Multicenter Stroke Preclinical Assessment Network (SPAN) analysis of cardiovascular risk factor subgroups treated with the poly(ADP-ribose) polymerase inhibitor (PARP) veliparib

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Introduction

- In the first round of the Stroke Preclinical Assessment Network (SPAN 1), 6 interventions were tested in a multi-site, multi-arm adaptive trial of transient MCAO in young mice (3 months-old), aging mice (15-17-months old), obese, hyperglycemic mice fed a high-fat diet, and spontaneously hypertensive rats (SHRs).
- One of the drugs was a PARP inhibitor, veliparib. After an interim analysis, it was declared futile based on the primary outcome (turning preference on the corner test at 30 days) with data pooled from all 4 animal models. It did not proceed to the end of the trial.

Objective

Assess primary and secondary outcomes (corner test at 7 and 30 days, foot-faults on a grid walk test at 7 and 30 days, MRI-determined lesion volume at 2 days and atrophy at 30 days) in the individual 4 subgroup models.

Rationale for selecting veliparib

- 24 publications from 13 laboratories supported a benefit of first and second generation PARP inhibitors on infarct volume and, in some cases, neurobehavior outcomes, in young male mice and in young male and female rats (although not in young female mice) (Koehler et al. Front Neurol. 2021 May 5;12:662034. doi: 10.3389/fneur.2021.662034).
- A requirement of SPAN 1 was to test agents that have a safety record in humans and had a strong rationale for repurposing for use in stroke.
- Veliparib is a third generation PARP inhibitor that had been shown to be safe in human oncology trials.

Statistical analysis

- Treatment effects were estimated using probabilistic index models (PIMs), which compares the probability that a random animal from the veliparib group has a better outcome than a random animal from the placebo group and is based on the data distribution.
- Data are presented as violin plots with box plots of medians and interquartile range without imputation.

Methods

- A Coordinating Center randomized enrolled animals to 5 drug treatments and a common placebo group across 6 lab sites.
- Secondary analysis of veliparib results was based on 344 animals receiving placebo and 231 animals receiving 1 mg/kg veliparib IV at reperfusion after 1 h MCAO with the filament technique (90-100 animals per site balanced by sex).

Corner Test in Pooled Subgroup Models
Modified corner test index = absolute value |(left – right turns)/(left + right turns)| after right-sided MCAO.

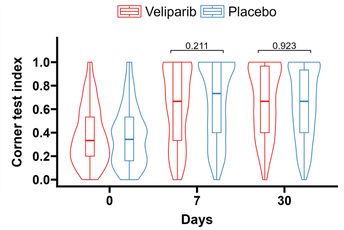

Figure 1. In data pooled from the 4 subgroup models, turning preference on the corner test increased from baseline at 7 and 30 days but was not different between veliparib and placebo groups.

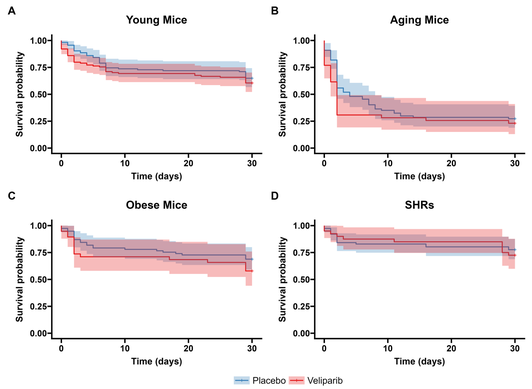

Figure 2. Kaplan-Meier survival curves did not show a difference between placebo and veliparib treatment in any subgroup (shaded areas are 95% CI). Compared to young mice, survival was lower in aging mice and higher in SHRs. Part of mortality at 2 and 30 days was attributable to respiratory arrest during isoflurane anesthesia for MRI.

Corner Test in Individual Subgroup Models

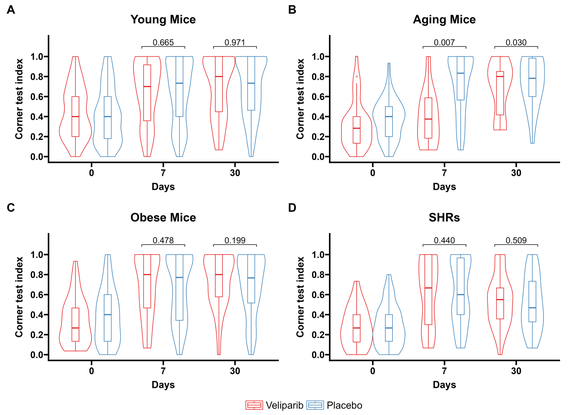

Figure 3. In corner test analysis of subgroup models, turning preference was significantly improved at 7 days (P = 0.007) and 30 days (P = 0.030) in aging mice with veliparib treatment. Differences remained significant with worse-case imputation for animal attrition (not shown). There was no significant interaction with sex in aging mice.

Infarct Volume at 2 Days

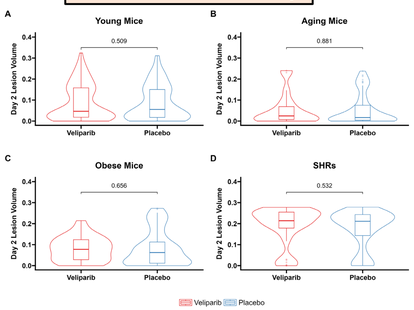

Figure 4. MRI measurements of lesion volume (fraction of combined hemisphere volume) at 2 days did not reveal a reduction with veliparib treatment in any subgroup model. A treatment effect also was not seen in hemisphere atrophy at 30 days (data not shown).

Foot-Faults in Individual Subgroup Models

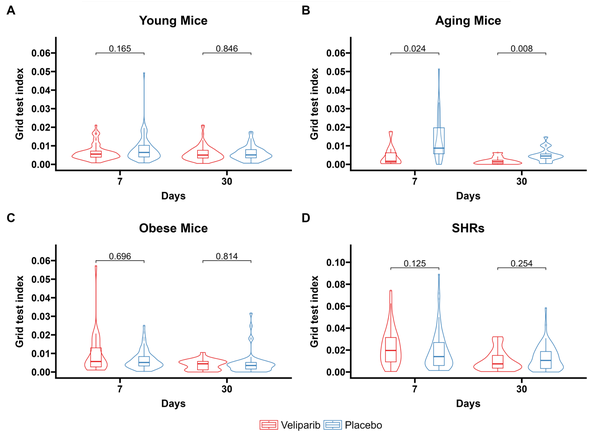

Figure 5. In the grid walk test, contralateral foot faults were significantly reduced at 7 days (P = 0.024) and 30 days (P = 0.008) in aging mice with veliparib treatment. Differences remained significant with worst-case imputation for animal attrition. There was no significant interaction with sex in aging mice.

Conclusions

- This secondary analysis of the SPAN 1 trial revealed that veliparib improved performance on two sensorimotor tasks at 7 and 30 days recovery from transient MCAO in aging mice.
- This benefit was independent of sex.
- Because ischemic stroke predominantly occurs in the aging population, further research into the benefit of PARP inhibitors in aged animal models of stroke is warranted.
- Because aging mice appear to be more prone to respiratory arrest during isoflurane anesthesia after ischemic stroke, it is recommended to avoid the use of gas inhalation anesthesia during the acute recovery period in MCAO studies in aging mice.

References for SPAN 1 Trial

- Lyden PD et al. Sci Transl Med. 2023 Sep 20;15(714):eadg8656. doi: 10.1126/scitranslmed.adg8656.
- Morais A et al. Circ Res. 2024 Aug 16;135(5):575-592. doi: 10.1161/CIRCRESAHA.123.324139.