Briquilimab, an Anti-Human CD117 Antibody, Effectively Treats Cockroach Allergen-Induced Asthma Model Elicited in Mice Expressing Chimeric Human/Mouse CD117

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Background
Stem cell factor (SCF) and its receptor CD117 (c-Kit) mediate critical signaling in mast cell (MC) growth, differentiation, migration, survival, and activation. Briquilimab, a humanized aglycosylated monoclonal antibody against human CD117 that can potently block SCF-CD117 signaling and deplete human MCs, has the potential for the treatment of MC-mediated diseases, including allergic asthma.

Method
To evaluate briquilimab in vivo in mouse models, transgenic C57BL/6 mice were developed to express chimeric human/mouse (h/m) CD117, consisting of human extracellular and mouse intracellular domains of CD117 in lieu of wild-type mouse CD117. Using these h/mCD117 mice, we established asthma models through intranasal sensitization (days 1 and 2) and challenge (days 15, 18, and 21) with cockroach allergen (CRA). On day 22, established h/mCD117 asthma models received intraperitoneal administration with a single dose of 25 mg/kg briquilimab (treatment group) or normal saline (placebo group), followed by an intranasal CRA challenge on day 24 to induce recurrence of asthma. On day 25, 3 days post-briquilimab, efficacy of briquilimab was assessed by lung function testing, bronchoalveolar lavage (BAL), and lung histopathology.

Results
In the briquilimab treatment group, h/mCD117 asthma models exhibited significantly reduced pulmonary resistance, BAL-recovered leukocytes, and leukocyte airway infiltration following recurrence of asthmatic attack elicited by allergen exposure, compared with the placebo group ($P < 0.05$, respectively). The number of peribronchial MCs in the placebo group was significantly increased compared with non-allergen-exposed healthy h/mCD117 mice (placebo group 45.1□4.8/mm^2 vs. healthy group 13.1□3.0/mm^2, $P < 0.05$), while therapeutic briquilimab treatment led to an approximate 70% reduction in peribronchial MCs, compared with the placebo group (briquilimab treatment group 12.8□4.0/mm^2 vs. placebo group 45.1□4.8/mm^2, $P < 0.05$). In non-inflamed back skin, there was no significant difference in the number of dermal MCs between the placebo group and the healthy h/mCD117 mice (placebo group 104.3□6.8/mm^2 vs. healthy group 102.8□6.5/mm^2, $P>0.05$). However, briquilimab treatment led to an approximate 50% depletion in dermal MCs within 3 days (treatment group 53.2□3.4/mm^2 vs. placebo group 104.3□6.8/mm^2 or healthy group 102.8□6.5/mm^2, $P<0.05$, respectively).

Conclusion
This study provides evidence that briquilimab has the potential to be a novel therapeutic agent for allergic asthma.