A recombinant, fully human ATG polyclonal antibody drug drives immune cell depletion in a model of graft-versus-host disease

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BACKGROUND

- Anti-thymocyte globulin (ATG) is a polyclonal immunoglobulin made by immunizing rabbits with thymocytes.
- ATG is used for immune cell depletion during transplantation to prevent solid organ transplant rejection.

CHALLENGES:

- ATG induces allergic responses to rabbit proteins.
- After treatment, cytokine release syndrome is caused by immune cell activation from ATG.
- There is lot-to-lot variability due to differences in animals or cells used.
- Anti-drug antibodies may reduce the half-life with repeated use.
- A central line is required for administration.
- Thromboocytopenia and red blood cell depletion is associated with infusion.

OBJECTIVE:

- To make a recombinant, fully human polyclonal (rATG) that has similar antigen specificities to rabbit ATG (iATG).
- To characterize ATG function in vitro.
- To demonstrate similar in vivo function of rATG to iATG.

METHODS

- Trianni human transgenic mice produce antibodies with fully human variable regions. When immunized with human thymocytes and T cells, high titer immune cell-specific antibodies are produced.
- B cells are harvested from anesthetized mice, individual cells are captured in droplets, native antibody heavy and light chain sequences are linked together and cloned as full-length (gk-lgk) into Chinese hamster ovary (CHO) cells for antibody production.
- Antibodies are characterized for function and antigen-specificity.
- Immune deficient (NSG; Jackson Labs) animals engrafted with human PBMCs are used as a model of graft-versus-host disease (GVHD). Six animals per group were treated with a single dose of 6 mg/kg rATG, iATG or vehicle negative control.
- Animals are monitored for immune modulation, clinical severity and death over 42 days.

CONCLUSION

From this study we have found that recombinant human ATG:

- Demonstrates similar in vitro function to rabbit ATG.
- Efficiently depletes immune cells in vivo and delays onset to GVHD.
- Can be produced at a large scale from a master cell bank and manufactured using standardized methods.

Pre-clinical and clinical studies will be performed to evaluate rATG for toxicity, pharmacokinetics, and function for inducing immunosuppression to prevent acute transplant rejection and reduce other inflammatory auto-immune reactions. Future studies may show improvement over rabbit ATG including:

- Longer half-life in vivo.
- Potential to treat repeated lower doses with reduced anti-drug antibody development.
- Easier administration with fewer side effects.
- A more potent and safer product.