AN EARLY PHASE OPEN-LABEL TRIAL OF A NOVEL TARP INHIBITOR

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**Objectives** ES-481 is a novel AMPA-Transmembrane AMPA regulatory protein (TARP) inhibitor that specifically targets hippocampal excitatory glutamate transmutation by disrupting protein-protein interactions between the AMPA receptor and the γ-8 TARP. Preclinical data predicts that ES-481 has broad spectrum anti-seizure effects. ES-481-C201 is a Phase 2A trial in four Australian Epilepsy Clinical Trial Network (AECTN) centres assessing efficacy, safety and pharmacokinetics in adult patients with drug resistant epilepsy. It has two phases: Double-Blind Treatment (DBT) and Open-Label Extension (OLE). Here we report the early experience from the OLE.

**Methods** Subjects completing the DBT Phase are offered enrolment in the OLE. OLE subjects are assessed at regular intervals for anti-seizure efficacy and safety. Anti-seizure efficacy is assessed by examining mean difference in seizure frequency in the OLE to baseline in the DBT Phase. Safety is assessed by monitoring AEs and changes in blood parameters. To continue in OLE, subjects have to demonstrate continued efficacy, tolerability and safety measures.

**Results** To date, eight subjects have completed the DBT Phase and enrolled in the OLE. One subject dropped out due to a non-treatment AE, and one withdrew consent. The six remaining subjects have shown clinically significant decreases in seizure activity, good tolerability, and no adverse safety signals after 3 to 9 months.

**Conclusions** The data to date from the OLE Phase indicates that ES-481 is well tolerated and potentially efficacious in controlling seizures in adult subjects with drug resistant epilepsy. Confirmation of this experience is awaited from the results of the DBT Phase.

ZEBRAS, NOT HORSES: AN ATYPICAL CASE OF NEUROSARCOIDOSIS

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**Objectives** Sarcoïdosis isolated to peripheral nerves and/or muscles is rare. 1,2 Clinical suspicion typically occurs when there are other systemic manifestations present. This case is an example of neurosarcoidosis presenting similarly to Guillain-Barre Syndrome. It also emphasises the significant impact nerve and muscle biopsies can have on diagnosis and management.

**Case** A previously well 64-year-old male presented with a severe symmetric, ascending weakness and numbness of all limbs with associated areflexia progressing over two weeks and culminating in an inability to walk. His presentation was of a severe subacute onset polyneuropathy and Guillaine-Barre syndrome was therefore suspected. Tests for autoimmune, infectious, malignant, and nutritional causes were negative. Cerebrospinal fluid showed a protein level of 2100 mg/L, white cell count of 45 x10^6/L, 99% of which were mononuclear. MRI of the brain and spine showed no nerve root enhancement or other relevant abnormality. Nerve conduction studies and electromyography demonstrated a severe axonal polyneuropathy with active denervation. The patient continued to deteriorate despite two courses of intravenous immunoglobulin and a sural nerve and vastus lateralis muscle biopsy was performed.

**Methods** Adults with newly diagnosed epilepsy between 1999–2016 were linked with state-wide databases to extract hospital admission, ambulatory psychiatric care, and mortality data from 1970–2019. Data were compared between patients receiving immediate, delayed and no treatment at up to 10 years post-diagnosis, adjusted for seizure type, age at onset, baseline comorbidity and others.

**Result** Of 603 patients (61% male; median age 40 years) with newly diagnosed epilepsy, 422 (70%) were treated immediately, 110 (18%) received delayed treatment, and 71 (12%) were untreated at the end of follow-up (median 6.8 years). Patients immediately treated had higher proportions of epileptogenic lesions on neuroimaging, seizure clusters and more pre-diagnostic seizures.

Immediately treated patients had a higher ten-year rate of all-cause admissions or emergency department presentations than the untreated (incidence rate ratio [IRR]=2.0; 95% confidence interval [CI]:1.4–2.9) and delayed treatment groups (IRR=1.7; 95%CI:1.0–2.8).

However, mortality was similar when immediate treatment was compared with delayed (hazard ratio [HR]=0.99; 95%CI:0.56–1.76) or no treatment (HR=1.31; 95% CI:0.55–3.10). Immediately treated patients also had similar ten-year risk of developing new physical and psychiatric comorbidities compared with the delayed (p=0.68; p=0.18, respectively) and untreated groups (p=0.69; p=0.28, respectively).

**Conclusions** Newly diagnosed epilepsy patients with deferred or no treatment did not have worse outcomes, compared to those immediately treated. Instead, patients treated immediately had greater healthcare utilisation, which may reflect more severe underlying epilepsy.