Alpha 1 Antitrypsin MZ Information & Research

News & Research Update

Jun 1, 2024

Dear Subscribers,

In this issue an update on the development of RNAi medication for Alpha1 patients with a liver disease associated with AAT deficiency. (Alpha 1 patients with the "Z" allele)

1. **RNAi therapeutics.** (Medicines)

What causes the liver problems

The liver or liver related problems, are induced by the so called "Z" mutation of the **SERPINA1 gene** which is inherited, and this mutation causes the abnormal formed production of the Alpha 1 Antitrypsin protein in the liver. This abnormal formed "Z" type protein gets "stuck" in the liver cells and may cause a reduced functional capacity of the liver and liver fibrosis/cirrhosis.

How RNAi Works

RNAi is a natural biological process in your body that **regulates gene expression** by interfering with messenger RNA (mRNA), which carries the DNA's instructions for making new proteins, (like the AAT protein), and as such regulates the amount of AAT produced.

RNAi therapeutics medication mimic this process by delivering specially designed small interfering RNAs (siRNAs) that bind to the disease causing mRNA and guide their destruction, and as such reduces the misfolded "Z" protein production in the liver.

You can find a more elaborated description on the Arrowhead website;
https://arrowheadpharma.com/patients-caregivers/what-is-rnai/

2. **Arrowhead / Takeda** (latest update)

Phase 2 trial of Fazirsiran

In Jan 2023 there was a press release from Arrowhead and Takeda about the results of their Phase 2 trial to test the safety and efficacy of Fazirsiran, which is an RNA interference therapeutic.

16 PiZZ patients with liver fibrosis were tested over a period of 18 months, and received a subcutaneous injection with Fazirsiran on day 1, then after 4 weeks and followed every 12 weeks. The result was a reduction of total liver Z-AAT of ~94% at the postbaseline liver biopsy visit.

PAS-D globule burden, a histological measure of Z-AAT accumulation in the liver cells, was reduced from a baseline mean of 5.9 to a mean of 2.3 at the postbaseline liver biopsy visit. Improvement in portal inflammation was observed in 42% of patients while only 7% showed worsening. Lastly, 50% of patients achieved an improvement in fibrosis of at least one point by METAVIR stage.

Phase 3 trial of Fazirsiran

In March 2023 Takeda started their Phase 3 trial, which is a randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of Fazirsiran in the treatment of alpha-1 antitrypsin deficiency–associated liver disease with METAVIR stage F2 to F4 fibrosis. Approximately 160 patients will be randomized 1:1 to receive Fazirsiran or placebo. The primary endpoint of this study is a decrease from baseline of at least 1 stage of histologic fibrosis METAVIR staging in the centrally read liver biopsy done at Week 106 in patients with METAVIR stage F2 and F3 fibrosis.
Note: The clinicaltrials.gov website mentions a preliminary end date of March 2027 and an estimated end date of March 2029

3. Summary / Opinion

The RNAi therapeutics, which are in development by Arrowhead / Takeda, provides for an excellent solution to prevent liver and liver induced morbidities in patients which inherited the “Z” gene(s).

Arrowhead and Takeda currently address the market for ~200.000 “ZZ” patients, but not the ~35Mil “MZ” and additional “SZ” patients. This is quite weird out from our perspective, because based on biobank data, the market for MZ’s may be a lot more lucrative. Data shows that 7% of MZ’s develop liver related issues during pregnancy (for mother and child) which may be avoided. Which is already a market of >1Mil persons. On top of that the market for the mature older MZ’s, getting their first liver induced issues >40 years of age, is even larger, and may results in > 10x market size.

For the MZ’s there may be even more benefits, because the “M” AAT level will most likely improve. As we know, in the polymerization process in the ER of the hepatocytes, about 6% of the M is polymerized with the Z. So, you will get a more M when the Z is significantly reduced.
Because the liver capacity reduction, caused by the continues ER stress, it may also resolve the morbidities of persons which have really low AAT levels. The AAT level will probably increase back up when the liver gets more “room” and opportunity for regeneration, returning back to homeostasis.