapy and carry a better prognosis than those associated with antibodies against intracellular antigens.[3] The response to immunotherapy, however, is often incomplete with variable relapse rates and abundant sequelae including cognitive impairment, affective disorders, fatigue, and sleep disorders, that contribute to long-term morbidity.[4 5 6 7] Although current AE treatment approaches are supported by consensus statements,[8 9] these recommendations are predicated on Class IV observational studies, which are susceptible to high degrees of bias.[10] Well-designed randomized controlled clinical trials (RCTs) are important to provide the higher-quality evidence required to grow scientific knowledge, support drug discovery, advance evidence-based treatment, and improve patient outcomes. However, implementation of such trials in AE is very challenging given the rarity and heterogeneity of this disease spectrum. Despite these challenges, several RCTs have begun to evaluate the safety and efficacy of established and novel therapeutics in AE (table-1).[11 12 13 14] Here, we review the proposed pathophysiology of AE, the available empiric therapies, the rationale and design of recent and ongoing RCTs, and the specific challenges that face these trials. The goal of this narrative review is to provide an update on pipeline AE therapeutics to clinicians caring for AE patients, discuss the challenges that face current clinical trials, and provide recommendations to support the next generation of AE clinical trials.

The pathophysiology of autoimmune encephalitis

AE encompasses several disorders characterized by immune-mediated inflammation of brain parenchyma mainly involving the cortical and/or deep grey matter with or without extension to the white matter, brainstem, meninges, and spinal cord.[8 15] Unlike multiple sclerosis and acute disseminated encephalomyelitis, demyelination is uncommon in AE,[16] although it may coexist with grey matter inflammation in certain AE subtypes.[17] AE patients may have antibodies against neural surface antigens or intracellular antigens (figure-1). The autoimmune pathology in patients with neural surface antibodies

is thought to be antibody-mediated, and may or may not be associated with a neoplasm (paraneoplastic or idiopathic).[16] In comparison, the inflammatory pathology in patients with antibodies against intracellular antigens is mostly T-cell-mediated and the antibodies themselves are often not pathogenic.[16] Most cases of AE in patients with antibodies against intracellular antigens are paraneoplastic and tend to be resistant to immunotherapy especially if the associated tumor is untreated. On the contrary, patients with neural surface antibodies are more responsive to empiric immunotherapies directed against antibody-mediated pathology. In addition to idiopathic and paraneoplastic etiologies, some cases are post-viral (e.g. after herpetic encephalitis)[8] or iatrogenic (e.g. in the setting of tumor-necrosis-factor-alpha inhibitors or immune-checkpoint inhibitors).[8]The two most common and widely-studied AE syndromes associated with neural surface antibodies are N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis[18] and Leucine-rich glioma inactivated-1 (LGI1) antibody encephalitis.[19]

NMDAR-antibody encephalitis commonly affects young females with ovarian teratoma but can also affect males, children, and the elderly.[20] It manifests with encephalopathy, speech dysfunction, seizures, involuntary movements, autonomic instability, and central hypoventilation.[15] Despite, the severe initial presentation and the prolonged disease course, most patients eventually improve.[20] The substantial potential for improvement is consistent with the relative absence of structural abnormalities on brain MRI, lack of prominent changes in biofluid neuroaxonal loss biomarkers ,[21] and rarity of neuronal loss in pathological specimens of NMDAR-antibody encephalitis.[15] [16] [17] Pathological studies in NMDAR-antibody encephalitis show modest perivascular T and B-cell infiltrates with copious interstitial/perivascular antibody-secreting plasmablasts and plasma cells.[22] This explains the intrathecal synthesis of NMDAR antibody and the higher reliability of cerebrospinal fluid (CSF) testing in this disorder. Although NMDAR antibodies are particularly of the IgG1 subclass, complement deposits are absent in NMDAR-antibody encephalitis pathology specimens.[16] [22] NMDAR-antibodies interact with surface NMDA receptors on neurons, and possibly oligodendrocytes, leading to receptor internalization resulting in neuronal dysfunction without neuronal loss. Recent studies have demonstrated the presence of NMDAR-antibody producing germinal centers in the cervical lymph nodes and teratomas in patients with this disease, as niduses of antibody production.[23] Further, CSF usually shows elevated levels of the pleotropic cytokine interleukin 6 (IL-6), a key factor in differentiation of B-cells into antibody-producing cells.[24]

LGI1-antibody encephalitis commonly affects older men, and presents frequently with the characteristic faciobrachial dystonic seizures followed by cognitive decline and behavioral changes concordant with limbic encephalitis, the typical anatomical phenotype of this disorder.[25] Most cases are idiopathic. The LGI1 antibodies are proven to be pathogenic, based on highly specific monoclonal antibody passive transfer approaches.[26] Similar to NMDAR-antibody encephalitis, pathological studies in LGI1-antibody syndrome demonstrate pathogenic antibody-producing plasmablasts and plasma cells in the CSF,[27] which are likely peripherally activated before entering the CNS. Although most pathogenic LGI1 antibodies are of the IgG4 subclass, tissue from these patients contrast with those in NMDAR-antibody encephalitis by showing more pronounced T and B cell infiltration, complement deposition, and neuronal death throughout the limbic system.[16] [28] IL-6 is elevated also in the serum of some LGI1-antibody encephalitis patients.[29] Longitudinal radiological studies of patients with LGI1-antibody encephalitis demonstrate hippocampal atrophy in a subset of patients after recovery from the acute phase. (Finke et al., 2017)

Autoimmune encephalitis empiric and experimental therapies

Current first-line acute therapies for AE include agents with general anti-inflammatory and immunosuppressant properties like intravenous methylprednisolone (IVMP), and agents that reduce or neutralize pathogenic antibodies in the circulation like plasma exchange (PLEX) and intravenous immunoglobulins (IVIg) (Figure 2).[8] Second-line therapies include the anti-CD20 B-cell depleting agent rituximab, and broad-spectrum immunosuppressants like cyclophosphamide and mycophenolate mofetil. Overall, retrospective studies suggest that more rapid administration of immunotherapies is associated with improved outcomes in AE patients.[20] Second-line therapies have been linked to further improvements and reduction of future relapses.[20] Given the pathogenic roles of antibody-producing plasmablasts and plasma cells in AE, there has been a growing scientific interest in targeting those cells. Rituximab depletes only few plasmablasts because they typically lack CD20. Inebilizumab is a humanized monoclonal antibody against the B-cell surface antigen CD19,[30] with the potential to not only deplete CD19+CD20+ B-cells (as with rituximab), but also a proportion of CD19+CD20- plasmablasts and subsets of plasma cells (many plasma cells are both CD19 and CD20 negative). Although antibody-secreting cells exist in the brains of AE patients, it is not known how many lack CD19 or if therapeutic antibodies can access this compartment. Therefore, whether targeting CD19 confers a real-world benefit over anti-

CD20 agents is unclear. Inebilizumab is licensed by the U.S FDA for the treatment of neuromyelitis optica spectrum disorder (NMOSD), with RCT data confirming robust, broad, and sustained B-cell suppression in AQP4-IgG positive patients. NMOSD is a rare antibody-mediated neuroinflammatory disorder that shares similar pathologic mechanisms to AE and is typically responsive to the same empiric therapies. Another approach to targeting plasma cells is by inducing their apoptosis through proteasome inhibition. Bortezomib is a proteasome inhibitor that primarily affects cells with high protein synthesis, in particular plasma cells, leading to apoptosis. Bortezomib is included in standard therapy schemes for patients with multiple myeloma and was shown to also induce plasma cell depletion and reduction of pathogenic autoantibodies in systemic autoimmune disorders.[31] Some case reports and non-controlled case series provided the first evidence of a potential beneficial effect of bortezomib in patients with severe AE[32] whereas others reported no significant therapeutic response.[33] Biological plausibility to this approach includes the strong evidence that plasma cells are present in the CSF, meninges and brains of AE patients.[22 27]

Another potential therapeutic approach to AE is preventing antibody recycling and accelerating IgG catabolism via inhibition of the neonatal Fc receptor (FcRn) in endothelial cells. FcRn normally binds to IgG and albumin to prevent their lysosomal degradation and recycles them back into the circulation prolonging their half-life. Rozanolixizumab is a humanized IgG4 monoclonal antibody developed to block IgG binding to FcRn without affecting albumin recycling.[34] By blocking FcRn, rozanolixizumab accelerates IgG catabolism, including pathogenic autoantibodies, thus reducing their concentration in patients with autoimmune diseases. It has been shown to have therapeutic efficacy in myasthenia gravis.[35]

Blocking the IL-6 receptor is another promising approach to AE treatment. Among other immune effects, IL-6 is implicated in the maturation of B-cells into antibody-producing plasmablasts including pathogenic AE antibodies. Observational studies suggest benefit from tocilizumab (a monoclonal antibody against IL-6 receptor) when added to standard AE therapy.[36] Satralizumab is a humanized monoclonal antibody that targets IL-6 receptor and has demonstrated efficacy with FDA licencing in NMOSD with AQP4-IgG.[37]

These novel therapeutic approaches are promising and may be more effective and possibly safer than existing empiric therapies. However, immunosuppression and increased infection risk remain viable concerns with these interventions. Precision medicine approaches like targeted antibody therapies that compete with pathogenic antibodies without inhibiting or activating the target receptor (e.g. anti-

NMDAR therapeutic antibodies, clinical trial NCT06575153 or NMDAR Fc fusion proteins). All approaches and substances described above show low CNS penetration, so it will be interesting to see if depletion of antibodies or immune cells in the periphery and the meninges is sufficient to ameliorate CNS disease at a sufficient rate. Evidence suggesting the presence of active germinal centre reactions in systemic lymph nodes provides data supporting ongoing peripheral immune activation in patients with estaslished CNS diseases.(Al-Diwani et al., 2022, Damato et al., 2022) Novel approaches with chimeric T-cell therapies directed against pathogenic B cells,[38] may be able to overcome this limitation, may avoid unnecessary immunosuppression, and can be studied in comparison to standard second-line therapies in future clinical trials.

Challenges to conducting clinical trials in autoimmune encephalitisA growing body of literature suggests that incomplete recovery is common after AE attacks and that some patients experience recurrences.[4] [5] [6] Available empiric therapies are only partly effective and carry potential serious side-effects. So, there is a pressing need for efficacious evidence-based therapies to improve AE outcomes, preferably with fewer side effects. However, numerous intertwined factors challenge the design and conduct of RCTs for rare disorders like AE. Below are some of the most important challenges that face AE clinical trials:

A) Recruitment:

Patients with rare diseases can be harder to enroll in numbers required to power therapeutic studies, particularly in the acute phases of disease when anticipated benefits are greatest. Previous AE trials have suffered from low recruitment, which resulted in early termination.[11] [12] For example, a single center double-blind RCT of IVIg in patients with LGI1-antibody or CASPR2-antibody AE was terminated prematurely due to slow enrollment.[11] Only 17 subjects out of the targeted 30 were enrolled despite >500 potential participants were identified in this period. Patients randomized to IVIg were more likely to achieve seizure freedom than those who received placebo, but the results were fundamentally underpowered. Likewise, a single center double-blind RCT of ocrelizumab, a humanized anti-CD20 agent, in patients with NMDAR-, LGI1-, CASPR2-, or DPPX-antibody AE was also terminated prematurely due to slow recruitment.[12] Only 3 out of the targeted 16 patients were recruited, hampering meaningful interpretation of the results. Given the patient recruitment

challenges faced by these early efforts, it became clear that multicenter studies are necessary for adequate recruitment—a lesson reinforced by successful studies in NMOSD.[30 39] Unlike NMOSD, AE is a heterogeneous group of disorders with different antibodies and variable underlying mechanisms.[8] Individual antibody subtypes are rare and even multicenter trials of individual subtypes have suffered from low recruitment. Exclusion of children and pregnant females from clinical trials adds to recruitment challenges. The lack of reliable neuronal antibody testing in certain geographical areas is another obstacle against enrollment in trials mandating neuronal antibody positivity. The inclusion of patients with probable NMDAR-antibody encephalitis based on clinical grounds only in some studies (e.g. CIELO) can partially overcome this problem, but it introduces a modest risk of enrolling subjects with an inaccurate diagnosis.

B) Heterogeneity of the disease:

The heterogeneity of the serological AE subtypes creates a special dilemma of inclusivity versus exclusivity of AE subtypes when designing RCTs, i.e. whether to study each antibody-associated disease as its own condition versus under the broader heading of AE. Most current studies focus on one specific homogenous antibody subtype (NMDAR-antibody in ExTINGUISH and LGI1-antibody in LEGIONE) or follow a basket study design (cohorts studying NMDAR and LGI1 antibodies in CIELO). The basket design enables the study of different AE syndromes under a “master” protocol, aiming to leverage the efficiencies of a shared trial infrastructure, particularly for a rare disorder. In a basket study design, the results from each cohort are analyzed independently. Although the basket approach may fail to power either of the two disease groups, planned sample sizes can be individualized for each group. Basket studies also allow for cohort-specific hierarchies of outcomes based on clinically relevant features of the specific AE syndrome. Whether the results of NMDAR-antibody and LGI1-antibody AE RCTs can be generalized to other neuronal surface antibodies (e.g. CASPR2-, GABAR-, AMPAR-antibody, etc.) is unclear but might be necessary from the practical standpoint since designing dedicated trials for each individual antibody might not be feasible given relative rarity. An inclusive study design allows recruitment of any clinically-relevant neuronal surface autoantibody (e.g. as in GENERATE-BOOST). This can potentially overcome the problem of low recruitment. However, including more than one AE subtype under a common trial design may

underpower the results for individual subtypes. It may also invite regulatory challenges for approval for specific indications, noting that regulatory agencies generally do not support the inclusion of multiple disease subtypes with potentially different pathomechanisms, prognosis, and treatment responsiveness within a single trial cohort. Moreover, study outcomes and endpoints may not be suitable for all disease subtypes. On the other hand, the rationale to include multiple pathogenic antibodies addresses the common underlying AE pathology of disease-inducing antibodies to neuronal surface antigens. This approach may provide clinical evidence if a therapeutic principle (e.g., plasma cell depletion using proteasome inhibition as in the inclusive GENERATE-BOOST study) has the potential to modulate disease severity in a broader range of AE subtypes.

Etiologically, current RCTs focus on idiopathic disease and exclude patients with AE associated with cancer or developing following herpetic encephalitis or exposure to immune-checkpoint inhibitors. These etiological subtypes are relatively common, accounting for about one-third of all-cause AE cases.[4] Future studies should consider inclusion of these etiological subtypes after the etiological triggers are sufficiently addressed although this will necessarily create etiological heterogeneity in the studies. Likewise, current trials do not include patients with neuronal antibodies against intracellular antigens and those with antibody-negative disease. Exclusion of such patients is understandable given the critical differences in pathomechanisms between the antibody-mediated pathogenesis in patients with neuronal surface antibodies and the T-cell-mediated mechanisms in those with antibodies against intracellular antigens (and the unknown pathogenesis in antibody-negative patients). However, these serological subtypes are relatively frequent and deserve their own RCTs especially since the results of the current trials are not generalizable to all forms of AE.

C) Challenges related to monotherapy, add-on therapy, and placebo control:

The availability of widely accepted off-label empiric therapies for AE creates additional challenges, as early exposure to immunotherapies may present safety risks when combined with investigational agents or confound the evaluation of their efficacy. Moreover, the severity of the disease and established response to first-line therapies renders placebo-controlled studies without first-line therapies unethical. Another important barrier against successful recruitment is the availability of effective empiric second-line therapies making it difficult for some patients and clinicians to elect to

participate in placebo-controlled studies even when first-line immunotherapies are allowed, especially in severe cases. Studying investigational drugs as add-on therapy to empiric second-line agents is a reasonable approach that has been proven successful in NMOSD clinical trials (e.g. Sakura Sky study).[38] However, combined or overlapping immunosuppression may increase risk including related to infection and malignancy. Combined therapy may also be unnecessary, and it impedes evaluating the potential benefit of the investigational agent as monotherapy. Determining treatment-refractoriness in patients receiving second-line therapy can be difficult due to the protracted improvement seen in some AE patients. This complicates decisions regarding candidacy to enrollment in clinical trials with refractory arms (e.g. CIELO).

D) Outcome measures:

Selecting an outcome measure for AE RCTs is one of the most challenging aspects of trial design. Most AE studies utilize the modified Rankin Scale (mRS), referencing early, retrospective observational studies in AE and infectious encephalitis that popularized this approach.[20] The mRS was mainly geared towards motor disability in stroke patients, which is rare in AE.[4] Structured interviews focused on AE symptoms, supported by standardized rater training, may be helpful with implementation. However, validated outcome measures for AE are still needed. The clinical assessment scale in autoimmune encephalitis (CASE) score was developed specifically to capture the multi-symptomatic aspects of AE, and is a promising outcome measure for AE RCTs.[39] However, the CASE score is relatively new and lacks robust validation studies, especially as a long-term measure. It also lacks categories for sleep dysfunction, autonomic dysfunction, and death.[4] The categories of the CASE score make it more suitable to measure outcomes in NMDAR-antibody encephalitis over other forms of AE. Most studies incorporated CASE as a secondary outcome, but an updated version of the CASE score may be suitable as a primary outcome in future studies. However, both mRS and CASE are ordinal scales, necessitating less powerful statistical analyses. They also both suffer from a ceiling effect, making them suitable for acute and subacute outcome analyses, but less suitable for more chronic outcomes. Seizure-freedom is a potentially suitable outcome for AE subtypes that present predominantly with seizures like LGI1-antibody and GABAR-antibody encephalitis but is not suitable for subtypes with multi-symptomatic presentations and variable seizure prevalence (e.g.

NMDAR-antibody encephalitis). Standardized measures of cognition may be ideal for AE subtypes with prominent cognitive dysfunction especially as long-term outcomes, but the best cognitive measure for AE is yet to be elucidated. Detailed evaluations of the various patterns of residual cognitive deficits after AE are needed to select the most suitable cognitive measure or design a new scale specific for AE. The Liverpool Outcome Score has been used in viral encephalitis in children, and can be a potential outcome measure for pediatric AE. The newly developed Patient-Reported Outcome Scale for Encephalitis (PROSE) may be a suitable future outcome measure that reflects patient perspectives (Brenner et al. presented at the 2024 AAN Summer Conference).

Challenge mitigation in current AE clinical trials and future recommendations:

Current clinical trials in AE include a study of inebilizumab in NMDAR-antibody encephalitis (Extinguish), a study of rosanolixizumab in LGI1-antibody encephalitis (LEGIONE), a basket study of satralizumab in NMDAR-antibody encephalitis and LGI1-antibody encephalitis (CIELO), and a study of bortezomib in AE with any neuronal surface antibody (GENERATE-BOOST). Table-1 includes details of each of these clinical trials. The current trials have implemented several mitigation strategies to address numerous challenges as detailed in table-2. Despite those mitigation strategies, AE clinical trials continue to struggle with various difficulties. Recently, LEGIONE has been put on hold due to slow recruitment. Interim analysis of patient data and LGI1 IgG titers are being performed to assess potential efficacy and safety signals.

We propose several recommendations for future clinical trials based on the lessons learned from the current studies as detailed in table-2

A roadmap for stakeholders:

Many lessons can be learned from the current and previous clinical trials in AE. To ensure the success of future trials, AE stakeholders should consider the following:

Considerations for patients and caregivers:

Unlike chronic immune-mediated neurological disorders (e.g. multiple sclerosis), AE is often an acute monophasic inflammatory event. Patients and caregivers are often introduced to the concept of AE for the first time at the time of initial presentation. Public knowledge of AE as a disease entity is limited. Agreeing to enroll in a clinical trial shortly after being diagnosed can be difficult, especially when those decisions must be made in some cases by surrogate decision-makers. Patients and caregivers need to be educated on the current empiric therapies including both their benefits and risks. The value of clinical trials in conditions without evidence-based therapies should be emphasized. Patients and caregivers need to be assured that all current clinical trials test investigational drugs as add-on to standard first-line therapies, and that second-line therapies are either mandatory or optional in all studies either before randomization or as a rescue thereafter. The fact that the investigational agents could be less toxic than empiric second and third-line therapies should also be explained. All current investigational agents in AE have been previously approved for other indications and have existing data from those indications informing safety and risk mitigation strategies. After the acute phase, recovering patients should be educated on the value of clinical trials in exploring the impact of long-term immunomodulation on residual symptoms and relapse rates. Patients and caregivers should be encouraged to participate in educational events, patient organizations, and registries related to AE. They should consider participation in future studies focused on cognitive rehabilitation and immune tolerization. Individualized recognition and appreciation of participant contributions to clinical trials and advancing clinical research is paramount.

Considerations for clinicians:

One of the greatest challenges that face AE clinical trials is low referral rates secondary to clinician hesitancy. In some institutions in which second-line therapy with rituximab is routine practice for most AE patients, making referrals to clinical trials that exclude rituximab can be less appealing. However, clinicians should consider the risks involved with the indiscriminatory use of second-line therapy in all patients including unnecessary immunosuppression in milder cases. They should understand that the value of the current AE trials is to test if second-line therapy is necessary and justified from the safety standpoint in all AE patients. Realizing that the empiric use of rituximab and/or cyclophosphamide is mainly derived from lower-quality evidence based on patients with severe NMDAR-antibody encephalitis can reduce clinician hesitancy and supports equipoise for clinical trials. Moreover, as

mentioned in the patient section, clinicians should be made aware that the use of empiric second-line therapies is allowed in all trials either before randomization or as a rescue therapy after randomization in non-responders. Gaining access to therapeutic agents with proven efficacy and safety in other neuroinflammatory disorders through AE clinical trials, is a strong advantage that should be considered by clinicians. Clinical trials also provide close clinical monitoring and access to supervision of medical care by experts in AE management.

Considerations for investigators:

Investigators designing the next generation of AE clinical trials should consider the challenges faced by the current trials and implement creative designs to ensure success of the future trials. Investigator-initiated studies of existing first and second-line therapies (e.g., cyclophosphamide + rituximab vs rituximab alone) remain important and should be considered. Designing clinical trials versus active comparators instead of placebo may also mitigate patient and clinician hesitancy and improve enrollment rates. Developing AE-specific outcome measures for future clinical trials should be viewed as a priority for collaborative research efforts. Addressing understudied AE subtypes (e.g. paraneoplastic and antibody-negative AE) is another critical area for future investigators. Table-2 details specific recommendations for future AE clinical trials.

Considerations for pharmaceutical sponsors and funding agencies:

An important barrier to AE clinical trials is the lack of access to reliable neuronal antibody testing in many parts of the world. Clinical trial sponsors should partner with neuroimmunology laboratories to make testing available without cost to underserved areas. There is a pressing need for an international AE registry and biobank to advance AE knowledge and expand the limited insights that are typically gained from smaller single center studies. Funding agencies and interested pharmaceutical companies should consider investing in such registries, which can serve as an important source to identify clinical trial candidates. Sponsors should also invest in novel approaches to AE management including precision medicine approaches, cognitive rehabilitation research in the post-acute phase, and tolerization therapy in patients with recurrent AE.

Considerations for regulatory agencies:

One of the biggest obstacles to sufficient recruitment in AE clinical trials is the mandatory recruitment of one or two specific antibody serotypes per the recommendations of regulatory agencies. Given the rarity of individual AE subtypes, regulatory agencies should consider inclusion of multiple antibody subtypes under a master protocol if they belong to the same broad category of antibodies (e.g., neuronal surface antibodies). This might improve recruitment while providing evidence-based therapies for rare subtypes that would otherwise be unsuitable for their own dedicated clinical trials. Regulatory agencies should also consider supporting clinical trials in well-defined antibody-negative AE phenotypes like limbic encephalitis. The mandatory utilization of validated outcome measures like the mRS should be revisited in favor of measures that are more relevant to AE like CASE or cognitive testing batteries.

Conclusion:

Current RCTs in patients with AE face numerous challenges including the need to recruit ample numbers of patients with rare disease, suboptimal outcome measures, and the dilemma of lumping versus splitting the various serological and etiological subtypes. Many lessons are expected to be learned from these trials, paving the way for better studies in the future. Gaining insights into AE pathogenic mechanisms, comparing established and novel outcome measures, and identifying obstacles to recruitment and the best approaches to mitigate those obstacles, are a few of the learning opportunities that can be gained from these trials.

Acknowledgements:

None.

Funding:

The EXTINGUISH clinical trial is funded by the NIH/NINDS and free drug is provided by Horizon/Amgen. LEGIONE is funded by UCB. CIELO is funded by Hoffman LaRoche. The GENERATE-BOOST clinical trial is supported by the German Federal Ministry of Education and Research (CONNECT-GENERATE #01GM1908E to Dr. Geis). Dr. Irani's research is funded in whole or in part by a senior clinical fellowship from the Medical Research Council [MR/V007173/1], Wellcome Trust Fellowship [104079/Z/14/Z], the Fulbright UK-US commission (MS-Society research award) and by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). For the purpose of Open Access, the author has applied a CC BY public copyright license to any Author Accepted Manuscript (AAM) version arising from this submission. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Financial disclosures:

Dr. Abboud is a steering committee member of CIELO. He serves as a consultant and speaker for Biogen, Genentech, BMS, Horizon/Amgen, and Alexion. He has served as a consultant and/or advisory board member for Cycle pharma, Alpine Pharma, and Axonics. He received honoraria from *Neurology Live*. He receives research support from Genentech, BMS, Novartis, Sanofi-Genzyme, UCB, COREVITA, and the Guthy-Jackson Charitable Foundation. He has served as an Assistant Editor for the *Neurology* Journal and is on the editorial board. He receives royalties from *UpToDate*.

Dr. Clardy is the principal investigator of EXTINGUISH and has received research support from NIH / NINDS (U01, The ExTINGUISH Trial), the Western Institute for Veteran Research , the Siegel Rare Neuroimmune Association , the Immune Deficiency Foundation , Viela Bio/Horizon , Alexion/AstraZeneca , the Barbara Gural Steinmetz Foundation , Sumaira Foundation for NMO , she has served on consulting/Scientific Advisory Boards for Alexion, VielaBio/Horizon, Genentech/Roche, she is on the medical Advisory Board of the Sumaira Foundation for NMO (unpaid), she is also the Section Editor of Neurology Podcast and Neurology Minute and on the Editorial Board for Neurology: Neuroimmunology and Neuroinflammation.

Dr. Dubey is the principal investigator of LEGIONE and has been on clinical advisory boards for UCB, Argenx and Arialys. All compensation for consulting activities is paid directly to Mayo Clinic. He is a named inventor on filed patent that relates to KLHL11 as marker of autoimmunity and germ cell tumor. He has patents pending for LUZP4-IgG, cavin-4-IgG and SKOR2-IgG as markers of neurological autoimmunity. He has received funding from the DOD (CA210208 & PR220430), David J. Tomassoni ALS Research Grant Program and UCB.

Dr. Wickel is a steering committee member of GENERATE-BOOST and has received research support from Ionis Pharmaceuticals.

Dr. Day is a Project PI for the ExTINGUISH Trial, which receives support from NINDS (U01NS120901) and Amgen Pharmaceuticals. He also receives support from NIH/NIA (U01AG057195, U01NS120901, U19AG032438). He serves as a consultant for Arialys Therapeutics and Parabon Nanolabs Inc, and as a Topic Editor (Dementia) for DynaMed (EBSCO). He has developed educational materials for Continuing Education Inc and Ionis Pharmaceutical. He owns stock in ANI pharmaceuticals. Dr. Day's institution has received in-kind contributions for radiotracer precursors for tau-PET neuroimaging in studies of memory and aging (via Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly).

Dr. Geis is the principal investigator of GENERATE-BOOST and serves as a consultant and/or advisory board member and speaker for Alexion, Roche, Argenx and Sobi.

Dr. Gelfand chairs the trial steering committee for CIELO and receives research support to his institution from Hoffman LaRoche. He also receives research support to his institution from Vigil Neurosciences and personal compensation for consulting for Arialys and Ventyx Bio.

Dr. Irani is a steering committee member of LEGIONE and CIELO. He has received honoraria/research support from UCB, Immunovant, MedImmun, Roche, Janssen, Cerebral therapeutics, ADC therapeutics, BioHaven therapeutics, CSL Behring, and ONO Pharma

Dr. Lee is a steering committee member of CIELO, serves as an advisory board member for Argenx and Advanced Neural Technologies, and receives research support to his institution from Hoffman LaRoche and Celltrion.

Dr. Titulaer is co-principal investigator of the ExTINGUISH study. He is a steering committee member of LEGIONE. He has filed a patent, on behalf of the Erasmus MC, for methods for typing neurological disorders and cancer, and devices for use therein, and has received research funds for serving on a scientific advisory board of Horizon Therapeutics / Amgen and Argenx, for consultation at Guidepoint Global LLC, and for consultation at UCB. He has received an unrestricted research grant from Euroimmune AG, and from CSL Behring. He receives royalties from *UpToDate*.

Figure legends:

Figure-1: Potential triggers, predisposing factors, immunopathogenesis, and neuronal/anatomical targets in autoimmune encephalitis:

Autoimmune encephalitis can occur without a known trigger (idiopathic) or can be triggered by the presence of a neoplasm (paraneoplastic), following viral infections (post-viral), or following exposure to immunomodulating agents (iatrogenic). Potential predisposing factors include certain HLA subtypes in specific autoimmune encephalitis syndromes, proneness to autoimmunity, and pro-inflammatory body environment (e.g. smoking, head trauma, etc.). The abnormal immune response can activate pathogenic B cells that secrete pathogenic antibodies against neural surface antigens or non-pathogenic B cells that secrete antibodies against neural intracellular antigens. Cytotoxic T cells play a key role in autoimmune encephalitis associated with antibodies against intracellular antigens and likely in subtypes related to synaptic vesicle proteins (e.g., GAD65 antibody) as well as antibody-negative disease. Anatomical targets include the limbic system, cerebral cortex, basal ganglia, brainstem, and/or the cerebellum.

* Neural surface antibodies include NMDAR, LGI1, CASPR2, DPPX, AMPAR, GABAAR, GABABR, and IgLON5 antibodies.

** Neural intracellular antibodies include Hu, Yo, Ri, CRMP5, Ma/Ta, and KLH11 antibodies.

*** Antibodies against synaptic vesicle proteins include GAD65 antibody.

Figure-2: Immunopathogenesis and therapeutic agents for autoimmune encephalitis:

An environmental trigger (viral infection, neoplasm, medication, or unknown trigger) initiates the immune response. An antigen-presenting cell activates T cells, which activate CD19+ CD20+ B cells. With the aid of interleukin 6, activated B cells mature into antibody-producing plasmablasts (some of which are CD19+). Pathogenic neuronal antibodies against surface antigens are released in the circulation and/ or intrathecally. FcRn receptors in endothelial cells support IgG recycling and decrease its intracellular degradation. Pathogenic antibodies and/or pathogenic B cells cross the blood-brain barrier and promote an inflammatory response in the brain comprised of perivascular and parenchymal T cell infiltrate, activated microglia, and inflammatory cytokines. Pathogenic antibodies interact with their neuronal surface antigen targets leading to their blockade, internalization, or disruption of the cell membrane (depending on the specific antibody). Standard therapies for autoimmune encephalitis include immunosuppressants that suppress multiple immune cells particularly T cells (e.g. corticosteroids, mycophenolate, cyclophosphamide), anti-CD20 agents (rituximab), and interventions that remove pathogenic antibodies from the circulation (IVIg and plasmapheresis). Investigational therapies actively being tested in clinical trials include anti-CD19 agents (inebilizumab), interleukin 6 receptor blockers (satralizumab), proteasome inhibitors that promote apoptosis of plasma cells (bortezomib), and FcRn inhibitors (rozanolixizumab).

Figure-3: Schematic designs of autoimmune encephalitis clinical trials:

IV: intravenous, IVIg: intravenous immunoglobulins, CSF: cerebrospinal fluid, mRS: modified Rankin scale, LGI1: Leucine-rich glioma inactivated 1, IVMP: intravenous methylprednisolone, SFU: safety follow up, EOS: exit of study, NMDAR: N-methyl-D-aspartate receptor, AIE: autoimmune encephalitis, DB: double blind, IST: immunosuppressive therapy

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Table-1: Clinical trials in autoimmune encephalitis:

	EXTINGUISH NCT04372615	**LEGIONE NCT04875975**	**CIELO NCT05503264**	**GENERATE-BOOST NCT03993262**
Design	Phase-2b randomized double-blind placebo-controlled	Phase-2 randomized double-blind placebo-controlled	Phase-3 randomized double-blind placebo-controlled, basket	Phase-2 randomized double-blind placebo-controlled
Intervention	Inebilizumab	Rozanolixizumab	Satralizumab	Bortezomib
MOA	Anti-CD19	Anti-neonatal Fc receptor: reduction of IgG	Anti-IL6 receptor	Proteasome inhibitor, depletes plasma cells

*MOA: mechanism of action, CD19: cluster of differentiation 19, Fc: fragment crystallizable, IgG: immunoglobulin G, IL6: interleukin 6, NMDAR: N-methyl-D-aspartate receptor, AE: autoimmune encephalitis, LGI1: Leucine-rich glioma inactivated 1, mRS: modified Rankin scale, CASE: clinical assessment scale for autoimmune encephalitis, GCS: Glasgow coma scale, MMSE: mini mental state examination, MoCA: Montreal cognitive assessment. * mRS change is penalized for the use of rescue therapy.*

Table-2: Challenges, current mitigation strategies, and future directions for autoimmune encephalitis clinical trials:

Challenges	Current mitigation strategies	Suggested future directions
Low enrollment:	- Multicenter study design (ExTINGUISH, LEGIONE, CIELO, GENERATE-BOOST). - International study sites (ExTINGUISH, LEGIONE, CIELO). - Allowing adolescent patients (ExTINGUISH, CIELO). - Allowing probable NMDAR-antibody encephalitis patients in areas without reliable antibody testing capability (CIELO).	- Allowing enrollment of pediatric AE patients below the age of 12. - Expanding neuronal antibody testing in underserved areas. - Identification of potential trial candidates at neuroimmunology labs. - Regional centralization of recruitment with preplanned strategies for regional case referrals. - Involvement of centers and organizations with infectious encephalitis initiatives and programs (e.g., the WHO). - Inclusion of chronic symptomatic AE patients in therapeutic and/or rehabilitative

NMDAR: N-methyl-D-aspartate receptor, WHO: world health organization, AE: autoimmune encephalitis,IVIg: intravenous immunoglobulins, mRS: modified Rankin scale, CASE: clinical assessment scale for autoimmune encephalitis