alpha-1 ORGANISATION AUSTRALIA INC

Alpha Times

Newsletter of Alpha-1 Organisation Australia inc *Issue 16/17 Autumn/Winter 2024*

From the President's Pen

Hi everyone,
Living with a rare disease is usually very challenging, especially when treatment is too expensive to privately purchase, you may not qualify for a clinical trial, or a desired trial is not offered in Australia. Other rare disease challenges relate to receiving a late diagnosis after years of seeking answers or living with chronic fatigue or pain. Most rare diseases (there are over 7,000 recognised) have no cure which can cause hardship, worry and dependency. The good news, however, for patients diagnosed with Alpha-1 Antitrypsin Deficiency is that this typically gloomy story may be about to change due to the smorgasbord of clinical trials currently on offer and news of other studies coming to Australia. New studies include inhaled antitrypsin and those offering precision genetic interventions or RNA editing trials that don't change genes but help secrete functional Alpha-1 protein. While we wait for emerging treatments, everyone needs to be their best advocate and live the best life possible. If anyone needs support, please consider joining our monthly Zoom patient support meetings.
On a different note, I would like to advise that we hold our Annual General Meeting (AGM) in August each year. At the AGM we appoint the Board for the next year. To support the annual replacement/renewal of Board members I call for nominations towards the end of July. If you would like to be considered as a Board member you can let me know prior to the end of July by emailing me at pres.a1oa@gmail.com. Please note: to be a Board member you will need to be a financial member of our charity. You can email contactus.a1oa@gmail.com to indicate that you would like to become a financial member at an annual fee of $20 or jump onto our website via Membership Tickets, N/A | TryBooking Australia to join up.

Wishing you all the best,
Gaynor Heading
President A1OA

Mental Health First Aid

Alpha-1 Organisation Australia has an accredited Mental Health First Aider who is ready to help if you are not coping after a diagnosis of A1AD for yourself or a family member. A new diagnosis can cause mental distress, anxiety, or depression. Please reach out to mentalhealth.a1oa@gmail.com

2024 AGM Mon 12 Aug 7pm AEST

Are you altruistic? An optimist?
Or
Why would you take part in a drug trial?

Clinical trials are essential in the process of bringing a drug to market. The process is a long one, with a defined and rigorous sequence of events to be followed.

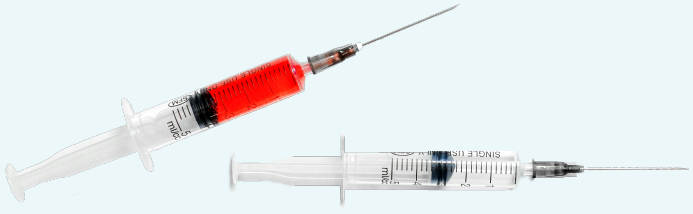
Often the first step is animal testing to determine if the drug has the desired effect in animals specially bred with the condition under study. If this is found to be efficacious, testing proceeds to stage 1 of human testing. In this phase, the drug is tested on a small number of people to check for any major unwanted side effects and to ensure that the drug is effective in treating the condition that it is targeting. If the drug passes this stage, it then proceeds to stage 2, in which a large sample of patients is recruited, and the process is repeated. After successful completion of stage 2, stage 3 is initiated. In this phase, a large cohort of patients is recruited with this stage typically lasting 3 plus years.

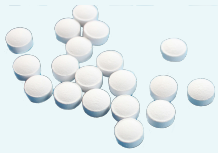
Generally, trials have 2 streams and sometimes 3 if different dosages are being compared. In order to determine if a drug is having the desired effect, there needs to be a control group to compare with the group that is receiving the treatment, the treatment group. For this reason, most trials are “double blind”, i.e. people are randomly assigned to one of the groups so that the doctor overseeing the trial as well as the nurse administering the treatment doesn’t know which patient is in which group. This is necessary to avoid any unintentional bias in the trial.

Would you enrol in a drug trial? What are the factors you would take into consideration? Things you would need to know are the time commitment involved, what are the potential side-effects you might experience, what tests you would need to undergo, how frequently and how invasive they are, is travel to the trial venue subsidised.

People join clinical trials for different reasons; some in the hope that they will be in the treatment group, and some who don’t see a benefit for themselves directly but hope that their participation will benefit future sufferers of the condition.

What do you think? Will you take part?





Clinical Trials

In layman's terms, clinical trials are a crucial part of the process in research and development of new treatments. In the case of alpha-1 antitrypsin deficiency these trials have historically been focussed on augmentation therapy, whereby a human blood derived product containing antitrypsin is infused into patients with the aim of increasing the level of antitrypsin, thereby lessening lung damage. Some A1OA members have taken part in one such trial in Australia (the Grifols SPARTA trial) which has now closed to new patients.

The good news is that several drug companies around the world are now adopting new approaches to treating A1AD in three main categories:

1. The development of antitrypsin products not dependent on human blood (thereby providing an increased supply at reduced cost)
2. The development of drugs designed to counter the effects of misfolded protein in the liver (thereby preventing cirrhosis and other liver damage), and
3. The development of gene editing techniques, whereby the impact of 'defective' genes is addressed in the liver (thereby preventing liver damage and/or raising antitrypsin levels in the blood and preventing lung disease)

With the number of drug companies doing research in this field there are many clinical trials in various stages of development (in the pipeline or underway as Phase 1/2 or 3). We are currently aware of the four below which either are, or will be available to Australian alphas this year (correct as of June 2024):

1. NCT05677971. A study by Arrowhead Pharmaceuticals to determine whether the drug Fazirsiran can help limit liver damage – running in South Australia and Victoria
2. NCT04764448. A study by Dicerna Pharmaceuticals to determine whether the drug Belcesiran can help limit liver damage – running in Victoria
3. NCT05856331. A study by Inhibrx Inc to determine whether their INBRX-101 recombinant alpha-1 proteinase product compares to blood derived product in raising antitrypsin levels – running in Queensland, South Australia, Victoria and Western Australia
4. NCT04204252. A study by Kamada Pharmaceuticals to evaluate the efficacy and safety of "Kamada-AAT for Inhalation" 80 mg per day – running in WA and elsewhere

(Note – the trial numbers above are those assigned by the US based National Library of Medicine which maintains the most comprehensive record of worldwide clinical trials here - Home | ClinicalTrials.gov.)

In addition to these trials which are underway, more exciting trials are planned to run in Australia (expected late 2024/early 2025). While locations and dates are yet to be finalised, Beam Therapeutics (www.beamtx.com) is planning to trial the Beam-302 product which aims to correct the PiZ mutation in the liver, and A1OA has been in discussions with Korro Bio (www.korrobio.com) regarding bringing their RNA editing approach to Australia as a

trial. Other companies (e.g. Wave Life Sciences - Wave Life Sciences) are also developing trials which may benefit those with A1AD.

Information about clinical trials is changing rapidly, but we aim to keep abreast of clinical trials planned and underway in Australia and will provide updates as we become aware of new trials, as well as reporting promising results of trials around the world. If you have any questions or information about trials (past/current or upcoming) you'd like to share, just drop us a message at contactus.a1oa@gmail.com 😊.

To keep up to date with clinical trials in Australia, visit
https://www.australianclinicaltrials.gov.au/

Moving Beyond Augmentation Alone: New Approaches to Treating Alpha1

By Assoc. Prof. Brooks Thomas Kuhm. Talk given at the Alpha1 Foundation 2024 Conference, Sacramento, USA

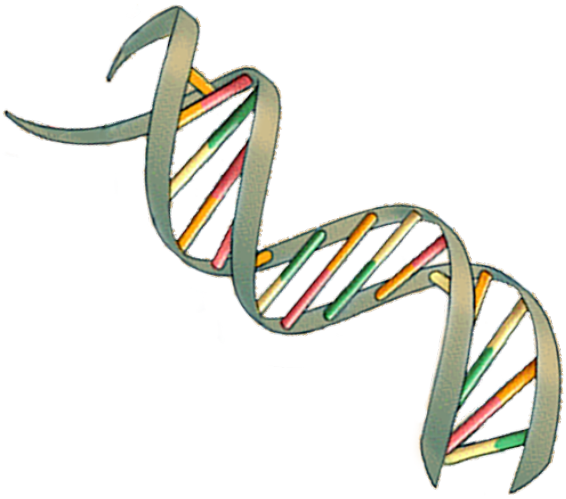
Key points were:

- Weekly infusions of alpha1 antitrypsin are the most common treatment but this has no effect on the liver damage. This is a limited resource as requires large numbers of blood donors and weekly infusions are difficult especially in rural areas.
- Two studies showed that higher doses of alpha1 antitrypsin lead to fewer lung flare-ups (exacerbations). The SPARTA stage 111 trial is now looking at double versus standard dose of alpha1 antitrypsin and has 329 patients enrolled for over 3 years.
- Kamada has started a phase 111 trial looking at inhaled manufactured alpha1 antitrypsin given by a special nebulizer with most trial patients in Europe. Unfortunately, inhaled alpha1 antitrypsin had a short half-life so must be given once or twice daily.
- INBRX has started a trial with recombinant lantitrypsin fusion proteins that have a long half-life. Theoretically this is scalable, and these proteins could be made in a large lab as this doesn't need blood donors. Phase 1 trial which looked at safety and efficacy showed the levels could last up to 3 to 4 weeks and were very safe. The next step is ELEVATE trials in the USA (UC Davis and UCLA) which is phase 11 and 111 and looking at higher doses and will compare every 3 and every 4 weeks dosing.
- The Australus trial is looking at oral tablets to reduce inflammation and proteinase but it is early days yet.

- "Fazirsiran for liver disease associated with Alpha1 Antitrypsin Deficiency" has been published in the New England Journal of Medicine. Fazirsiran turns off the Z protein expression which causes local liver damage. Turning off the Z protein doesn't matter as it provides little protection to the lungs. Alpha1 antitrypsin blood and liver levels are reduced, as are liver inflammation markers. Currently in trials.
- Gene targeted therapies are the goal, but the challenge is to not make other unfavourable changes despite only 1 known gene being involved. Treatment is aimed at benefiting both lung and liver patients. Currently enrolling healthy MM people for a Phase 1 trial.
- Vertex is researching small molecules that untangle and fix the broken protein (alpha1 antitrypsin) and then it can be released into the blood. Vertex has a great track record with cystic fibrosis therapy.

What is Gene Editing?

"Gene editing" refers to making changes to specific nucleic acid sequences in genetic material at the cellular level. The CRISPR (clustered regularly interspaced short palindromic repeats) system has been well documented in the media and is considered to be "efficient, convenient and programmable, leading to promising translational studies and clinical trials for both genetic and non-genetic diseases". Congting Guo, Xiaoteng Ma , Fei Gao, Yuxuan Guo). Often the name CRISPR is written CRISPR)/Cas9. Cas9 refers to the enzyme, obtained from the bacterium Streptococcus pyogenes, which is used to cut the double stranded DNA at the gene sequence that is the target of the procedure.



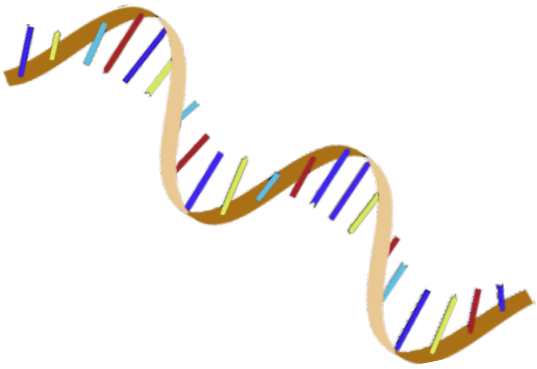
DNA double helix

Artwork by Leonie Robison

Off Target Effects in genome editing

CRISPR systems rely on creating a double strand break in DNA (DSBs). This can result in unwanted mutations and mosaicism, as well as off-target cleavage, chromosomal structural variations and exogenous DNA integrations have raised concerns for clinical safety and potentially deleterious outcomes.

Numerous types of approaches have been developed to reduce off-target effects. Wang et al (16) have developed an improved system, single-strand annealing proteins (SSAPs). In this they coupled microbial SSAPs with catalytically inactive dCas9 for gene editing. This is a cleavage-free gene editor, dCas9–SSAP, and promotes the knock-in of long sequences in mammalian cells. This was found to have low on-target errors and minimal off-target effects, showing higher accuracy than standard Cas9 methods.



Strand of RNA

Artwork by Leonie Robison

Base Editing

Base editing is a newer technology than CRISPR, a more precise technique that chemically changes just one base or “letter” of the genetic code without causing a double-strand break in DNA like CRISPR does. An important characteristic of a therapeutic genome editor is high editing efficiency.

A major restriction of base editing is the limited types of base pair conversions (C•G to T•A and A•T to G•C only). Additionally, early base editors were limited in their targeting scope due to the restrictive editing window being limited to positions 4 through 8 in the most widely used editors. The most important limitation of base editors from a therapeutic perspective are unintended edits. These can be “bystander edits”, occurring in the same area as the intended edit, the wrong type of edit being installed at the target nucleotide, e.g., C•G instead of T•A), or “off-target edits”, which occur at a different locus in the cell. These unintended editing events may be benign or deleterious.

Techniques have improved and continue to do so, making base editing much safer to use in vivo.

Alpha1 Liver Disease

Dr Charlie Strange's talk at the 2024 Alpha1 Foundation Conference Sacramento, USA

Key points were:

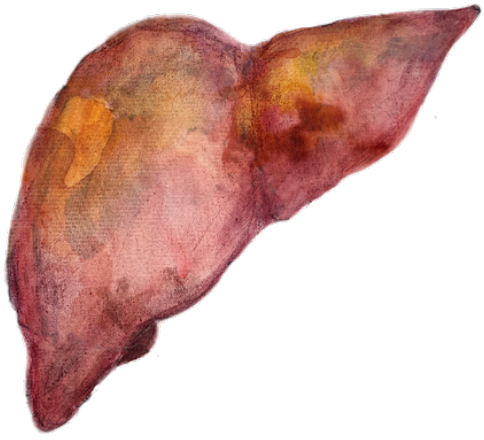
- Liver disease is caused by retained misfolded Alpha1 antitrypsin which is stuck inside the liver cells.
- The defective gene is on chromosome 14 but if changing your DNA, you want it to be changed just in the liver.
- Approximately 1/3rd of patients present with liver disease but 2/3rds present with lung disease. Liver specialists generally check for Alpha1.
- ZZ patients get liver disease but not ZNull patients as ZNull make no Alpha1 to store in the liver.
- Fatty liver is now called metabolic syndrome liver disease. Fatty livers develop scarring over time.
- It is recommended that all ZZ patients get an ultrasound annually to pick up early liver cancers after age 50 years. Liver cancers can be cut out if caught early. Liver cancers don't spread early on like some other cancers.
- If the liver gets a lot of scar tissue the blood from the gut can't get through the liver easily so you get portal hypertension and the blood is diverted elsewhere e.g. to the spleen (making it large), oesophagus (varices) or large intestines (haemorrhoids). It can also affect your brain.
- In severe cases of liver disease, you get ascites (fluid in the abdomen).
- Liver disease affects platelet and clotting factor manufacture. Liver enzymes can increase and more importantly can get an increase in bilirubin.
- Liver biopsies check for scar tissue but have a 1 in 1000 chance of bleeding.
- General therapy for liver disease is as follows:
    - Lose weight if overweight
    - Limit alcohol consumption
    - Vaccinate for Hepatis A and B and screen for C
    - Annual liver blood tests and ultrasound after age 50.
    - If portal hypertension is diagnosed, use a beta blocker
    - Stop taking aspirin and non-steroidals
- There are 3 current trials underway, including an injection of Fazirsiran every 3 months.

Non-alcoholic fatty liver

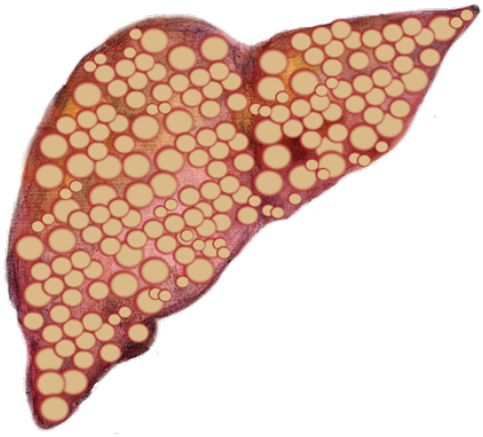
Non-alcoholic fatty liver disease, NAFLD, can affect people who drink little to no alcohol. In NAFLD, too much fat builds up in the liver. It is seen most often in people who are overweight or obese but can also be a complication of Alpha-1 Antitrypsin Deficiency. NAFLD is becoming more common as the number of people with obesity rises. It is the most common form of liver disease in the world. NAFLD ranges in severity from hepatic steatosis, called fatty liver, to a more severe form of disease called non-alcoholic steatohepatitis (NASH).
NASH causes the liver to swell and become damaged due to the fat deposits in the liver. NASH may get worse and may lead to serious liver scarring, called cirrhosis, and even liver cancer. This damage is like the damage caused by heavy alcohol use.
Research supporting this was done by Huan Su, et al and published in *Liver International* in the *Wiley Online Library.*

https://www.mayoclinic.org/diseases-conditions/nonalcoholic-fatty-liver-disease/symptoms-causes/syc-20354567
https://onlinelibrary.wiley.com/action/doSearch?ContribRaw=Su%2C+Huan&SeriesKey=14783231

Healthy liver

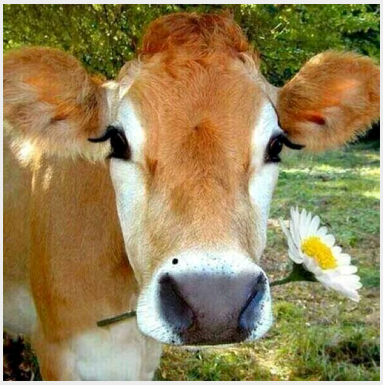


Liver with fatty deposits



Artwork by Leonie Robison

Benefit to the liver of not eating meat



An interesting study was recently published showing that reducing meat intake can have a beneficial effect on the liver in patients with cirrhosis. The study was limited by its small sample size, focussing on the impact of only one meal, lack of clinical outcomes, sarcopenia assessment, cognitive testing, or urine collection.

Despite this, the authors concluded that intermittent meat substitution with vegetarian or vegan alternatives could be helpful in reducing ammonia generation in cirrhosis. This is important as with cirrhosis the liver is unable to excrete ammonia normally and ammonia therefore builds up in the blood and around the brain, causing confusion and the development of other symptoms, including irritability, headache, vomiting, and gait abnormalities in milder cases. In severe cases seizures, encephalopathy, coma, and even death can occur.

Larkin, M. (7)

Long term overeating leads to liver disease

There are many studies on the deleterious effects on the liver of overeating. One such is by Yasatuke, K., et al. (17)
A study on mice that were fed a long-term high fat diet (HFD) for 24 and 52 weeks found that animals had more liver fibrosis, enhanced numbers of inflammatory cells as well as increased Kupffer cell activity (Kupffer cells are liver macrophages that play a critical role in maintaining liver functions. They are immune cells and protect the liver from bacterial infections). Increased hepatocyte cell turnover and ductular proliferation were evident in the mice livers. Microbiome diversity was decreased after HFD feeding and the mice had more faecal bile acids.

Surprising Things that can Damage Your Liver Summarised from Sheik (13)

Sugar

The liver uses sugar to make fat, too much causes a build-up that can lead to liver disease. Some studies show that sugar can be as damaging to the liver as alcohol, even if you're not overweight.

Herbal Supplements

Natural is not necessarily good for. For example, the herb kava kava, that some women take for relief of menopause symptoms, can interfere with the proper working of the liver. Check the safety of any herbal supplement before taking.

Being Overweight

The extra fat can build up in your liver cells, leading to NAFLD. The liver can swell, harden and scar (cirrhosis). NAFLD is more likely if you are overweight, middle aged, or have diabetes. Diet and exercise can help turn this around.

Too much Vitamin A

We need vitamin A but too much is toxic to the liver. Excess is stored in cells in the liver and can lead to their activation and hypertrophy, excess collagen production and fibrosis. Vitamin A is readily available in fruit and vegetable and most people don't need to take as a supplement.

Soft Drinks

A correlation has been found between people drinking a lot of soft drinks and having NAFLD, possibly due to the sugar content.

Paracetamol

If you are experiencing pain, you might take a pain reliever. Always stick to the recommended dose, especially if taking more than one medication.

Trans Fats

These are man-made fats in many processed and fast foods, listed on packaging as “partially hydrogenated ingredients”, and make you more likely to gain weight.

Less alcohol than you might think

A standard drink is approximately 150ml of wine, 360ml of beer, 45ml spirits. It is recommended that women drink no more than 1 drink per day and 2 per day for men.

Foods that are Beneficial for the Liver

- Foods that are high in fibre such as oatmeal
- Broccoli and other vegetables
- Coffee
- Green tea
- Water
- Almonds and other nuts
- Spinach
- Blueberries
- Fruit

Pi*MZ Phenotype (MZ) and the Liver

As many Alphas with MZ phenotype have experienced there has been a dearth of research and peer reviewed publications on MZ phenotype and the liver. The good news is that during the last few years several studies have focused on the MZ liver as shown in the key findings below from a range of articles which highlight liver risks for MZ Alphas.

According to Murali AR, Prakash S, Sanchez AJ. (3) Alpha1-Antitrypsin Pi*MZ variant increases risk of developing hepatic events in non-alcoholic fatty liver disease (NAFLD) patients. They recommend that clinicians should consider testing for alpha1 antitrypsin phenotype in patients with NAFLD, and that patients with NAFLD should be counselled about increased risk of hepatic decompensation (i.e. the occurrence of severe functional damage of the liver and one or more complications of liver cirrhosis) and offered aggressive interventions.

Luukkonen et al (2) report that people with the Pi*MZ allele had a nearly 2-fold higher 10-year cumulative incidence estimate of liver-related out-comes (0.92%) as compared with noncarriers (0.55%) by competing risk analysis. This difference persisted at 20 years. When adjusting for age, sex, and BMI, Pi*MZ Alphas had significantly increased risk of liver- related outcomes. The impact of Pi∗Z appears to be markedly modified by obesity, highlighting the importance of lifestyle modification in counselling individuals with the Pi∗MZ genotype. Diabetes, alcohol use and smoking were not found to significantly modify the effect on liver-related outcomes in MZ Alphas.

Kaserman et al (1) found evidence that a single Z allele is sufficient to disrupt hepatocyte homeostatic function.

Aunty Alpha

Dear Readers,

Aunty Alpha is signing off for a while. If you have any questions about Alpha-1 related issues, you can still contact me at contactus.a1oa@gmail.com or through the A1OA newsletter newsletter.a1oa@gmail.com

Bye for now,
Your Aunty

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