TRV045, a novel, selective S1PR receptor modulator is efficacious in acute, chronic and prevention modes in mouse models of chronic neuropathy, without causing lymphopenia

Ruihua Chen, PhD1, Mark A. Demitrack, MD1, Torin Honaker3, Matthew Harding, PhD2, Dana E. Selley, PhD3, and M. Imad Damaj, PhD3,4
1Trevena, Inc., Chesterbrook, PA; 2Pharmacology Consultant, Meredith, NH; 3Dept of Pharmacology and Toxicology, 4Translational Research Initiative for Pain and Neuropathy, Virginia Commonwealth University, Richmond, VA

BACKGROUND
Chemotherapy-induced peripheral neuropathy (CIPN) occurs in up to 70% of oncology patients undergoing chemotherapy. There is an unmet need for prophylactic and symptomatic treatment of CIPN. Previous studies have suggested a beneficial role for non-selective sphingosine-1-phosphate receptor (S1PR) modulators in treating neuropathic pain. However, at doses which produce analgesia, these compounds also affect lymphocyte trafficking, resulting in profound reductions in circulating peripheral lymphocytes. This limits their utility for use in clinical conditions, like CIPN, where immunosuppression would not be desirable.

OBJECTIVE
Evaluate TRV045, a selective S1PR subtype-1 specific modulator that does not cause lymphopenia, following single or repeat oral dosing in a mouse model of CIPN induced by paclitaxel.

METHODS

CIPN Test Model: Paclitaxel (8 mg/kg) or vehicle was administered intraperitoneally (i.p.) once per day on Days 1, 3, 5 and 7. Baseline behaviors were measured on Day 0 and 14. The complete testing methods are described briefly here, the full methods are available elsewhere (Caillaud, 2021).

Mechanical withdrawal thresholds were measured by applying von Frey filaments in incremental force from 0.07 grams to 3.6 grams to the plantar surface of each hind paw with the intent to elicit an appropriate response (paw withdrawn, licking or shaking). Stimulation of the same filament was applied 3x at 10 second intervals. The results are presented as the average of the data from both paws. Cold hypersensitivity was assessed via acetone test. 20 µL of acetone (Sigma-Aldrich, MO, USA) was applied onto the plantar surface of each hind paw via pipette. Time spent licking or shaking the hind paw was recorded for 10 seconds. Voluntary wheel running was done by placing mice in polycarbonate wheels (diameter 21.5 cm; width 6 cm) with a steel rod axle containing an electronic sensor recording the number of rotations each 60-minutes. Data are expressed as the number of rotations completed (Figure 5).

Acute Reversal of CIPN Nociception: (Figure 1) Following acquisition of CIPN, on day 15, mice were received TRV-045 at different doses (0.1, 0.3, 3 and 10 mg/kg) or its vehicle (10% DMAC + 10% Cremophor EL + 80% in water) via oral gavage (p.o.). Mice were tested for mechanical and cold hypersensitivity. (Figures 2A and 2B) Following acquisition of CIPN, TRV-045, on day 15, male mice received FTY-720 at 1 mg/kg, TRV-045 at different doses (0.1, 0.3, 3 and 10 mg/kg) or its vehicle (10% DMAC + 10% Cremophor EL + 80% [10% HPBCD in water]) via oral gavage (p.o.). Mice were tested for mechanical and cold hypersensitivity at 1, 3 and 6 hr after the drug administration. Female mice study design same as male except without the acetone test and cold stimulus-evoked nociception in a dose-related manner in a mouse model of CIPN

Chronic Reversal of CIPN Nociception: (Figure 3) Following acquisition of CIPN, on day 15, mice received TRV045 at different doses (1, 3 and 10 mg/kg) or its vehicle (p.o.) repeatedly for 7 days (once per day at 8:00 am). Mice were retested on days 21 (at 1, 3, 6 and 24 hr after the last administration (half of the animals were tested at 24 hr) and 28. In addition, on day 21, mice were tested in the voluntary wheel running assay 6 hr after the last administration of drugs.

CIPN Prevention: (Figure 4) Paclitaxel (8 mg/kg) or vehicle were administered intraperitoneally (i.p.) once per day on days 3, 5, 7 and 9. Baseline behaviors were measured on day 10. Mice received TRV045 at different doses (0.3, 1, 3, 10 and 100 mg/kg) or its vehicle daily from day 1 through day 14. Mice were tested for mechanical and cold hypersensitivity on day 15 (24 hr after last dose) and day 22 (168 hr after last dose). Mice were also tested in the voluntary wheel running assay after the hypersensitivity test on day 15.

RESULTS

All data are expressed as mean ± SEM (Standard Error of the Mean). Normality and equal variance were verified by Shapiro-Wilk or Brown-Forsythe tests. Mechanical and cold data were compared using 2-way analysis of variance (ANOVA) with repeated measures, followed by post-hoc Tukey’s comparison. Wheel running data were analyzed using a 1-way ANOVA followed by post-hoc Dunnett comparison. Analyses were performed with GraphPad (GraphPad Software 9.3, Inc., La Jolla, CA, USA). Significance was assumed at P <0.05.

CONCLUSIONS

- Oral administration of TRV045 reduced mechanical and cold stimulus-evoked nociception in a dose-related manner in a mouse model of CIPN
- These effects were demonstrated in single-dose acute reversal and were sustained following repeated administration of TRV045 for 14 days; effects were evident at doses of 3mg/kg and 10mg/kg
- In a prevention mode paradigm examining the potential effect of TRV045 to prevent the development of CIPN, TRV045 administered at 100mg/kg reduced both mechanical and cold hypersensitivity 24 hours following the last dose; the reduction in cold hypersensitivity was present at 168 hours after the last dose of TRV045

REFERENCES

Disclosure: TRV045 is an investigational new drug that has not been approved by the FDA.