The Epilepsy Pipeline

Are better pharmacologic options in the future?

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In any disorder, the pipeline is the lifeblood of patients’ and physicians’ hopes for more promising care and better results. And epilepsy’s pipeline has several drugs worth keeping an eye on.

INS001 (Insero Health). In May, a Phase Ib trial of the compound INS001 showed the drug appeared safe and well tolerated. INS001 is a naturally occurring compound that has shown promising activity in multiple preclinical epilepsy models, according to the company. Insero believes that INS001 exerts its anti-epileptic effects through a unique combination of mechanisms: it is both a potent acetylcholinesterase inhibitor and an NMDA-receptor antagonist. The compound has previously demonstrated good safety and signs of therapeutic activity in a Phase II trial in Alzheimer’s disease, as well as in preclinical models of multiple sclerosis and neuropathic pain. The Phase I single-center, inpatient, open-label, rapid dose escalation study in patients with drug-resistant epilepsy showed INS001 was safe and well tolerated at doses expected to be therapeutic. The company expects to begin a Phase II proof of principle trial in patients with drug-resistant epilepsy by early 2014.

Eslicarbazepine acetate. One drug that is much further along, comparatively, and has been bandied about the past few years is Eslicarbazepine acetate. ESL is a prodrug of eslicarbazepine ([S]-licarbazepine), a third-generation drug in the carbamazepine group and the active metabolite of oxcarbazepine. Currently, it is in a Phase IV study with an estimated end date in late 2013. The study will investigate the safety and efficacy of eslicarbazepine acetate as adjunctive therapy for partial seizures in elderly patients.

Study results appeared in Epilepsy Research (103(2-3):262-9). Patients received a starting dose of 800mg once daily for four weeks. The dose could then be individualized within the 400-1,200mg range. Compared to the baseline period of the double-blind study completed prior to this open-label extension study, “median seizure frequency decreased by 32 percent in weeks 1-4, and between 37 percent and 39 percent thereafter. The responder rate (seizure reduction ≥ 50 percent) was 37 percent during weeks 1-4 and thereafter ranged between 38 percent and 42 percent per 12-week interval.” The proportion of seizure-free patients per 12-week interval ranged between five percent and 11 percent and “improvements from baseline in several Quality of Life in Epilepsy Inventory-31 (QOLIE-31) and Montgomery Asberg Depression Rating Scale (MADRS) scores were observed.” Adverse events were reported by 83 percent of the 223 patients who completed the study. AEs occurring in ≥10 percent of patients were dizziness, headache and somnolence. The authors noted AEs were usually of mild to moderate intensity.

Brivaracetam (UCB). Brivaracetam is chemically related to levetiracetam (Keppra). Its binding affinity for the synaptic vesicle protein 2A (SV2A) is 10-fold higher than that of levetiracetam and it shows an ability to inhibit sodium channels. (Neurotherapeutics 4(1):84-87) Efficacy has been established in the Phase IIb/III studies. Brivaracetam is well tolerated, the company notes, with a drop-out rate similar to placebo and a favorable CNS tolerability profile across doses and without titration.

The Phase III study is evaluating brivaracetam as adjunctive therapy for partial onset seizures in adults with epilepsy. It is a randomized, double-blind, placebo-controlled, multicenter, parallel-group study with more than 700 patients to evaluate the efficacy and safety of brivaracetam 100mg/day and 200mg/day on seizure frequency. The “headline results” are expected in the second half of 2014. UCB has previously applied for and received orphan drug designation status for brivaracetam in Europe in August of 2005, and in the US in November of 2005.

USL261 (Upsher-Smith). USL261 (midazolam) is a benzodiazepine in an investigational formulation that is delivered intranasally. It is intended to be administered by a caregiver in an outpatient setting for the rescue treatment of seizure clusters without active inhalation by the patient. Phase I data demonstrate that maximum midazolam plasma concentrations were rapidly achieved after dosing with USL261. Additionally, both midazolam and its metabolite were rapidly eliminated. Single doses up to 7.5mg were generally well-tolerated with no significant adverse events. USL261 is also the subject of the ongoing, global Phase III ARTEMIS1 study.