Targeting the CD6-ALCAM Pathway to Prevent and Treat Graft vs Host Disease

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Background

Clinical need:
- Acute graft versus host disease (aGVHD) causes significant morbidity and non-relapse mortality (NRM), occurring in ~50% of patients receiving allogeneic hematopoietic stem cell transplant (HSCT) with standard GVHD prophylaxis regimens.
- aGVHD commonly affects the skin, liver and gastrointestinal tract (GI). Of these, the GI manifestation is the most difficult to treat, with up to 60% incidence, and is a major cause of GVHD-related mortality.
- There are currently no FDA approved therapies for the initial treatment of newly diagnosed aGVHD.

T cells are a major driver of aGVHD:
- T effector cells, particularly CD4+ T helper cells, play a central role in the pathogenesis of aGVHD.
- CD6 is a co-stimulatory receptor that is highly expressed on CD4+ T helper cells and binds activated leukocyte cell adhesion molecule (ALCAM or CD166), a ligand expressed on antigen presenting cells and various epithelial and endothelial tissues.
- The CD6-ALCAM pathway plays an integral role in modulating T cell activation and trafficking and is central to immune mediated inflammation.

Targeting the CD6-ALCAM pathway:
- Itolizumab is a humanized IgG1 mAb that binds to CD6 and blocks interaction with ALCAM, thereby inhibiting both the activity and trafficking of T cells without causing T cell depletion.
- Itolizumab has previously been developed and is approved for the treatment of Psoriasis in India, suggesting that it may be used to treat T cell driven skin diseases. However, it has not been tested previously in gastrointestinal inflammation.

Objective:
We set out to test whether blockade of the CD6-ALCAM pathway was a relevant target to ameliorate aGVHD and if this approach could specifically be used to treat the GI manifestation of aGVHD.

Methods

CD6 blockade with itolizumab in humanized model of aGVHD
- Disease induction: On Day 0, female NOD.Cg-Ptk-Null Elgn1W(NJ) mice (NSG, Jackson Labs) were irradiated with 100 cGy/day, followed by intraperitoneal injection of 1 x 10⁶ human PBMC four hours later. This induces aggressive acute, xenogeneic GVHD.
- To evaluate the efficacy of itolizumab to prevent the onset of GVHD, mice were administered itolizumab (50 or 200 μg), abatacept (150 μg), belatacept (75 μg) or vehicle (PBS) every other day via IP injection for 30 days beginning on Study Day 1 (Day 0=tumor). Table 1. Mice were evaluated every other day for body weight, clinical signs and survival. To evaluate the extent of human T cell proliferation, peripheral lymphocytes were immunologically by flow cytometry at Day 15 and Day 35. Study was repeated to examine tissue histology and inflammation at Day 16.
- To evaluate the efficacy of itolizumab (CD6/CD166) in both prevention and therapeutic treatment settings, itolizumab was administered every other day starting on Day 1 (prevention) or Day 5 (treatment) of disease induction. Table 2. The Day 5 time point was chosen for treatment as this was the half-way point between disease induction and median survival time. Moreover, significant suppression of human CD45+ cells was observed at this time point.

- To evaluate the efficacy of CD6 blockade on inflammation in this tissue, mice were treated with anti-CD6 mAb (clone 12.17), anti-
1024 mAb anti-CD6 mAb or vehicle (control) (Table 3).

- Itolizumab showed a marked reduction in colonic weight and length, indicating a protective effect on the gut.

- Examination of colon tissue revealed significant decreases in the amounts of IL-10, IFN-γ, IL-6, IL-17 and TNFα in the treated groups compared to the control group.

- Infiltration of CD45+ CD3+ T cells into tissue was also significantly reduced in the treated groups compared to the control group.

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Conclusions

- We demonstrate for the first time that in vivo blockade of the CD6-ALCAM pathway can reduce incidence and severity of GVHD and associated gut inflammation, highlighting itolizumab as a promising therapeutic approach for GVHD and other T cell driven inflammatory diseases.

- Currently, a Phase 1b is ongoing to assess itolizumab in the treatment of newly diagnosed aGVHD. The EUVATE trial is currently open at US Centers; more information can be found on clinicaltrials.gov (NCT#03763318).