Characterization of VRDN-001, a High Affinity and Potent anti-IGF-1R Inhibitory Antibody for the Treatment of Thyroid Eye Disease

RACHEL NEWELL, LINDA PESTANO, ANGELA SHE, VAHE BEDIAN

INTRODUCTION

VRDN-001 is an antagonist antibody to insulin-like growth factor-1 receptor (IGF-1R) under development by Viridian Therapeutics for potential treatment of Thyroid Eye Disease (TED). TED is driven by Thyroid Stimulating Hormone Receptor (TSHR) agonistic autostimulants and cross-talk between TSHR and IGF-1R. TED is characterized by recruitment of fibrocytes that express IGF-1R and TSHR in orbital tissues, where they mediate deposition of hyaluronan and expansion of orbital muscle and fat. IGF-1R antagonism has been found to reverse this orbital tissue expansion and robustly relieve symptoms in TED patients.

VRDN-001 is a humanized monoclonal targeting IGF-1R. VRDN-001 shares the same amino acid sequence as AVE1642, previously developed for oncology. Clinical data from this prior program showed a robust PD profile and safety profile in oncology patients, with suggested receptor saturation at doses as low as 3 mg/kg.

Here, we evaluated the IGF-1R binding and antagonist characteristics of VRDN-001.

METHODS

Surface plasmon resonance (SPR): Antibodies were captured by immobilized anti-Fc, and recombinant IGF-1R extracellular domain (ECD) was flowed as analyte. Association and dissociation rate constants (k_a and k_d, respectively), and equilibrium dissociation constant K_D were derived by global fit of data to single site model.

Cell binding: A549 human lung adenocarcinoma cells or primary human corneal stromal fibroblasts (HOCF) were incubated with varying concentrations of VRDN-001 or teprotumumab. Cells were then washed and incubated with FITC-labeled goat anti-human Fc secondary antibody for 30 minutes at 4°C. Phosphorylated IGF-1R (pIGF1R) of biological duplicates was measured using the R&D Systems pIGF-1R ELISA kit. Cytometric analysis was performed using a flow cytometer and FlowJo software. Dose curves were fitted using a non-linear regression model; log(inhibitor) vs response-variable slope (four parameters).

Cell internalization: Cells were incubated with varying concentrations of antibodies of interest at 4°C and 37°C for 60 minutes. Cells were then washed and incubated with FITC-labeled goat anti-human Fc secondary antibody for 30 minutes at 4°C. The MRI of viable cells was measured by flow cytometry and the data were analyzed using FlowJo software.

Cell surface marker expression: HOCF cells were incubated with directly labeled antibodies or IgG1 isotype control for 30 minutes. The median fluorescence intensity (MFI) of viable cells was measured by flow cytometry and the data were analyzed using FlowJo software.

Antagonism: Cell binding was measured by flow cytometry and the data were analyzed using FlowJo software.

VRDN-001 binds A549 cells with sub-nanomolar EC_50 concentrations. VRDN-001 potently inhibits IGF-1 stimulated IGF-1R phosphorylation on A549 (IC_50 = 0.4 nM). VRDN-001's potential to reverse TED pathophysiology and improve symptoms in a randomized placebo-controlled trial in TED patients.

DISCUSSION

• VRDN-001 and teprotumumab epitopes on IGF-1R overlap
• VRDN-001 binds to IGF-1R on cells with sub-nanomolar EC_50
• VRDN-001 promotes IGF-1R internalization
• VRDN-001 inhibits IGF-1R phosphorylation with sub-nanomolar IC_50
• VRDN-001 binds, antagonizes, and internalizes IGF-1R at sub-nanomolar concentrations, suggesting potential for potent inhibition of the pathophysiology driving TED. Viridian plans to interrogate VRDN-001's potential to reverse TED pathophysiology and improve symptoms in a randomized placebo-controlled trial in TED patients.

ACKNOWLEDGEMENTS

SPR, epitope binning, and internalization assays conducted at FairJourney Biologics.

References:

*VRDN-002 is another anti-IGF-1R monoclonal antibody being developed by Viridian Therapeutics for investigation in TED. See poster #37.*