LGMD-1D DNAJB6 Foundation

and

MYOSYND™

A 501 (C)(3)

8/16/2022

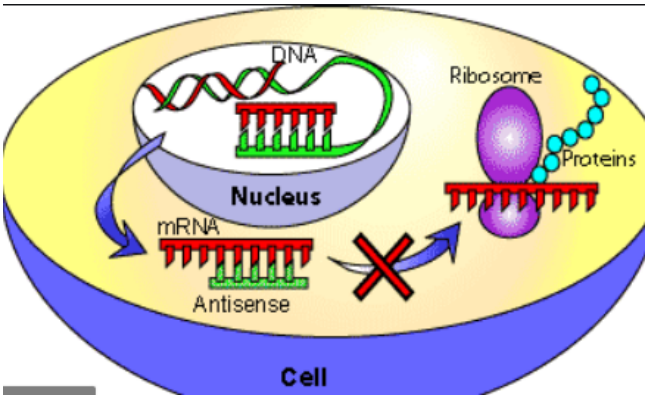
Volume: 1, issue: 9

Table of Contents:

Emerging Genetic Therapy

Blocking the protein expression of a bad gene is the key to curing the 8,000 monogenic conditions. This is true for the LGMDs whether autosomal recessive, dominant or X linked varieties. Gene editing like document editing allows for a permanent fix for a bad gene. Gene editing for LGMD is extensively reviewed HERE . CRISPR technology is the highlighted process but requires a neutered viral vehicle or other synthetic package to deliver the editor to the specific cell that is the target of gene repair. Each step in the CRISPR delivery has challenges.

Other methods of blocking bad protein production are called ASOs (antisense oligonucleotides) and RNAi (interfering RNA) which given periodically can block a bad protein but requires continued dosing. ASOs and RNAi achieve the same endpoint as far as blocking the bad protein and they are discussed in detail for LGMD HERE. The illustration and video link below show the relatively simple pathway to block any protein production.



Four minute video HERE

Emerging Genetic Therapy

The following article and 2 minute video (page 4) from the New England Journal of Medicine August, 2022 illustrate the use of a RNAi to reverse a severe autosomal recessive liver condition called Alpha-1 Antitrypsin Deficiency. The important details are as follows:

1. **As a delivery system to the liver, the RNAi therapy was attached to a molecule that helps bind to the liver, not a viral vector (viral vectors/vehicles are needed in the more complex gene therapies like CRISPR). In this study, RNAi attached to a small molecule avoided immune system interaction seen with therapies involving viral vectors.**
2. **The subcutaneous injections given every 3 months were safe and effective with documented improvement in the majority of cases.**
3. **This type of injection can be done at home as opposed to a hospital or infusion center.**
4. **On an editorial note, ASOs are currently being used for Duchenne's muscular dystrophy, spinal muscular atrophy, familial hypercholesterolemia with many more in the pipeline. This technology is applicable to all LGMDs and is being actively pursued.**

RESEARCH SUMMARY

Fazirsiran for Liver Disease Associated with Alpha$_1$-Antitrypsin Deficiency

Strnad P et al. DOI: 10.1056/NEJMoa2205416

CLINICAL PROBLEM

The gene *SERPINA1* encodes alpha$_1$-antitrypsin (AAT). Patients with a homozygous "Z" mutation in *SERPINA1* (i.e., the proteinase inhibitor [PI] ZZ genotype) have AAT deficiency owing to production of a mutant protein called Z-AAT. Accumulation of Z-AAT in hepatocytes can lead to progressive liver disease and fibrosis, and targeted treatments are needed.

CLINICAL TRIAL

Design: A phase 2, multinational, open-label trial examined the safety, pharmacodynamics, and efficacy of fazirsiran, an RNA interference therapeutic, in patients with liver disease associated with AAT deficiency.

Intervention: 16 patients with the PI ZZ genotype and fibrosis received subcutaneous fazirsiran (100 mg or 200 mg) on day 1, at week 4, and every 12 weeks thereafter. The primary end point was the change from baseline over time in liver Z-AAT concentrations, assessed by means of liquid chromatography–tandem mass spectrometry of liver-biopsy samples.

RESULTS

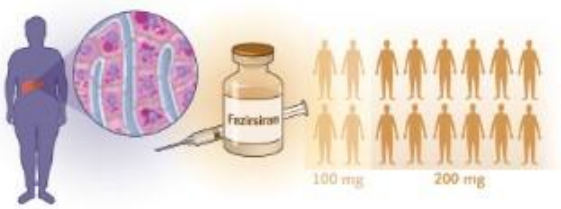
Efficacy: All 14 evaluable patients had reductions in total liver Z-AAT concentrations at week 24 or 48 of follow-up.

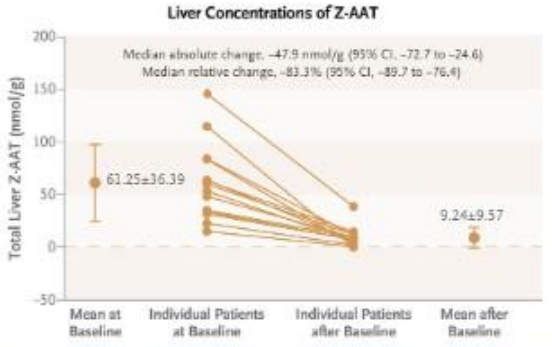
Pharmacodynamics and Safety: Serum Z-AAT concentrations decreased in all patients. The nadir was reached at week 6. Over a period of 1.5 years, no deaths, treatment discontinuations, or dose interruptions occurred. Four serious adverse events — viral myocarditis, diverticulitis, dyspnea, and vestibular neuronitis — were reported, and all resolved.

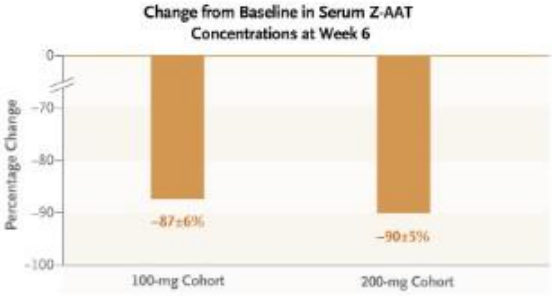
LIMITATIONS

- The trial was small and lacked a control group.

Links: Full Article | NEJM Quick Take

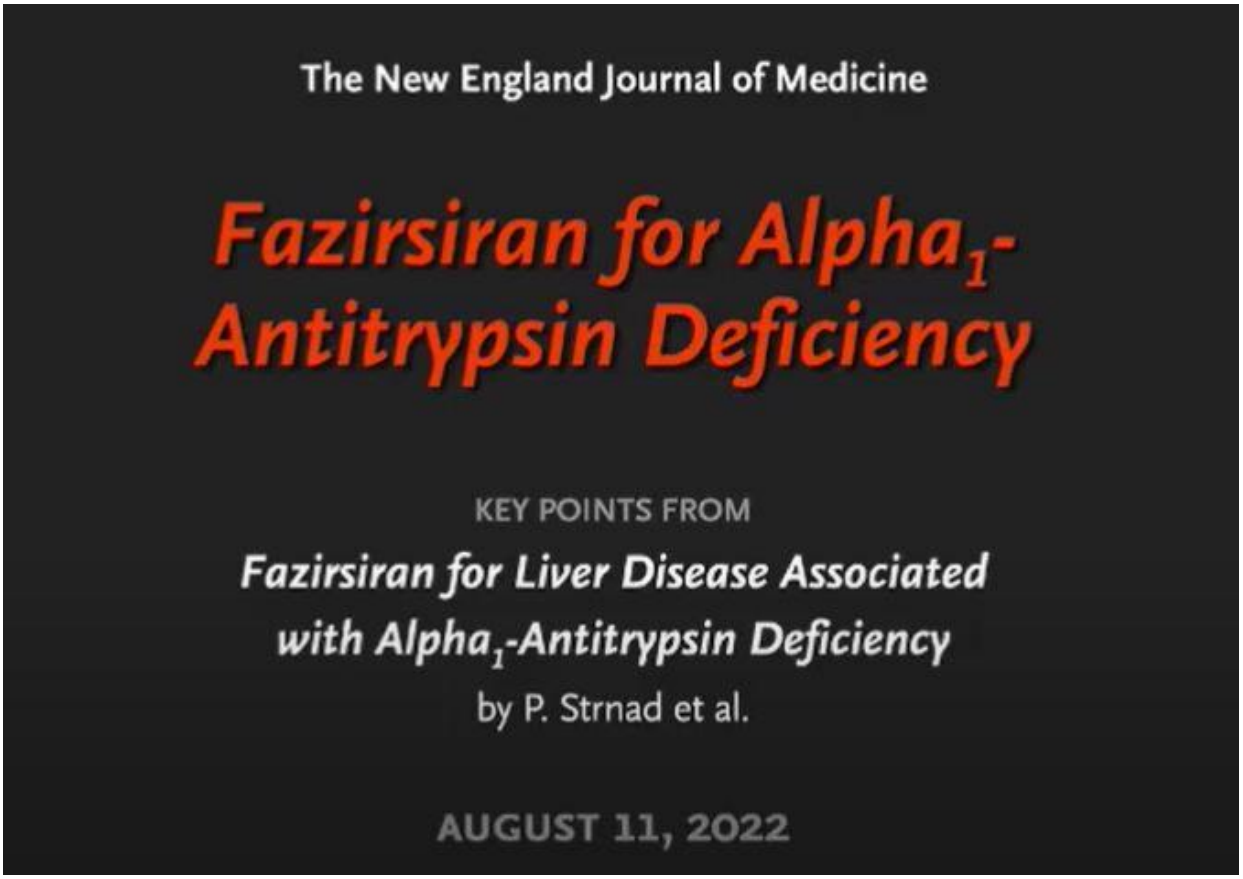






CONCLUSIONS

In a small trial involving patients with AAT deficiency–associated liver fibrosis, the RNA interference therapeutic fazirsiran reduced concentrations of Z-AAT in the liver and serum, without apparent safety concerns.



Two minute video [HERE]

Important Links

Since our inception in 2018 we have collected links to help everyone's journey. Due to the onboarding of new members and new links I am adding this as an evergreen list to our newsletter.

LGMD1D DNAJB6 Foundation

LGMD1D Foundation YouTube Archive

LGMD1D Foundation assisted sponsored genetic testing

LGMD1D Foundation Autosomal Dominant Registry

LGMD1D Foundation: Solving Your Variant of Uncertain Significance (VUS)

Sponsored Whole Genome Sequencing: (next step for VUS resolution)

NIH

Harvard

Are You Having a Muscle Biopsy?

Tissue referral to University of Iowa

University of Iowa Muscle Biopsy Requisition

Do I really have a genetic muscle disorder? See HERE

Gene matching sites: MyGene2, GenomeConnect, Rare-X

Upcoming Events

LGMD Awareness Foundation Calendar 2022

Speak Foundation FaceBook 2022

Ways to Donate

1. **OUR WEBSITE** **(a secure site with all the listings below)**
2. **AMAZON SMILE** **(list the LGMD-1D DNAJB6 Foundation for donation with each purchase at no cost to you.)**
3. **PAYPAL** **(Our foundation's secure site)**
4. **CREDIT CARD** **(Network For Good credit card portal)**
5. **VENMO** **(@lgmd1d) Foundation Account**
6. **EVERY.ORG** **(ALL CRYPTO CURRENCIES)**
7. **SQUARE**
8. **If you are over 72 consider a Qualified Charitable Distribution (QCD) from a traditional IRA and lower that dreadful RMD and avoid that higher tax bracket. Also available to Roth IRA participants.**

   RMD calculator HERE, medicare income bracket HERE. tax bracket for SS HERE.

Thank you for your support and all the best from us!

William Lowery MD