P801 EVALUATION OF COMMON GAMMA CHAIN CYTOKINE SIGNALING BLOCKADE WITH REGN7257, AN INTERLEUKIN 2 RECEPTOR GAMMA (IL2RG) MONOCLONAL ANTIBODY, ON IMMUNE CELL POPULATIONS ACROSS SPECIES

Topic: 11. Bone marrow failure syndromes incl. PNH - Biology & Translational Research

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Background:

The common γ chain cytokine receptor (γc; IL2RG) family of cytokines includes interleukin 2 (IL2), IL4, IL7, IL9, IL15, and IL21. This set of cytokines exhibits broad pleiotropic actions on both the innate and adaptive immune system with each cytokine sharing the IL2RG chain as part of its signaling receptor complex. Mutations in the IL2RG gene result in X-linked severe combined immunodeficiency (XSCID) in humans, whereby patients present with dramatically diminished numbers of T cells and NK cells, and dysfunctional B cells.

Aims:

Given the crucial role for γc cytokines in the development and function of lymphocytes, modulating their activities may offer therapeutic potential in a range of immune-mediated diseases. To understand the effects of γc cytokine blockade on immune cells including T-cell subsets, we utilized REGN7257, a fully human IL2RG monoclonal antibody that inhibits γc cytokine-induced signaling, and tested its ability to suppress immune cell populations and their functions across species (mouse, cynomolgus monkey [CM] and human).

Methods:

We evaluated the effects of γc cytokine signaling blockade with REGN7257 on immune cell populations in Il2rghu/hu mice and CM by flow cytometry. Mixed lymphocyte reaction assays were performed to look at the impact of γc cytokine signaling blockade on activation/proliferation of human T cells. To further analyze the contribution of γc cytokines to T-cell differentiation and function, we performed in vitro transcriptomic studies on human peripheral blood mononuclear cells stimulated with anti-CD3/CD28 beads.

Results:

γc cytokine signaling blockade with REGN7257 in Il2rghu/hu mice efficiently reduced circulating B, NK and T cell populations, with no changes in blood neutrophil counts. In addition, the impact of γc cytokine signaling blockade on lymphocyte populations in vivo were investigated in CM in a single dose pharmacokinetick/pharmacodynamic study and a repeat-dose toxicology study. Inhibition of γc cytokine signaling with REGN7257 in CM led to similar phenotypic changes to that observed in Il2rghu/hu mice, with decreases in peripheral T cells and NK cells, without impacting B cells, granulocytes, platelets or red blood cells. γc cytokine signaling blockade led to a reduction in both CD4+ and CD8+ T cell counts with effector memory T cells being the most impacted T-cell population studied. Furthermore, blockade of γc cytokine signaling led to reduction in activated and proliferating T cells in CM and demonstrated potent inhibition of allogeneic responses in mixed human lymphocyte reaction assays, by preventing T-cell activation and proliferation. Two-tailed gene set enrichment analysis identified 4 distinct patterns of significantly enriched gene sets that were impacted by γc cytokine signaling upon CD3/CD28-induced activation of human T cells: gene sets involved in inflammatory responses, differentiation and proliferation, activation and immune responses, as well as those related to adhesion and migration. These signatures were blocked with REGN7257 treatment.

Summary/Conclusion:

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Taken together, these pharmacological observations highlight the major role for γc cytokine signaling in maintenance of lymphocyte populations (i.e. NK cells and T cells) in mouse and CM, but not other immune cell populations (i.e. granulocytes, platelets and red blood cells). Furthermore, our data highlight the importance of γc cytokines in driving functions of CM and human T cells, opening a potential new route for the management of T cell-mediated diseases.