ALN-TMP: A Subcutaneously Administered RNAi Therapeutic Targeting Tmprss6 for the Treatment of β-Thalassemia

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Abstract

Blood

>90% suppression of Hepcidin mRNA
>2x increase in serum hepcidin
Combination with transfusion and chelation
>50% decrease in serum iron, transferrin saturation

RNA interference
Serum hepcidin vs hepcidin mRNA
0.5-1 million copies/cell
Stand alone therapy

TfSat vs serum hepcidin
Reduce dietary iron uptake, prevent non-transferrin bound iron (NTBI) accumulation

ALN-TMP: A Subcutaneously Administered RNAi Therapeutic Targeting Tmprss6 for the Treatment of β-Thalassemia

ALN-TMP is an siRNA-GalNAc conjugate targeting hepatic Tmprss6, which in the β-Thalassemia disease setting, corrects ineffective erythropoiesis, ameliorates anemia, and mitigates secondary iron overload.

Previously, we demonstrated that intravenous administration of an siRNA targeting hepatic Tmprss6 gene suppression for up to 3 weeks post-dose. This leads to concomitant increases in RISC degradation of Tmprss6 mRNA, removes this negative regulator, ultimately leading to an increase in Hepcidin mRNA concentration.

Consequently, Hepcidin mRNA increases in parallel with a decrease in Tmprss6 mRNA. The β-Thalassemias are a group of hereditary blood disorders resulting from insufficient beta globin production, ultimately giving rise to the th3/+ Tmprss6 gene, which encodes for the protein Matriptase-2 which negatively regulates Hepcidin gene expression by cleaving the Hepcidin regulatory protein Tmprss6.

In animal studies, Tmprss6 mRNA is decreased as early as 1 day after treatment, and Hepcidin mRNA increases to peak 3 days post-dose. This effect is conserved across species and suggests ALN-TMP is a potent RNAi therapeutic with the potential producing disease modifying effects in patients.

The therapeutic hypothesis is systemic iron restriction reduces iron overload, ameliorates Thalassemia Intermedia disease phenotype. "The mean value; error bars represent the standard deviation of each dose level. Data fit to Hill equation. Fitted single dose mean value; error bars represent the standard deviation of each dose level."

Figures

Figure 1. ALN-TMP therapeutic approach

Figure 2. ALN-TMP therapeutic hypothesis

Figure 3. Single-dose administration of ALN-TMP

Figure 4. Multi-dose administration of ALN-TMP

Figure 5. Correcting Tmprss6, hepcidin, and serum iron

Summary

ALN-TMP is an RNAi therapeutic targeting hepatic Tmprss6, which encodes for the protein Matriptase-2. In animal studies and human disease models, ALN-TMP reduces hepatic Tmprss6 mRNA, increases Hepcidin mRNA, reduces serum iron, and improves anemia. This therapeutic approach reduces iron overload in a disease modifying manner.

References