The Safety Evaluation of NKTT120, an Invariant NKT (iNKT) Cell Depleting Antibody in the Cynomolgus Monkey

Sue Macdonald, Ph.D.1, Felix Scheuplein, Ph.D.1, Abraham Thariath, Ph.D.1, Elen LeBel, M.Sc.2, Brandon Zeigler, Ph.D.2, Alem Truneh1, Robert Mashal, M.D.1 and Robert Schaub, Ph.D.1

1NKT Therapeutics, Waltham, MA
2MPI Research, Mattawan, MI

Abstract

Invasive Natural Killer T (iNKT) cells are a small subset of T lymphocytes (ranging from 0.01 – 0.1% of CD3+ T cells). iNKT cells recognize glycolipid antigens presented by the MHC class-I-like protein CD1d rather than peptide antigens. In contrast to most T cell sub-populations, which have diverse sequences for their T Cell Receptors (TCRs), iNKT cells express a uniquely rearranged, highly conserved, semi-invariant TCR-α chain (Vα24-Jα18 in humans), which preferentially pairs with specific TCR-β chains (Vβ11 in humans). iNKT cells are similar to innate cells in their rapid release of cytokines following TCR antigen binding. They are also adaptive-like, with T cell properties including thymic positive selection and antigen recognition by CD1d presentation. iNKT cells are involved in mediating tissue injury and inflammation in multiple organ systems. Chronic inflammation is associated with the pathophysiology of sickle cell disease (SCD) and our studies and those of others have found an increased ratio of activated iNKT cells in peripheral blood of patients with SCD. The role of iNKT cell activation in the pathology of SCD is supported by studies in a mouse model of SCD (Wallace et al. Blood 114:667, 2009). These data suggest that iNKT cell reduction and/or depletion would be effective in reducing the inflammatory state in SCD. To this end, we have developed a humanized monoclonal antibody (NKTT120) that exclusively binds to the CDR3 loop of the human and non-human primate (NHP) invariant T cell receptor and depletes iNKT cells. This antibody could provide an effective therapeutic intervention to modulate iNKT cell numbers, and thus their ability to mediate inflammation in SCD. The current study was designed to assess the overall safety of NKTT120 in the cynomolgus monkey (Macaca fascicularis). The cynomolgus monkey was selected for testing because NKTT120 is only active in human and old world NHP species. Thirty-two cynomolgus monkeys (3-5 kg) equally divided between males and females were studied. The groups consisted of a vehicle control and treatment groups that received 0.3 mg/kg, 3 mg/kg, and 10 mg/kg NKTT120 IV weekly for a total of 5 doses. Two animals per sex in the vehicle and the 10 mg/kg groups were recovered for an additional 2 months following the last dose. Animals were evaluated weekly for a total of 5 doses. Two animals per sex in the vehicle and the 10 mg/kg groups were recovered for an additional 2 months following the last dose. Animals were evaluated for food intake, body weight and general health. Standard hematology, coagulation testing and clinical chemistry testing were also performed. In addition, iNKT cell number and other lymphocytes were monitored during the study by FACS analysis. The repeat dose injections were well tolerated by all dose groups. No deaths or serious adverse events were reported during dosing or in the recovery period. Body weight, food intake and clinical evaluation, hematology, coagulation assays, and clinical chemistry were similar for vehicle control and treatment groups that received 0.3 mg/kg, 3 mg/kg, and 10 mg/kg NKTT120 IV weekly for a total of 5 doses. Two animals per sex in the vehicle and 10 mg/kg groups were recovered for an additional 2 months following the last dose. Animals were evaluated for food intake, body weight and general health. Standard hematology, coagulation testing and clinical chemistry testing were also performed. In addition, iNKT cell number and other lymphocytes were monitored during the study by FACS analysis. The repeat dose injections were well tolerated by all dose groups. No deaths or serious adverse events were reported during dosing or in the recovery period. Body weight, food intake and clinical evaluation, hematology, coagulation assays, and clinical chemistry were similar for vehicle control and all dosing groups. As expected, iNKT cells were depleted within 24 hours to below level of detection and remained depleted throughout the dosing period at all doses tested. The iNKT cell numbers of the 10 mg/kg recovery animals remained depleted throughout the 2 month recovery. However, there was no change in other cells of the lymphocytic series at any dose or at any time point evaluated.

Conclusion

Overall our study showed that we can safely and specifically deplete iNKT cells in non-human primates following administration of NKTT120. These data support the use of NKTT120 as a therapeutic intervention in conditions such as sickle cell disease where iNKT modulation could be beneficial.