The Bruton's Tyrosine Kinase Inhibitor Evobrutinib Ameliorates Meningeal Inflammation in Experimental Autoimmune Encephalomyelitis

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Disclosures

- Sol Kim has no disclosures to declare.
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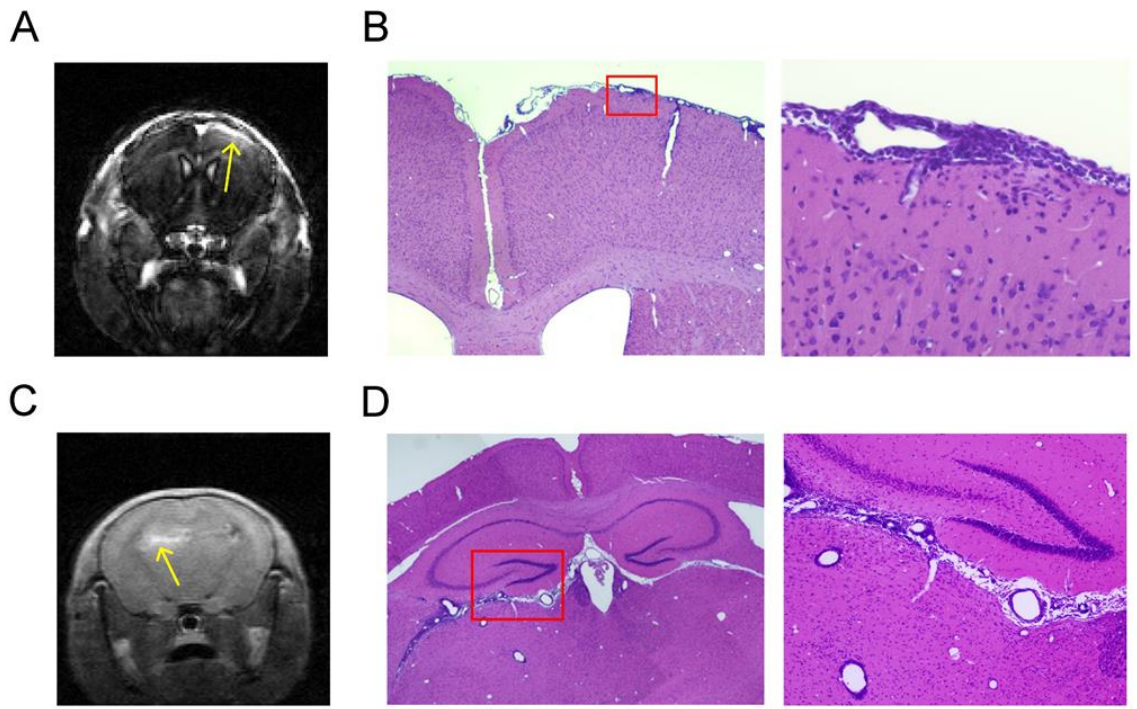
- Roland Grenningloh is an employee of EMD Serono, Billerica, MA, USA (a business of Merck KGaA, Darmstadt, Germany).
- Ursula Boschert is an employee of Ares Trading SA, Switzerland (an affiliate of Merck KGaA, Darmstadt, Germany).

BACKGROUND

- Leptomeningeal inflammation in MS is associated with worse clinical outcomes and greater cortical pathology
- Ultra-high field contrast-enhanced magnetic resonance imaging (MRI) can identify and track areas of meningeal contrast enhancement (A &C) that correspond to meningeal inflammation (B &D) in a relapsing-remitting EAE model
- B cells and myeloid cells are abundant in areas of meningeal inflammation in MS tissue and in EAE
- Bruton' Tyrosine Kinase (BTK) mediates activation of B cells via the B cell receptor. BTK also mediates activation and differentiation of myeloid cells via Fc receptor and GM-CSF receptor, respectively

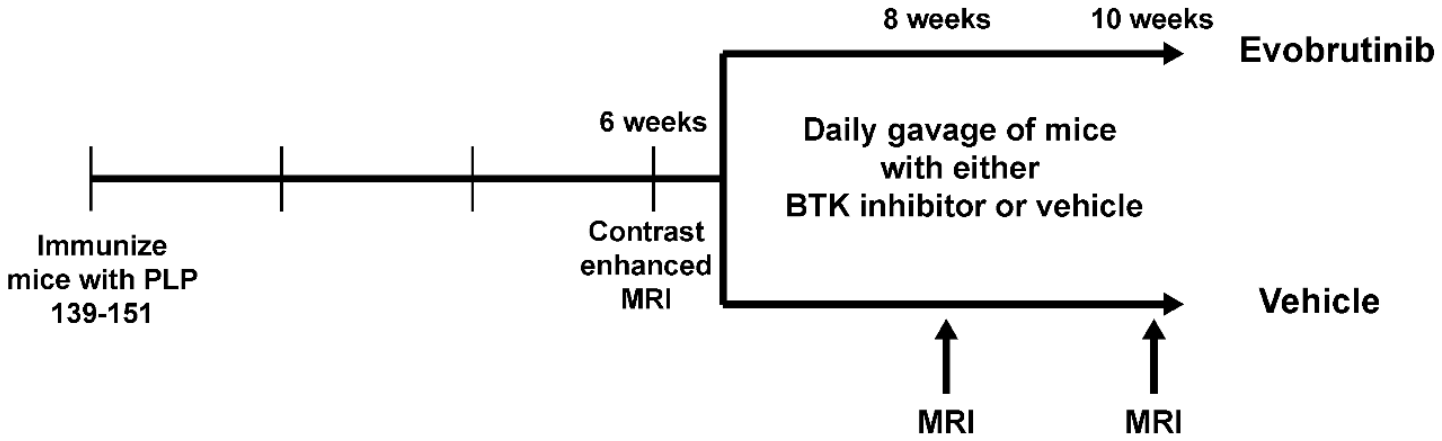


- Evobrutinib, a highly-selective BTK inhibitor, has been shown to reduce disease activity in a relapsing-remitting MS phase 2 clinical trial and in EAE

OBJECTIVE

To test the effect of evobrutinib as a potential therapy targeting meningeal inflammation in a mouse model of MS

METHODS



- EAE: 7-8 week-old female SJL/J mice immunized with $PLP_{139-151}$ and CFA
- Daily scoring and weighing starting 7 days post-immunization
- Gadolinium-enhanced MRI (11.7 Tesla) at week 6 post-immunization to identify the animals demonstrating meningeal contrast-enhancement
- Mice were randomized and received daily oral treatment of evobrutinib (10mg/kg) or vehicle for 4 weeks (week 6-10 post-immunization)

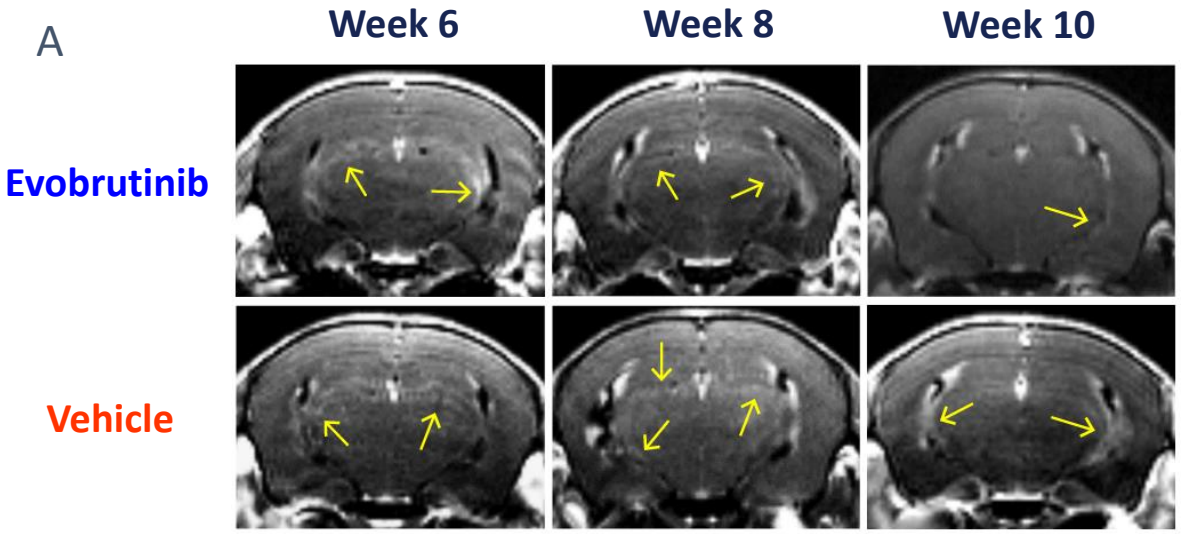
METHODS

- MRI was repeated at weeks 8 and 10 post-immunization
- Tissues collected for histopathological analysis following last imaging time-point and stained for immune and glial cell markers
- Images were analyzed by two blinded raters and the number of contrast enhancements on each slice were counted and summed – to provide a semi-quantitative assessment of volume of meningeal contrast enhancement
- We compared change in meningeal contrast enhancement between two groups using a mixed-effects model and compared pathological measures using a Mann-Whitney U test

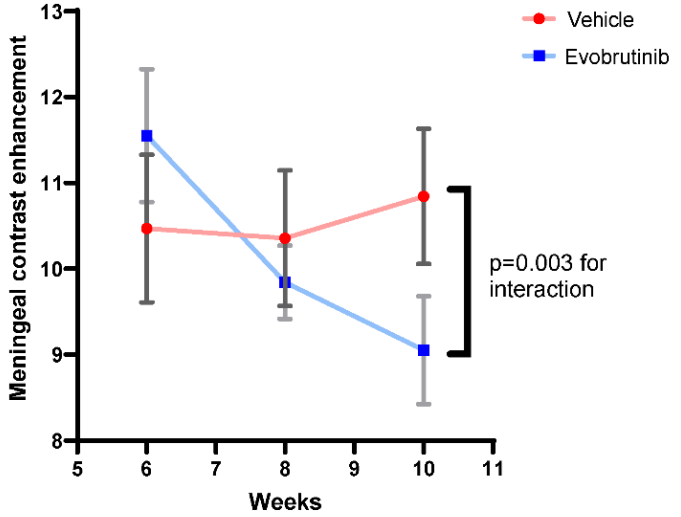
RESULTS

- Similar baseline (week 6) meningeal contrast enhancement noted in both vehicle and evobrutinib groups (median:10.5 vs 11, p=0.25)
- Reduction (median change: -3 vs 0.5, p=0.003) in meningeal contrast enhancement in evobrutinib group at the end of the treatment (week 10) (Panel B)

A



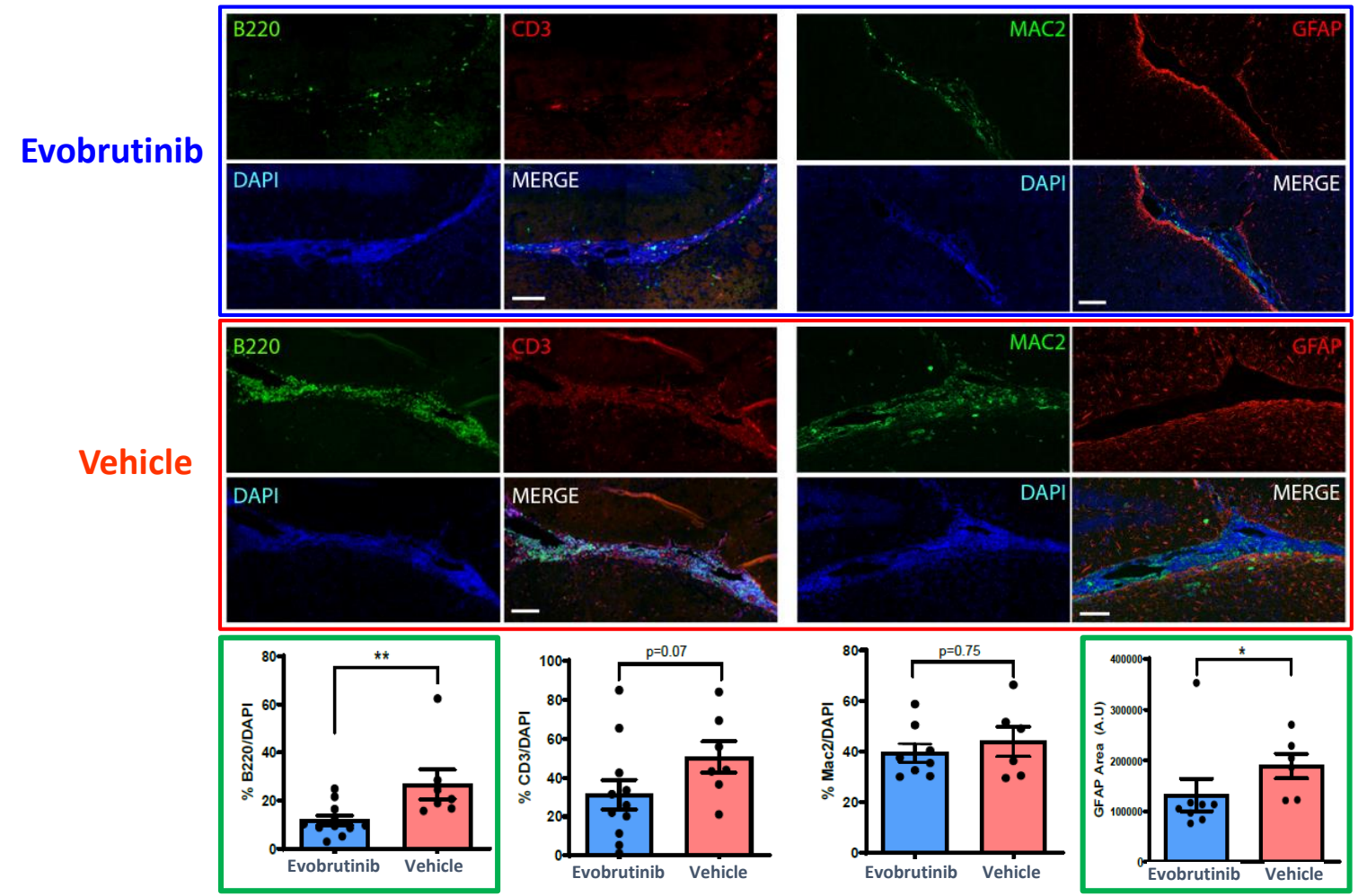
B



NVeh=16
NEvo=19

RESULTS

- Significant decrease in B-cell population (B220+) in areas of meningeal inflammation in evobrutinib vs vehicle group ($p<0.01$)
- No significant difference in T-cell or myeloid cell populations between groups
- Reduction in astrocytosis in the cortex adjacent to meningeal inflammation in the evobrutinib vs vehicle group ($p<0.05$)



CONCLUSIONS

- Evobrutinib ameliorated established meningeal inflammation assessed by high-field MRI imaging and histopathology in a relapsing-remitting EAE model

- This suggests potential utility of evobrutinib to target this pathological phenomenon in MS patients