TRV045, a novel, selective SIP receptor subtype-1 modulator that does not cause lymphopenia is efficacious in acute and chronic rodent epilepsy models

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BACKGROUND

Epilepsy is caused by the aberrant synchronized firing of neurons resulting from the imbalance in excitatory and inhibitory neurotransmission. The mainstream antiepileptic drugs (AEDs) are direct modulators of ion channels, but they are unable to control seizures in 30% of patients. There is a need to discover and develop AEDs with novel mechanisms.

SIP and its receptors, especially subtype 1 (S1PR1), play important roles in neuroinflammation, a process underlying seizures and epileptogenesis. S1PR receptor expression is increased in experimental post status epilepticus (SE) TLE mouse models. Fingolimod, a nonselective S1PR modulator but with high potency for S1PR1, has shown anti-epileptic effects in a diverse range of preclinical epileptic models, possibly through anti-inflammatory mechanisms as well as preservation of neuronal and blood brain barrier integrity. However, by design, existing S1PR modulators cause lymphopenia.

TRV045 is a highly selective S1PR1 modulator that has no effect on peripheral lymphocyte concentrations in nonclinical studies. Through collaboration with the NINDS Epilepsy Therapy Screening Program (ETSP) we previously showed that subcutaneous dosing of TRV045 reduced seizures in the corneal-kindled (CK) mouse model and the rat maximal electroshock seizure (MES) model, but other models were confounded by a vehicle effect. Here, a new vehicle (10% cremophor, 20% Captisol in water) was used for dosing in the mouse CK, rat MES, and rat post-kaolin acid spontaneous recurrent seizures (post-KA SRS) model of temporal lobe epilepsy.

Because astrogliosis plays an important role in epileptogenesis, we also examined the in vitro effect of TRV045 on inflammatory cytokines and chemokines in mouse astrocyte cultures. Additionally, the anti-inflammatory effects of TRV6589 (TRV045 analog) were measured in vivo in the spinal cords of paclitaxel-treated mice in a chemotherapy induced peripheral neuropathy (CIPN) model.

OBJECTIVE

Investigate the efficacy of a selective, non-immunosuppressant S1PR1 receptor modulator in rodent epilepsy models

METHODS

In the CK seizure model, male C57BL/6 mice were fully kindled to reach the criterion of 5 consecutive stage 5 seizures. Mice (n=8/gp) were dosed PO with 10 or 15 mg/kg TRV045 5-7 days after the last stimulation and tested 1 and 2 hr postdose to determine the time of peak effect (TPE). A full dose response was then performed with testing at the TPE (1 hr) to identify an ED50 dose.

In the post-KA SRS model, status epilepticus was induced in male SD rats with repeated low-dose kainate treatment. Following a 7-day baseline period, rats (n=6/gp) received intraperitoneal (i.p.) doses of TRV045 or vehicle for 5 days. Following a 2-day washout period, animals were crossed over to the opposing treatment arm for a second 5-day period. Seizure burden was calculated as the summation of all Racine scale seizures during treatment divided by the number of treatment days. Seizure freedom was based on an animal having zero seizures from the time of first dose through 12 hr post-final dose.

RESULTS

In the MES model, 60Hz of alternating 150 mA current was delivered to male Sprague Dawley (SD) rats for 0.2 seconds by corneal electrodes. Rats (n=8/gp) were dosed PO with 30 or 60 mg/kg TRV045 and tested for seizure activity 0.25 to 2 hr postdose to identify the TPE. An animal was considered “protected” from convulsive action upon abolition of the hindlimb tonic extensor component of the seizure. A full dose response was then performed with testing at the TPE (0.5 to 1 hr).

Primary astrocyes were isolated from P1-P2 mouse brains with trypsin digestion. The identity of astrocytes was confirmed with GFAP (Glial fibrillary acidic protein) staining. Confluent astrocyte monolayers were treated with 5 µM TRV045 and the culture media were collected after 26 hours for analysis by ELISA.

In the CIPN model, paclitaxel (6 mg/kg i.p.) was administered to C57BL/6 mice (n=4-6) on Days 1, 3, 5 and 7. Following confirmation of mechanical allodynia on Day 13, mice were dosed with TRV6589 (TRV045 analog) on Day 14 and spinal cords were harvested, homogenized and analyzed for IL-6 and IL-10 levels by Western blot.

CONCLUSIONS

- TRV045 reduced or prevented seizures in the CK mouse and rat MES models of acute epilepsy
- TRV045 reduced seizure burden and increased seizure freedom in the rat post-KA SRS model of chronic epilepsy, demonstrating anti-epileptogenic effects
- TRV045 inhibited proinflammatory cytokines while stimulating the release of anti-inflammatory cytokines in cultured mouse astrocytes

The TRV045 analog, TRV6589, reduced IL-6 levels and increased IL-10 levels in the spinal cords of paclitaxel-treated mice, providing evidence of in vivo anti-inflammatory effects

- Efficacy data from three nonclinical epilepsy models, in conjunction with evidence of an anti-inflammatory mechanism, suggest that selective modulation of S1PR1 receptors by TRV045 may provide a new therapeutic option for the treatment of epilepsy

REFERENCES

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