747 Amelioration Of Mrgprb2-Mediated Anaphylactoid Drug Reactions With Briquilimab, An Anti-CD117 (c-Kit) Antibody, Through Mast Cell Depletion In Mice Expressing Chimeric Human/Mouse CD117

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Introduction and Methods:

- Stem Cell Factor (SCF) signaling through c-Kit (CD117) plays a key role in mast cell (MC) survival, and inhibition of this pathway has the potential to treat MC-related disorders.
- Briquilimab, a humanized aglycosylated monoclonal antibody targeting c-Kit, blocks SCF binding to c-Kit and SCF/c-Kit signaling leading to apoptosis of MCs.
- Novel mice expressing a chimeric CD117, consisting of human extracellular and murine intracellular regions of CD117 in place of wild-type mouse CD117, were generated and are referred to here as "h/mCD117 mice".
- MC depletion in various tissues was assessed after one-time administration of briquilimab IV in h/mCD117.
- Compound 48/80 (C48/80) is a mixed polymer that binds to Mrgprb2 in mice (Mrgprx2 in humans) and widely used for non-IgE dependent MC activation. h/mCD117 mice were administered briquilimab or untreated, and the severity of C48/80-induced anaphylactoid reactions was measured by serial body temperature monitoring and clinical scoring.

Results:

Figure 1. The SCF/c-Kit pathway is essential for mast cell function and survival. Drugs or ligands binding to MRGPRX2 on mast cells (MC) can induce MC degranulation and pseudo-allergic reactions. Blocking SCF/c-Kit signaling with briquilimab induces MC apoptosis and may provide protection from severe anaphylactoid reactions.

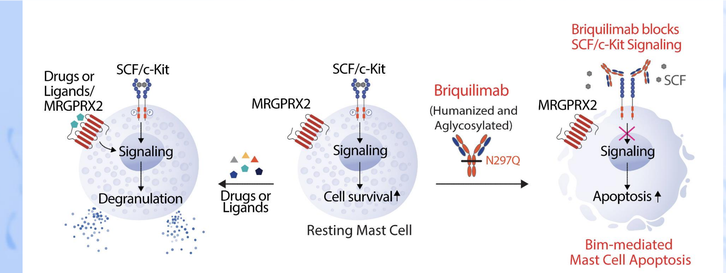


Figure 2. Briquilimab prevents IgE-independent Mrgprb2-mediated anaphylactoid reactions in h/mCD117 mouse model. (A) Experimental schema for evaluation of C48/80-induced anaphylactoid reactions. One-time briquilimab 25mg/kg IV was administered to h/mCD117 mice compared to briquilimab untreated controls. The core body temperature and clinical signs (Clinical Anaphylaxis Score) were monitored over time after 5 mg/kg C48/80 IV administration at the specified timepoints post-briquilimab. (B) While briquilimab untreated mice (red line) showed significant drops of core body temperature (hypothermia) in response to C48/80, briquilimab treated mice (blue line) were partially to completely protected from severe hypothermia at 2 and 3 weeks after briquilimab treatment. Protection from anaphylactoid reactions were not observed at 4 weeks post-briquilimab. Black line represent animals that received neither briquilimab nor C48/80, and only received isofluorane. (C) Clinical anaphylaxis scores correlated with severity of hypothermia.

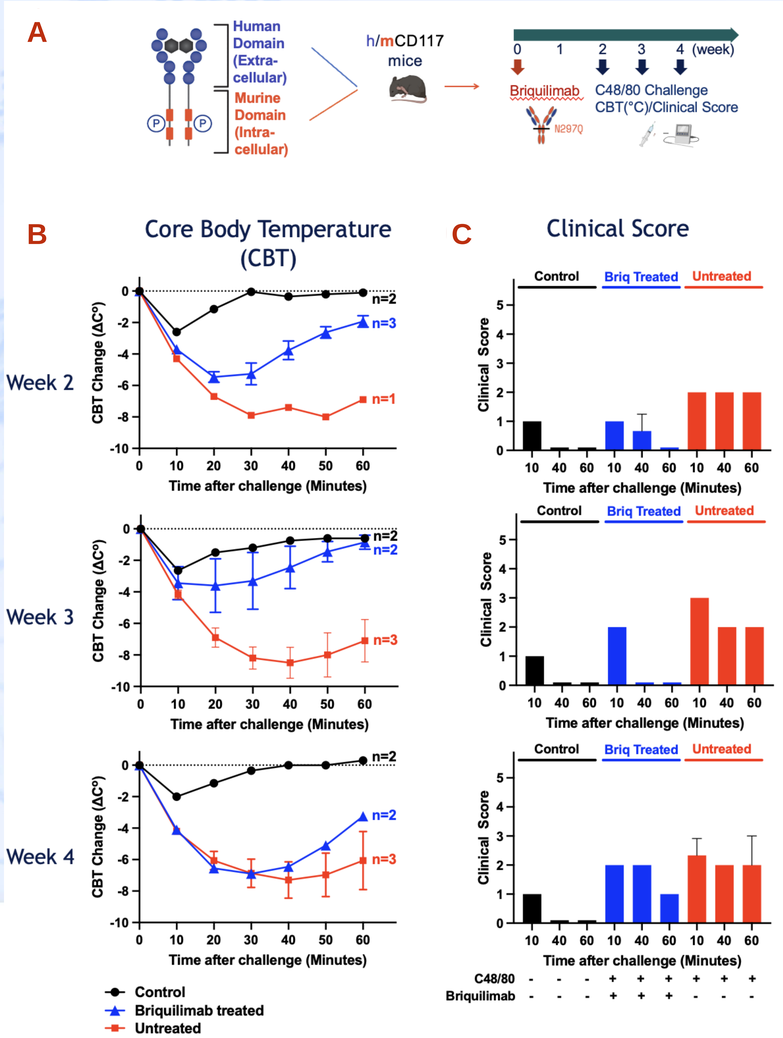
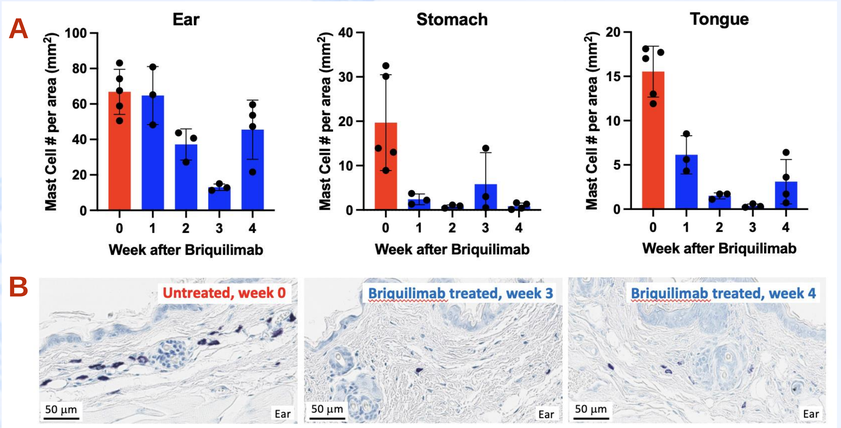


Figure 3. Differential kinetics of mast cell depletion and recovery in various tissues of h/mCD117 mice after one-time administration of briquilimab. Mast cells were detected by toluidine blue staining of tissue sections (A) Mast cell numbers from ear skin, stomach, and tongue in h/mCD117 mice at 1-4 weeks after one-time briquilimab 25 mg/kg IV (blue bar) compared to untreated controls (red bar). (B) Representative images of mast cells (dark purple) in ear skin.



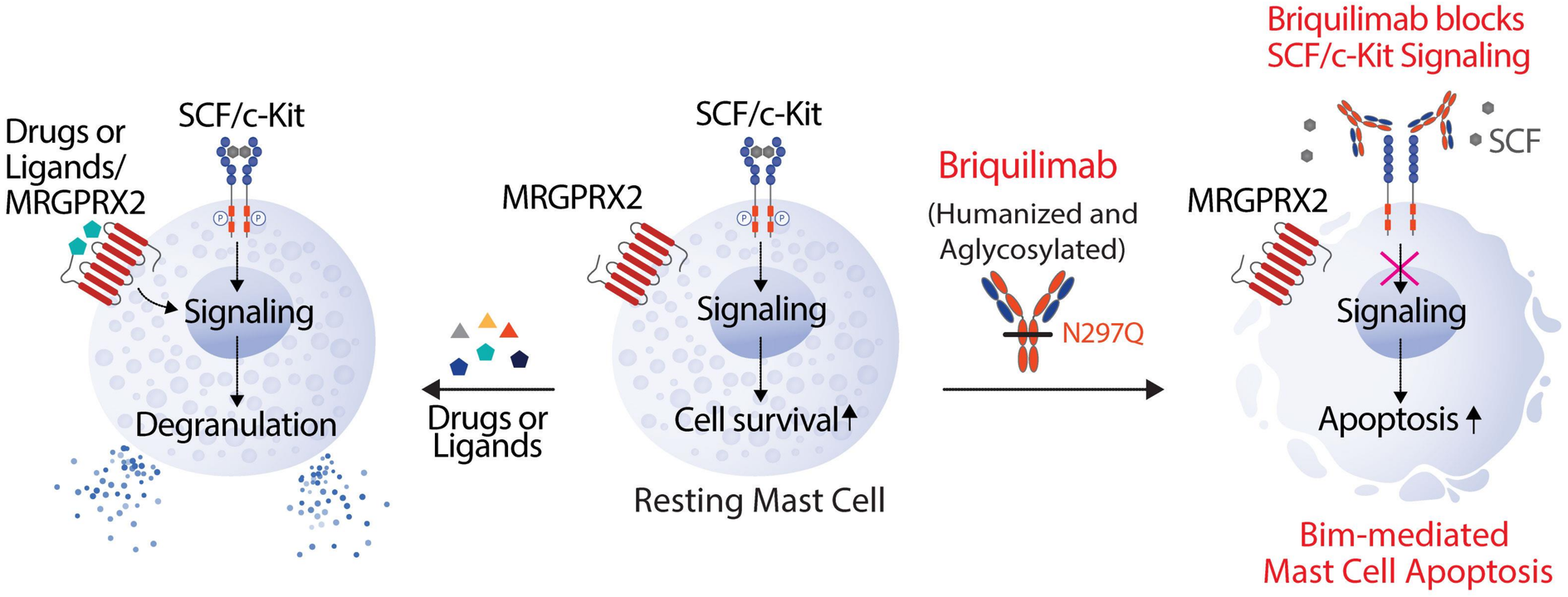
Summary and Future Directions:

- Briquilimab inhibits SCF/c-Kit signaling, leading to apoptosis of mast cells.
- One-time administration of briquilimab effectively ameliorates C48/80 mediated anaphylactoid reactions in h/mCD117 mice at 2-3 weeks post-dose.
- Briquilimab depletes mast cells in various tissues of h/mCD117mice. Depletion and recovery kinetics of mast cells appears to be different among various tissue types.
- This study establishes early proof of concept that briquilimab may be a promising treatment option for non-IgE-mediated mast cell disorders.
- Jasper is actively enrolling participants in a phase 1a/2b trial evaluating briquilimab in patients with chronic spontaneous urticaria (NCT06162728).

Clinicial Anaphylaxis Scoring:
0, No clinical signs;
1, repetitive facial/ear scratching;
2, decreased activity, self isolation, labored breathing;
3, prolonged periods of motionless, lying prone;
4, paresis, no/minimal response to stimuli;
5, seizures, moribundity, death.

JASPER THERAPEUTICS

Briquilimab is an investigational product and not approved for any indication



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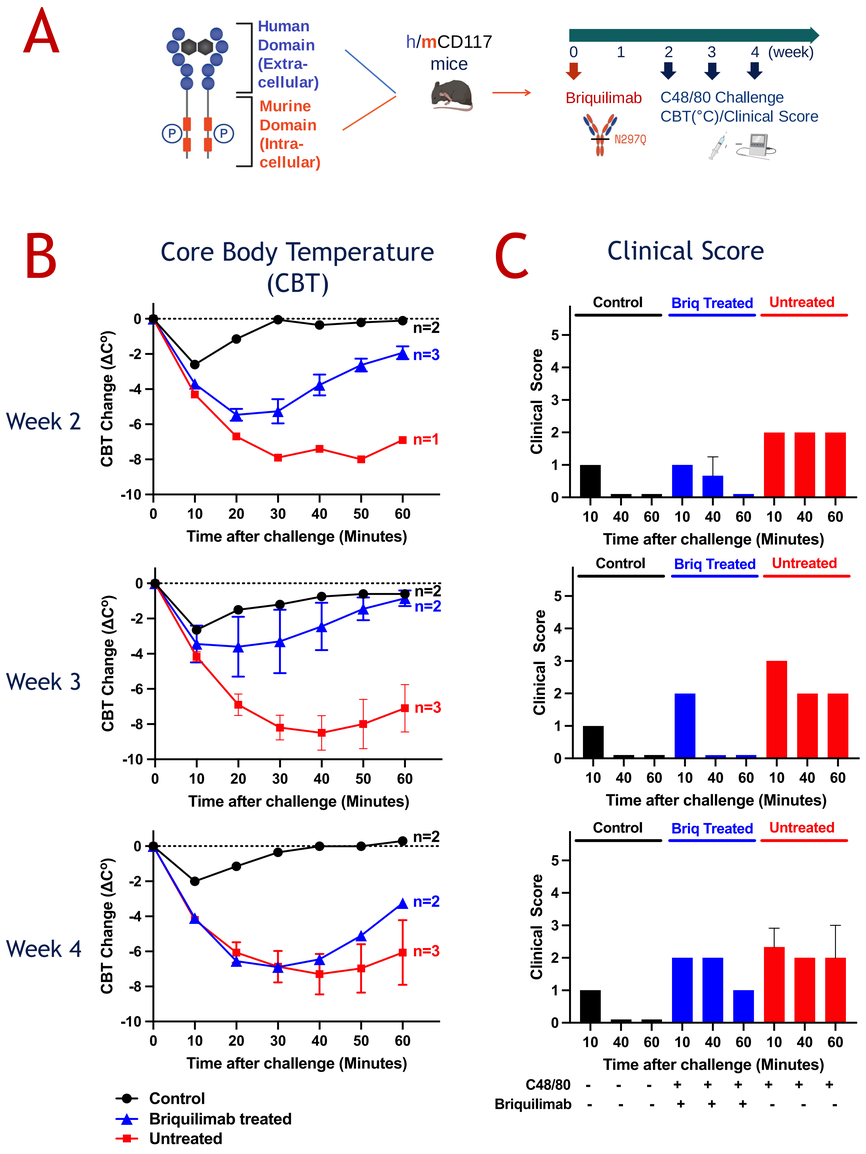

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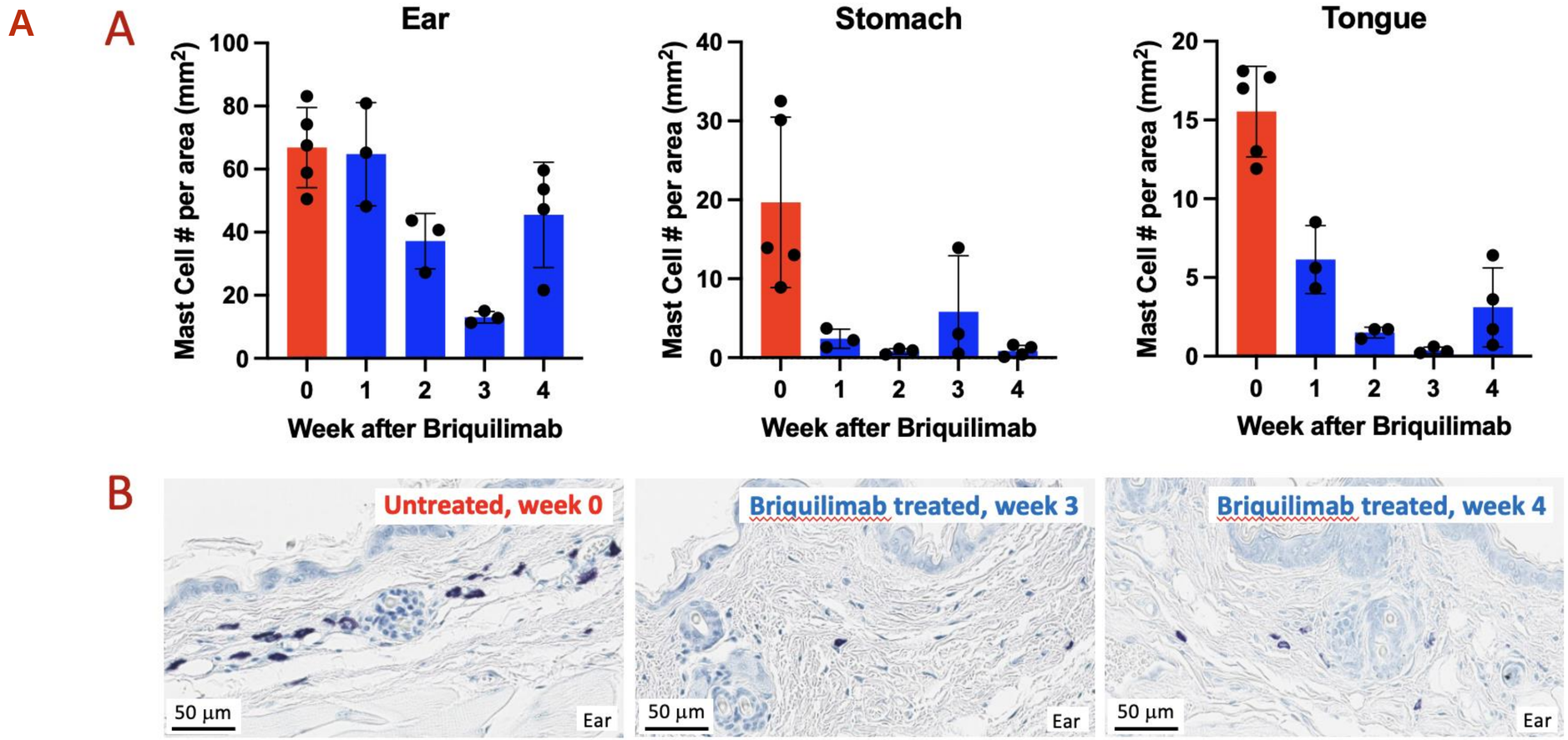

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