024

Briquilimab, An Anti-CD117 (c-Kit) Antibody, Prevents Passive Systemic Anaphylaxis In Mice Expressing Chimeric Human/Mouse CD117 Through Mast Cell Depletion

Ajay Sharma, Song Lee, Charles Chang, Andrew Wells, Revati Nerkar, Karl Meneses, Hye-Sook Kwon, Wendy W. Pang

Jasper Therapeutics Inc., Redwood City, CA, USA

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 (c-Kit), 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.
- Passive systemic anaphylaxis (PSA) can be induced in animal models through the administration of IgE and subsequently an allergen/antigen that crosslinks the IgE, leading to IgE-mediated MC degranulation. h/mCD117 mice were administered briquilimab or untreated, prior to PSA challenge, and the severity of PSA was measured by serial core body temperature monitoring and clinical scoring.

Results:

Figure 1. The SCF/c-Kit pathway is essential for mast cell function and survival. Mast cell (MC) recognition of allergens by cross-linking of FcεRI-associated IgE induces degranulation and allergic symptoms. Blocking SCF/c-Kit signaling with briquilimab, which induces MC apoptosis, may provide protection from severe allergic reactions.

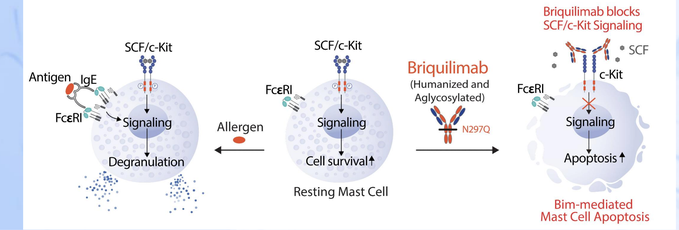


Figure 2. Briquilimab prevents IgE-dependent anaphylaxis reactions in h/mCD117 mouse model. (A) Experimental schema for evaluation of PSA in h/mCD117 mice administrated with one-time briquilimab 25mg/kg IV compared to briquilimab untreated controls. PSA challenge at the specified timepoints post-briquilimab comprised of administration of α-dinitrophenol (DNP)-IgE IP followed by administration of DNP-HAS (human serum albumin) IV, which can crosslink DNP-IgE. The core body temperature and clinical signs (Clinical Anaphylaxis Score) were monitored over time after PSA challenge at the specified timepoints post-briquilimab. (B) While briquilimab untreated mice (red line) showed significant drops of core body temperature (hypothermia) in response to PSA challenge, briquilimab treated mice (blue line) were partially to completely protected from severe hypothermia at 1-4 weeks after briquilimab treatment. Black line represents animals that received neither briquilimab nor PSA challenge, and only received isofluorane. (C) Clinical anaphylaxis scores correlated with severity of hypothermia.

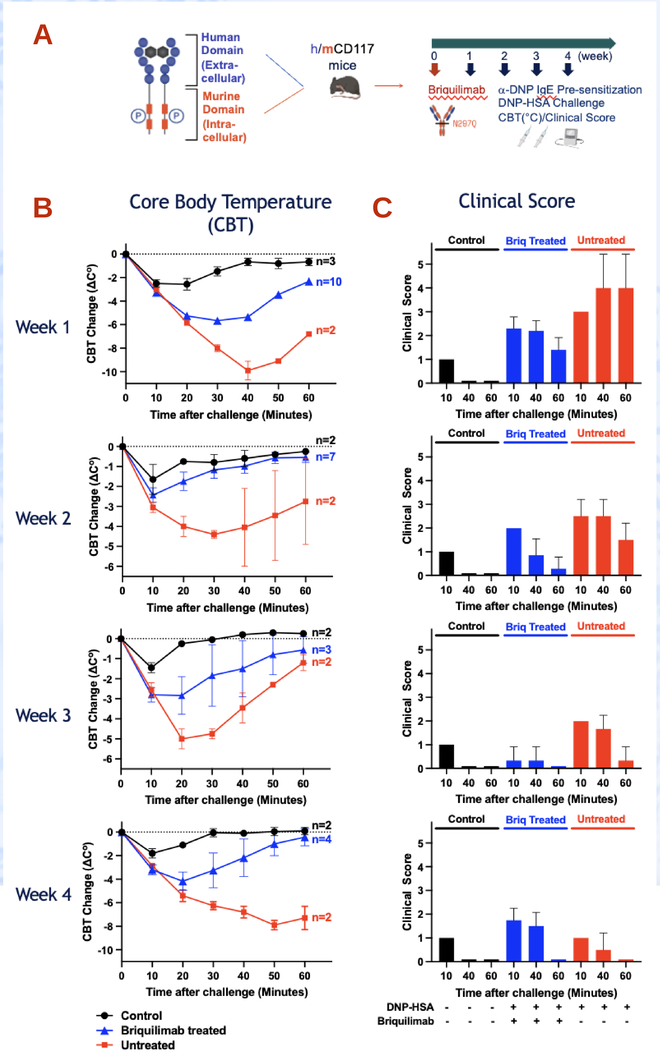
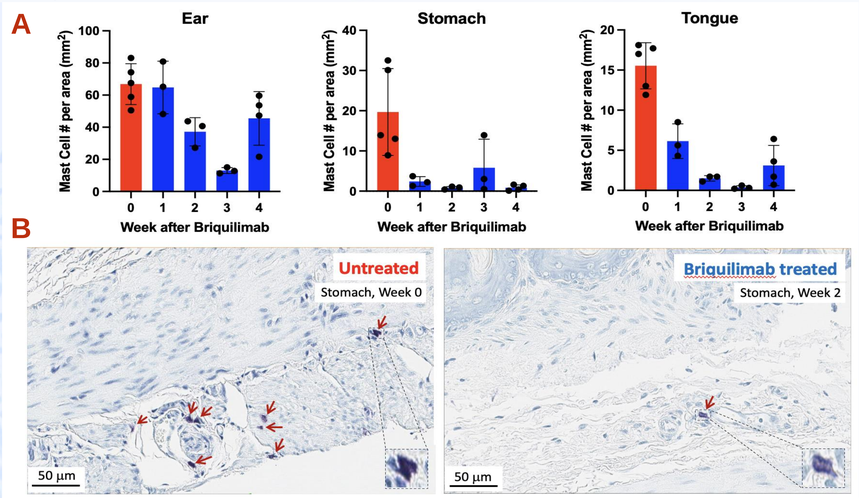


Figure 3. Differential mast cell depletion and recovery kinetics after briquilimab in various tissues of h/mCD117 mice. Mast cells were detected by toluidine blue staining of tissue sections. (A) Mast cell numbers from ear skin, stomach, and tongue in h/mCD117 mice at 1-4 weeks after one-time briquilimab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



Summary and Future Directions:

- Briquilimab inhibits SCF/c-Kit signaling, leading to apoptosis of mast cells.
- One-time administration of briquilimab effectively prevents PSA induced by α-DNP IgE/DNP-HSA in h/mCD117 mice at 2 weeks post-dose. Partial protection from PSA challenge was observed at 1, 3, and 4 weeks post-briquilimab.
- This study establishes early proof of concept that briquilimab may be a promising treatment option for IgE-mediated mast cell disorders
- Briquilimab depletes mast cells in various tissues of h/mCD117 mice. Depletion and recovery kinetics of mast cells appear to be different among various tissue types.
- 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

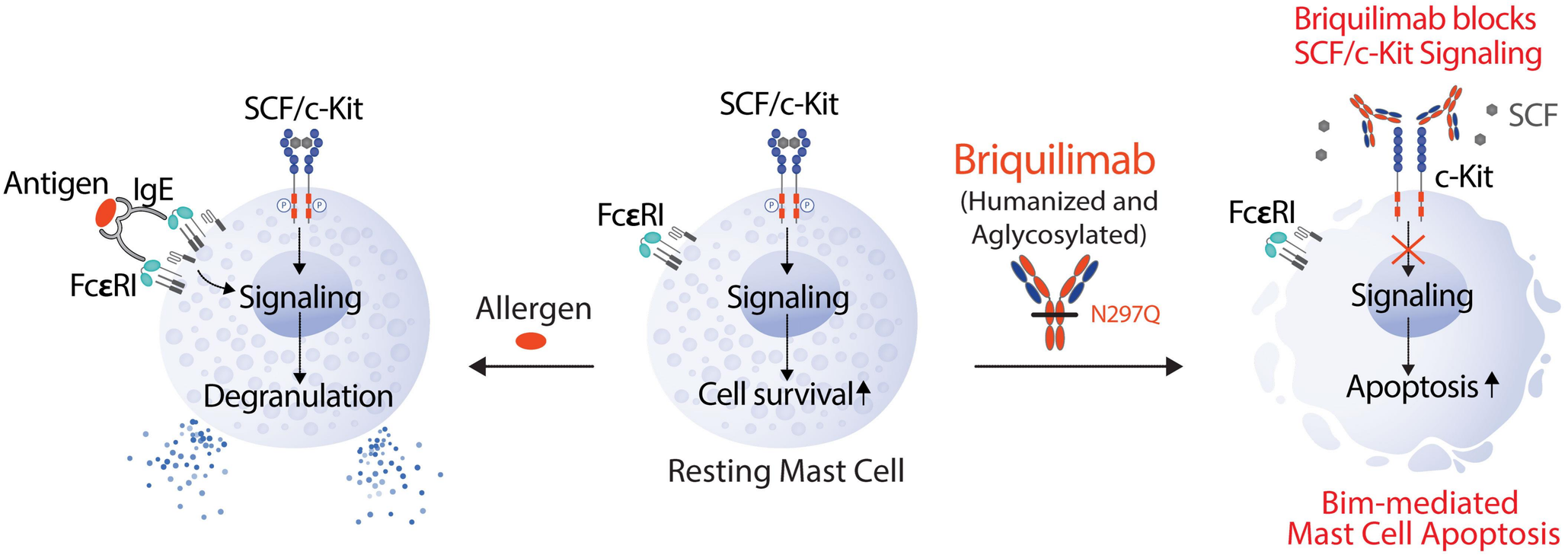


Figure 1. The SCF/c-Kit pathway is essential for mast cell function and survival. Mast cell (MC) recognition of allergens by cross-linking of FcεRI-associated IgE induces degranulation and allergic symptoms. Blocking SCF/c-Kit signaling with briquilimab, which induces MC apoptosis, may provide protection from severe allergic reactions.

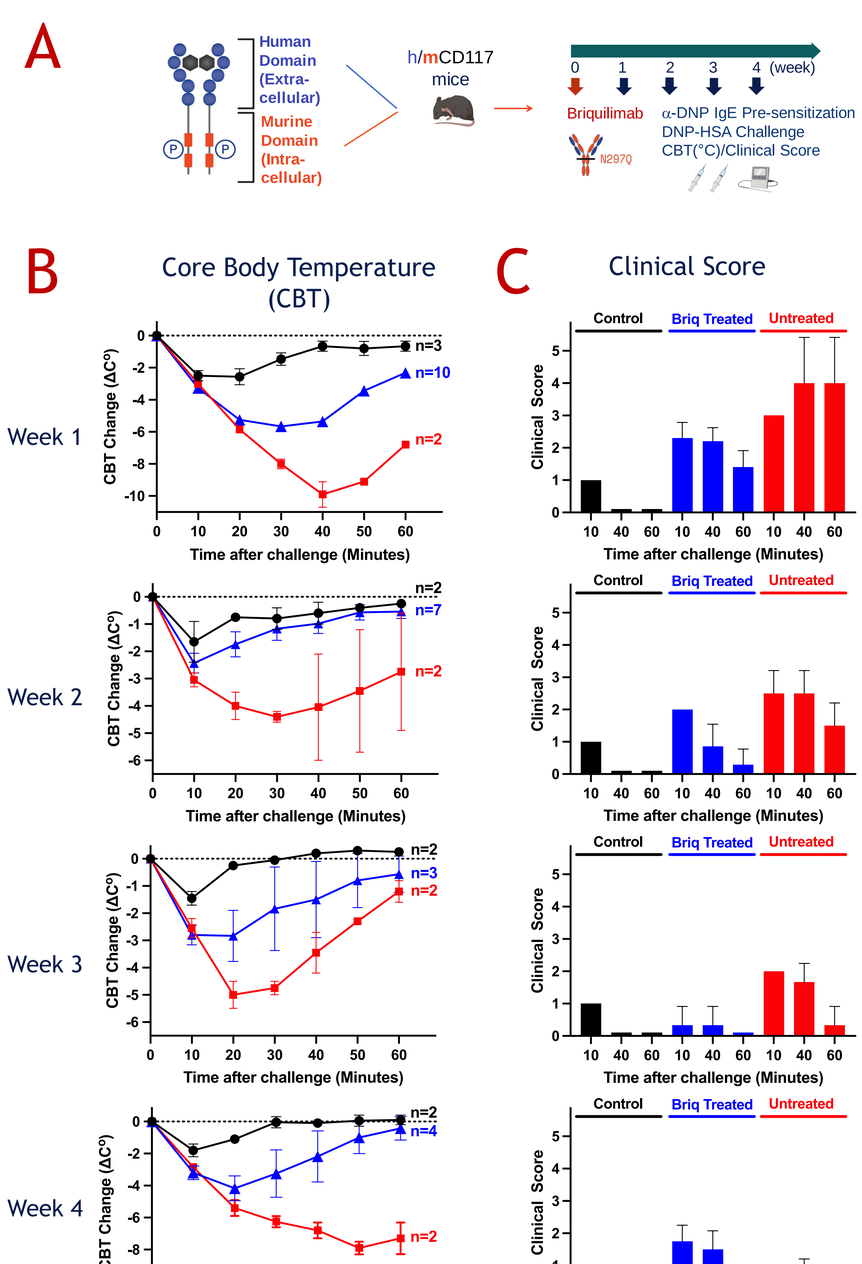


Figure 2. Briquilimab prevents IgE-dependent anaphylaxis reactions in h/mCD117 mouse model. (A) Experimental schema for evaluation of PSA in h/mCD117 mice administrated with one-time briquilimab 25mg/kg IV compared to briquilimab untreated controls. PSA challenge at the specified timepoints post-briquilimab comprised of administration of α-dinitrophenol (DNP)-IgE IP followed by administration of DNP-HAS (human serum albumin) IV, which can crosslink DNP-IgE. The core body temperature and clinical signs (Clinical Anaphylaxis Score) were monitored over time after PSA challenge at the specified timepoints post-briquilimab. (B) While briquilimab untreated mice (red line) showed significant drops of core body temperature (hypothermia) in response to PSA challenge, briquilimab-treated mice (blue line) were partially to completely protected from severe hypothermia at 1-4 weeks after briquilimab treatment. Black line represents animals that received neither briquilimab nor PSA challenge, and only received isofluorane. (C) Clinical anaphylaxis scores correlated with severity of hypothermia.

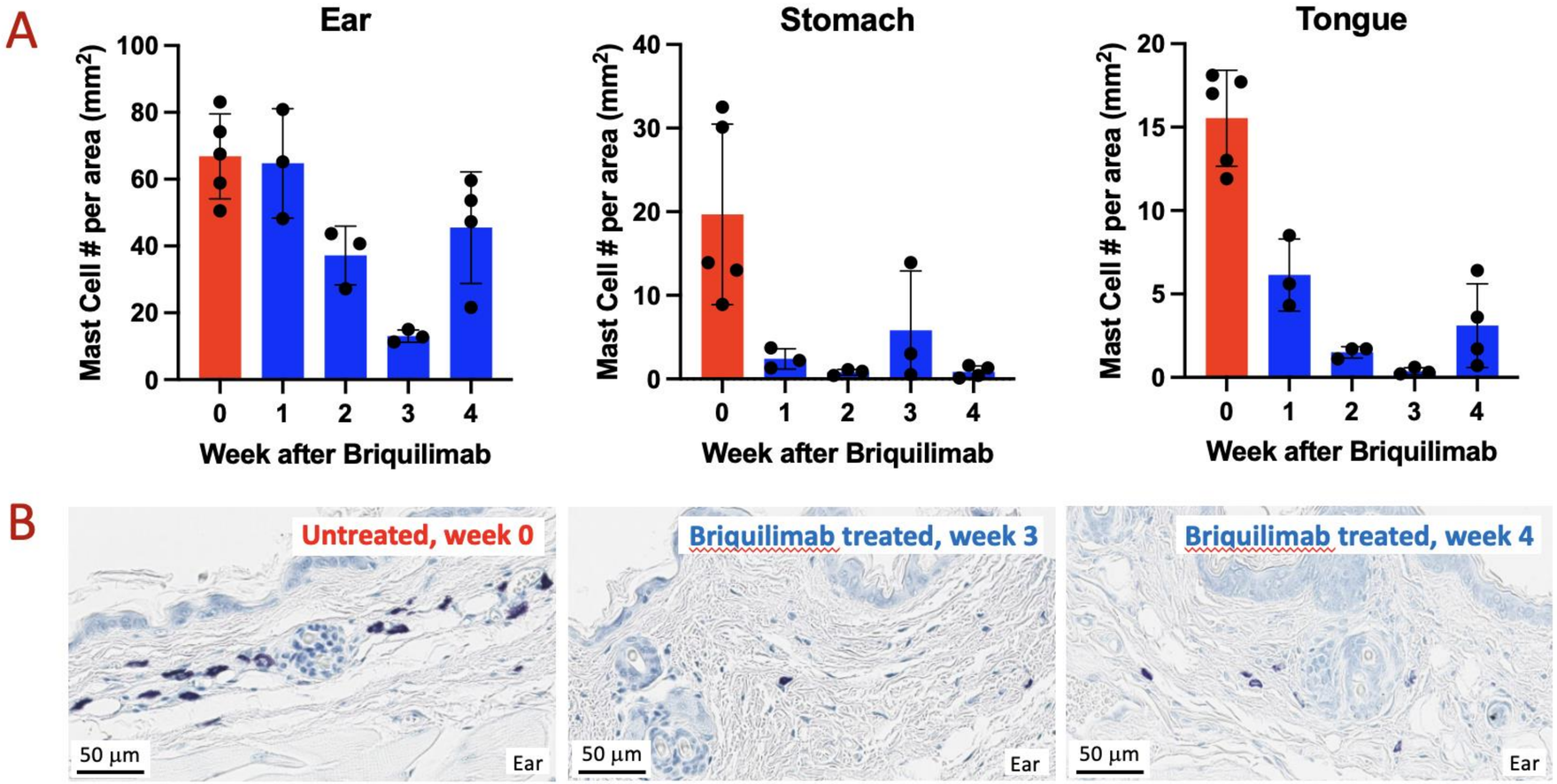


Figure 3. Differential mast cell depletion and recovery kinetics after briquilimab in various tissues of h/mCD117 mice. Mast cells were detected by toluidine blue staining of tissue sections. (A) Mast cell numbers from ear skin, stomach, and tongue in h/mCD117 mice at 1-4 weeks after one-time briquilimab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