Briquilimab, an anti-CD117 antibody, prevents passive systemic anaphylaxis in mice expressing chimeric human/mouse CD117

Charles A. Chang, Ajay Sharma, Andrew Wells, Revati Nerkar, Karl Meneses, Hye-Sook Kwon, Wendy W. Pang
Jasper Therapeutics Inc., Redwood City, CA, USA

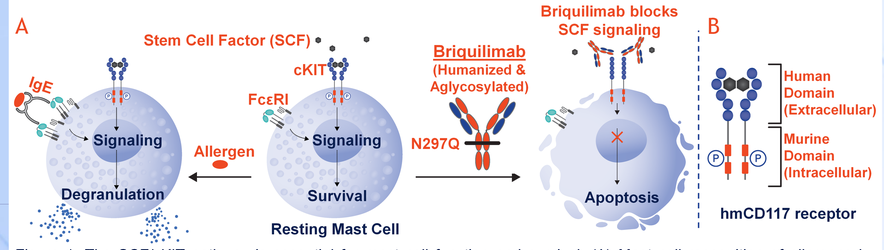


Figure 1. The SCF/cKIT pathway is essential for mast cell function and survival. (A) Mast cell recognition of allergens by FcεRI-associated IgE induces degranulation and allergic symptoms. Blocking SCF signaling through cKIT with briquilimab induces mast cell apoptosis and may provide protection from severe allergic reactions. (B) Novel hmCD117 mice, expressing chimeric CD117 consisting of human extracellular and murine intracellular domains, are used to evaluate the potential of briquilimab in mast-cell driven disorders such as anaphylaxis.

Introduction:

- Stem Cell Factor (SCF) signaling through cKIT (CD117) plays a key role in mast cell differentiation and survival, inhibition of this pathway has the potential to treat mast cell-related disorders
- Briquilimab, a humanized aglycosylated monoclonal antibody targeting cKIT, prevents SCF signaling and can deplete human mast cells. It is being assessed in clinical trials at doses from 0.1mg/kg and above. The highest dose (280mg) has been assessed in prior healthy volunteer trials

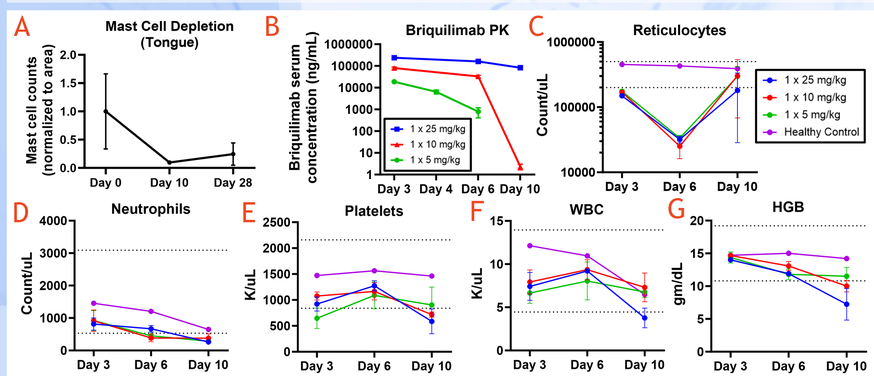


Figure 2. PK/PD of briquilimab in hmCD117 mice. (A) Administration of 25 mg/kg briquilimab (~2 mg/kg human equivalent dose via body-surface area conversion) resulted in a ~90% decrease in mast cell numbers 10 days after administration. (B) hmCD117 mice were given 5, 10, and 25 mg/kg of briquilimab and serum was collected on post-administration days 3, 4, 6 and 10. The PK of briquilimab was dose-dependent in a nonlinear manner. (C-G) CBC results showed transient changes in reticulocyte counts and dose-dependent deviations in certain parameters.

Methods:

- Novel mice expressing 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 “hmCD117 mice”
- The pharmacokinetics and pharmacodynamics of briquilimab were evaluated in hmCD117 mice using CBC analysis and toluidine blue staining of tissue sections
- Briquilimab was assessed in a model of IgE-induced passive systemic anaphylaxis (PSA)

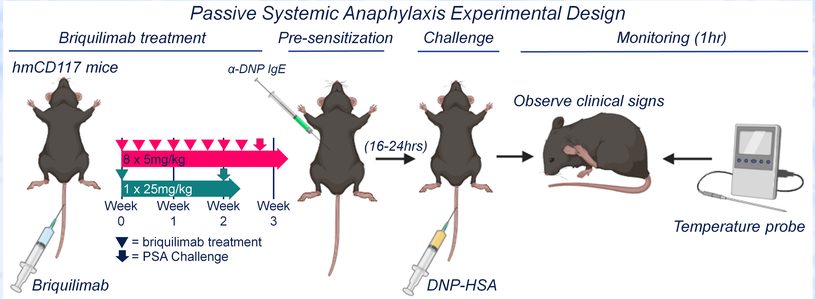
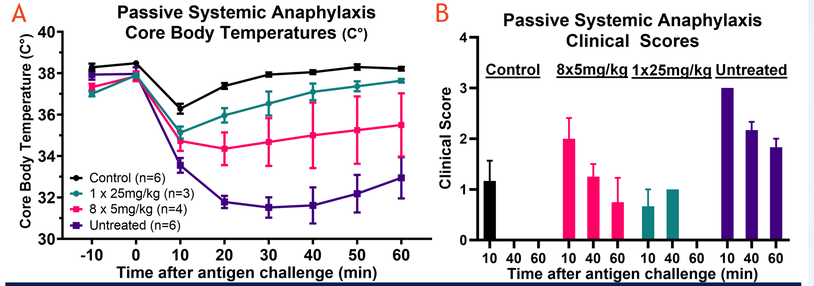


Figure 3. In vivo passive systemic anaphylaxis experimental design. hmCD117 mice were administered 8 x 5 mg/kg briquilimab over 2.5 weeks (days 0, 2, 4, 7, 9, 11, 14, 16), or a single 25 mg/kg dose two weeks before challenge. One day prior to challenge, mice were pre-sensitized with α-dinitrophenol (DNP) IgE by i.p. injection. On the day of challenge, mice were administered DNP-HSA i.v. and subsequently monitored for core body temperature changes and the onset of clinical signs (Clinical Anaphylaxis Score).

Results:

- Chimeric hmCD117 receptor is responsive to mouse SCF and briquilimab
- Robust mast cell depletion after briquilimab administration was confirmed with toluidine blue staining of tongue sections
- The pharmacokinetic clearance of briquilimab in the serum was dose dependent in a nonlinear manner
- Briquilimab administration in hmCD117 mice caused transient or varying degrees of dose-dependent deviations in peripheral blood counts
- A single 25 mg/kg dose (~2 mg/kg human equivalent dose) two weeks before PSA challenge prevented severe anaphylactic reaction



Clinical Anaphylaxis Score	
Score	Signs
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

Figure 4. Briquilimab administration reduces severity of anaphylaxis. (A) Systemic anaphylaxis in mice results in a drop of core body temperature (hypothermia). Untreated mice (purple line) exhibited severe hypothermia after challenge. Mice administered the 8 x 5mg/kg briquilimab regimen (magenta line) displayed moderate protection from hypothermia. The 1 x 25 mg/kg group (teal line) was substantially protected from hypothermia and rapidly recovered. Controls (black line) were given antigen but not IgE. (B) Clinical scores correlated with severity of hypothermia.

Conclusion and future directions:

- Briquilimab effectively depletes mast cells and is well tolerated in hmCD117 mice
- This study establishes early proof of concept that briquilimab may be a promising treatment option for mast cell-mediated disorders
- Jasper is opening a phase 1a/2b trial evaluating briquilimab activity/effects in patients with chronic spontaneous urticaria

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