A pre-clinical evaluation of an APRIL targeting antibody strategy in grouped ddY mice and non-human primates and correlation to pathogenic and immune related mechanisms

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ABSTRACT 0107

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Objectives: A PRoliferation Inducing Ligand (APRIL) has emerged as a potentially key B cell modulating factor in the pathogenesis of IgA nephropathy based on a convergence of genetic and translational data and its proposed immunological role in IgA class switching, autoantigenic IgA production and the promotion of autoreactive B cell survival. The efficacy of antibody targeted inhibition of APRIL was evaluated preclinically in grouped ddY (gddY) mice, an early-onset disease model which recapitulates several pathogenic mechanisms of human disease and progression. We also extend these findings of antibody-targeted inhibition of APRIL to non-human primates based on its proposed mechanism of action using VIS649, a humanized IgG2 antibody targeting and neutralizing human APRIL and currently in development for therapeutic evaluation in humans.

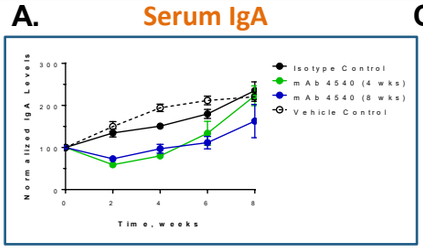
Materials and Methods: Six-week old gddY female mice were randomized into the four groups (n=6/group): Vehicle control, isotype control, mAb 4540 (8-week treatment) and mAb 4540 (4-week treatment followed by a 4-week recovery period). MAb 4540 and isotype matched control were administered once weekly by IP dosing (10 mg/kg). Study endpoints included quantification of serum IgA and IgA-IgG complexes and IgA glycosylation by ELISA. Additional disease relevant endpoints included histological evaluation of immune deposition in kidneys by IFC and proteinuria (uACR) following spot urine collection. Cynomolgus monkeys (n=4/group) were IV administered vehicle or VIS649 25 mg/kg once weekly for up to 8 weeks. Study endpoints included serum immunoglobulin levels by ELISA and cellular immunoprofiling of lymphocytes in peripheral blood and tissues by flow cytometry and IHC staining.

RESULTS AND DISCUSSION

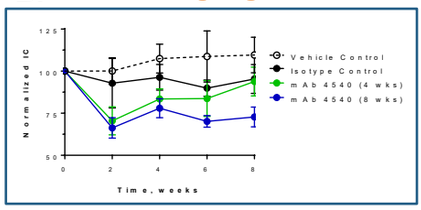
Grouped ddY Mice

ANTIBODY TARGETING OF APRIL EFFECTIVELY REDUCES PRODUCTION OF DISEASE-INSTIGATING IgA AND IgA-IgG IMMUNE COMPLEXES

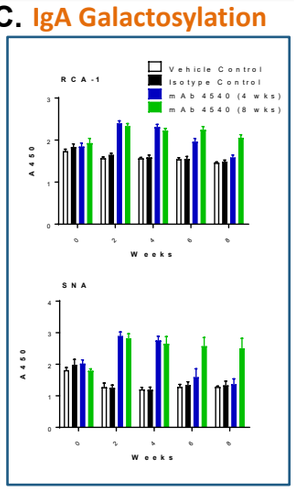
A. Serum IgA



B. Serum IgA-IgG ICs

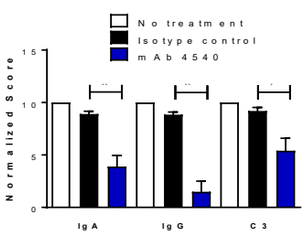


C. IgA Galactosylation

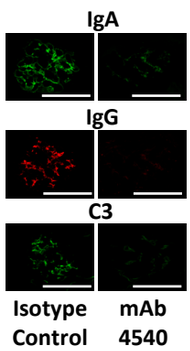


Immune Deposits in Kidney

D.



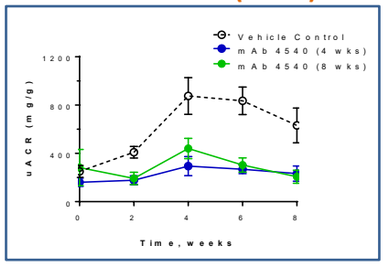
E.



- Reduction in serum IgA (A) and hypo-glycosylated IgA (autoantigen), (C).
- Leading to reduction in steady-state levels of serum IgA-IgG (B.)
- Leading to reduction in pathogenic immune deposits in kidneys (D, E).
- Reversible effect following treatment discontinuation suggesting need for chronic anti-APRIL antibody administration

TARGETING APRIL REDUCES PROTEINURIA AND PRESERVES KIDNEY FUNCTION IN gddY MICE

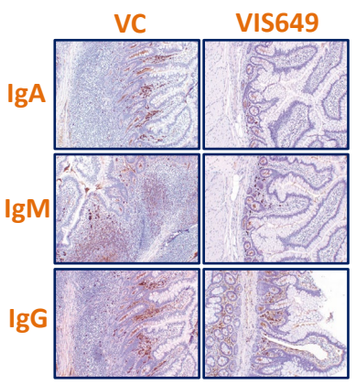
Proteinuria (uACR)



- Treatment with anti-APRIL antibody suppresses proteinuria, maintaining uACR at baseline relative to VC.
- Treatment efficacy is maintained following discontinuation of treatment after 4 weeks, suggesting prolonged benefit.

Non-Human Primates

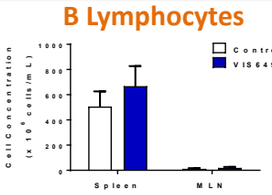
VIS649 REDUCES Ig+ B CELLS IN GALT



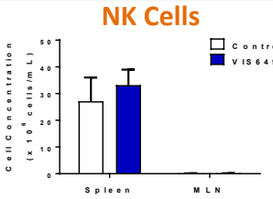
- Reduction in IgA-, IgM-, IgG-positive mononuclear cells in the gut-associated lymphoid tissue (GALT) in a subset of individual VIS649-treated animals (25 mg/kg dose). compared to control animals.
- Similar effect of VIS649 treatment on histology observed in GALT and tonsils in follow up GLP NHP study suggesting a mucosal effect consistent with APRIL immune mechanisms (data not shown).
- No apparent effect on Ig+ B cell population in bone marrow as assessed by cytology (data not shown).

VIS649 TREATMENT DOES NOT GLOBALLY PERTURB CELLULAR IMMUNE POPULATIONS IN TISSES OR PERIPHERAL BLOOD IN NON-HUMAN PRIMATES

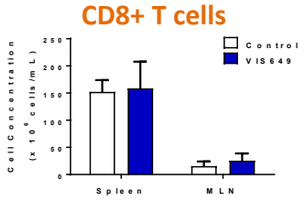
B Lymphocytes



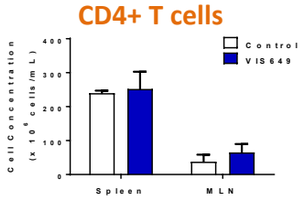
NK Cells



CD8+ T cells



CD4+ T cells



- No effect of VIS649 treatment (25 mg/kg for 8 weeks) on total B-, T-, or NK cell populations in peripheral compartments evaluated (spleen and mesenteric lymph node).
- Immune profiling of PBMCs also unaffected by VIS649 treatment (data not shown).

SUMMARY

These data validate an APRIL-targeting strategy for potent reduction in key pathogenic, immune-based mechanisms of IgAN disease and progression, point to a selective mechanism of target engagement and immunomodulatory activity, and along with the very favorable safety, pharmacokinetics, and pharmacodynamics of VIS649 in non-human primates described elsewhere (**Abstract 0090**) support the advancement of VIS649 development into human clinical trials.