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SGE-102: A novel therapy for refractory status epilepticus

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Summary

Refractory status epilepticus (SE) has a mortality rate of up to 35%. Current treatment protocols for the treatment of SE begin with benzodiazepines and then proceed to conventional anticonvulsants. If seizures continue, SE is considered refractory (RSE) and treatment with anesthetic agents in undertaken. Twenty-four h to 48 h after initiation of anesthesia with midazolam, pentobarbital or thiopental, or propofol, an attempt is made to wean the anesthetic. If this fails and seizures recur, SE is considered highly refractory (HRSE) and repeated attempts are undertaken. No randomized trial data are available to guide the choice of anesthetic agent in either RSE or HRSE status. Medication resistance in established SE is thought to result, in part, from internalization of synaptic γ-aminobutyric acid (GABA) receptors, making them unavailable for modulation. Neurosteroids act on both synaptic and extrasynaptic $GABA_A$ receptors, which are not internalized, and are therefore hypothesized to have a role in the treatment of RSE. SGE-102 is a neurosteroid metabolite of progesterone with demonstrated anticonvulsant properties in animal seizure models. A randomized double-blind placebo-controlled adjunctive trial of SGE will include subjects randomized at the time that initial treatment with anesthesia is initiated. Subjects will receive midazolam and either SGE-102 or placebo. Midazolam will be tapered and discontinued between hours 24 and 48. SGE-102 or placebo will be continued through hour 120. The primary end point will be the difference in proportion of subjects from each arm who remain seizure free through hour 120. Secondary end points will include the proportion of subjects who are seizure free at hour 168, 2 days after discontinuation of the experimental agent. The study will be powered to have a 90% chance of detecting a clinically meaningful reduction in seizure recurrence at 120 h. Comprehensive safety and pharmacokinetic data will also be obtained during the course of the trial.

KEY WORDS: Clinical trial, Neurosteroid, Anticonvulsant, Randomized, Phase II.

Status epilepticus (SE) is acknowledged as a neurologic emergency with significant morbidity and mortality; the prognosis of the subgroup of patients who are refractory to first- and second-line therapies is particularly grim. The mortality rate among such patients is estimated to be about 35% and, at least one third of the patients who recover, do so with significant neurologic morbidity (Claassen et al., 2002; Shorvon & Ferlisi, 2011; Hocker et al., 2013; Sutter et al., 2013).

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There is, therefore, a dire need for more effective treatment for patients in "refractory" SE (RSE). There are established therapies for "early" status epilepticus (benzodiazepines) and for "established" SE (fos-phenytoin, valproic acid, and so on) that have been approved for marketing by regulatory agencies in several countries. There are, however, no approved treatments for patients in RSE. The commonly used medications for patients whose seizures have been refractory to first- and second-line agents include midazolam, propofol, and pentobarbital; however, all of these medications are used "off-label" and none of them has proven efficacy in SE. The use of these agents to treat patients in RSE has been the subject of several retrospective reviews (Lowenstein & Alldredge, 1993; Mayer et al., 2002; Holtkamp et al., 2005; Rossetti et al., 2005). One attempt at a prospective, randomized, double-blind

trial aimed at evaluating the comparative efficacy and side effect profile of two of these agents failed because of inadequate enrollment (Rossetti et al., 2011).

SGE-102 for the Treatment of Refractory Status Epilepticus

To address the need for a proven treatment for RSE, a novel compound, SGE-102, based on allopregnanolone is being developed. Allopregnanolone, a neurosteroid, allosterically modulates both synaptic and extrasynaptic $GABA_A$ receptors. As seizures become prolonged benzodiazepine-sensitive $GABA_A$ receptors, which are only present in synapses, become internalized and functionally inactive (Naylor et al., 2005). Extrasynaptic receptors are not internalized as seizures continue and therefore are a target through which allopregnanolone might treat SE, even when benzodiazepines have become ineffective (Reddy & Rogawski, 2012).

Allopregnanolone has been shown to be effective in preclinical models of seizures and status epilepticus. This includes the enhancement of GABA-evoked chloride currents in cultured hippocampal neurons (Kokate et al., 1994), the protection against pilocarpine- or kainate-induced limbic seizures and SE, with higher protective index values than clonazepam (Kokate et al., 1996), protection against bicuculline- or picrotoxin-induced seizures (Belelli et al., 1989), the lack of tolerance to pentylenetetrazol (PTZ)–induced seizures in mice (Kokate et al., 1998), and a complete suppression of generalized amygdala-kindled convulsions (Lonsdale & Burnham, 2007). A rat model of SE induced by kainate has shown that allopregnanolone (30 mg/kg, i.p.) eliminated SE whether administered at 10 min or at 70 min following chemoconvulsant administration, whereas diazepam (50 mg/kg, i.p.) was only effective at 10 min (Lossin, 2012).

Phase 2 Clinical Trial of SGE-102 for RSE

In that there has never been a successfully completed clinical study to prove the efficacy of a therapy for RSE, a novel trial design is presented. The design is a double-blind, placebo-controlled, add-on trial in adult patients in RSE for <24 h, that is, those patients who have failed to respond to first- and second-line treatments and are being considered for drug-induced suppression of seizure activity/coma. In this trial, at the point when the physician decides to induce suppression of seizure activity and clinical coma in a patient who has not responded to first- and second-line medications, the patient will be assigned in a randomized fashion, to SGE-102 + midazolam intravenous (IV) *or* placebo + midazolam IV. This study will be performed only in selected centers where continuous EEG (cEEG) can be performed and at which there is experience in treating RSE. Except for the treatment with study drug (placebo or SGE-102) + midazolam IV, all subjects will receive the standard of care, as per the center's protocol, for adults in RSE. All patients will be intubated.

After starting treatment with midazolam + study drug for 24 h, the patient will be progressively weaned off midazolam over hours 25–48. The patient will remain on study drug for 72 additional hours (through 120 h), unless rescue medication is required. If no rescue medication is required and the patent remains seizure free, the study drug will be tapered and discontinued over 24 h. If while on midazolam, hypotension (systolic blood pressure [BP] <90 mm Hg) occurs, the midazolam infusion will be suspended or reduced by half and the patient will be treated clinically as appropriate (e.g., vasopressors). If seizure activity resumes at any time during or after the weaning of midazolam, the patient will be treated as medically appropriate in view of the investigator (including possibly restarting the midazolam IV at the same dose as before, or administration of another general anesthetic).

The primary end point will be the proportion of treated patients with no clinical or electrographic seizures lasting >1 min from 60 min after loading dose of SGE-102 until treatment cessation (days 1–5). Secondary end points will include the proportion of patients with no clinical or electrographic seizures lasting >2 min for 2 days after cessation of SGE-102 treatment (days 6–7), and the functional outcome at 1 month posttreatment. Safety data will be summarized using descriptive statistics.

Safety will be addressed through an assessment of the incidence and severity of treatment emergent adverse events and clinically important changes in safety assessments (including vital signs, clinical laboratory tests, electrocardiographic monitoring, electroencephalographic monitoring, and physical and neurologic examinations). All patients will be in neurologic intensive care units where constant monitoring for adverse events will take place.

A preliminary power calculation to determine sample size was derived according to data from retrospective and observation studies on the success rate of midazolam IV in treating RSE. The studies used to derive this efficacy assumption used efficacy end points similar to the ones that will be used in his protocol. The sample size will be derived to have 90% power to show a difference between the SGE-102 group and the placebo group with an alpha level of 0.05.

Disclosures

Dr. Reddy is an employee of Sage Therapeutics and Third Rock Ventures. Dr. Reife is an employee of Sage Therapeutics. Dr. Cole is a consultant to Sage Therapeutics. He has served as a consultant to Eisai Pharmaceuticals, Impax Pharmaceuticals, Upsher-Smith Pharmaceuticals, and Neuropace, Inc. He has received funding for conducting clinical trials sponsored by Suovion and Neuropace.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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