alpha-1 ORGANISATION AUSTRALIA INC

Alpha Times

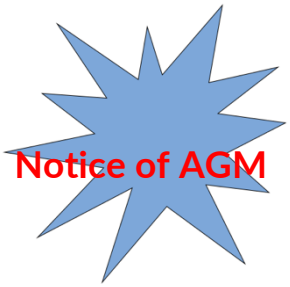
Newsletter of Alpha-1 Organisation Australia inc *Issue 13 Winter 2023*

From the President's Pen

Hi everyone,
Welcome to our Winter Edition,

If you know me at all, it will come as no surprise that this season I am talking about research. Scientific research plays such an important role in health, disease investment and disease management. Research has taught us many things e.g., that regular exercise can improve cognitive function, wellbeing and prevent some diseases. When it comes to Alpha-1 research there is a lot going on, especially in the form of clinical trials, but there is room for more research especially at the basic science and pre-clinical trial phase. Developing a researchable question is one of the important tasks that researchers face when initiating a project. However, while tools exist (e.g., PICO) to help researchers develop a focused question, it may be the wrong question from a patient perspective.
The interplay between Alpha-1 genetics and the environment is one area that is of interest to many, particularly when siblings or twins with the same Alpha-1 phenotype have different lung disease experiences. Another area often discussed is which inhalers work for individuals and why? We know that current inhaled treatments do not cure COPD (chronic obstructive pulmonary disease) and new treatments are very similar to those currently available - apart from inhaled antitrypsin currently under clinical trial, which offers great hope to lung-affected Alphas.
From my perspective many COPD questions (Alpha-1 emphysema and chronic bronchitis) remain unanswered. So, you can image my excitement this month when **a team of Australian COPD researchers** with an interest in Alpha-1 wellbeing and new treatments, **asked for consumer input** to help them form relevant COPD questions. Such questions could be linked to patient concerns, experiences or what patients see as research priorities!
There are potentially thousands of COPD research questions. If you have a potential COPD research question, I would love to hear it so I can forward it to this passionate group of researchers who are keen to make a difference to both Alpha-1 and non-Alpha-1 COPD patients. Please email your COPD related questions to president@a1oa.org.au.
Looking forward to seeing everyone's great COPD research ideas!

Wishing you all the best,
Gaynor Heading
President A1OA



A1OA AGM 2023

Monday 14 August
7pm AEST

Join the AGM via Zoom:

https://us02web.zoom.us/j/6269450754?pwd=ZkhlejhvZFlicTFEdDJrZkVPazFidz09

Meeting ID: 626 945 0754

Passcode: 345858

The Alpha-1 Foundation 2023 Alpha-1 National Conference

The US Alpha-1 national conference took place in Dallas this year (June).
Some international Alpha-1 patients did register for the conference knowing that time zones may preclude online attendance, and that presentations are taped and can be viewed online for many days after the conference, at a convenient time.
If you didn't register or missed this event the great news is that the Alpha-1 Foundation places conference highlights on its website and on Vimeo. View this year's highlights at 2023 Alpha-1 National Conference on Vimeo.

Some of the highlights of the 2023 event are listed below. Monitor the link for presentations.

Biomarker Consortium (presented by Andrew Wilson)

- A US biomarker consortium has been set up to follow a cohort of patients in the US patient registry with confirmed PiZZ Alpha-1 Antitrypsin Deficiency, to measure several biomarkers in blood and sputum and to obtain high resolution CT scans at baseline, 18 months and 3 years later. If the study can determine markers that allow the identification of patients at risk for lung function decline, the investigators may be able to study early interventions and find ways to avoid serious complications.
- *A biomarker is a quantifiable parameter that is measured and evaluated as an indicator of a disease process or a response to therapy.*

Imaging and predictors of mortality (presented by Mike Wells)

- The COPD Gene study – a large COPD study - has shown that CT lung density predicts mortality. "Emphysema progression on CT scans scored using a deep learning algorithm was associated with increased functional impairment and mortality at 5-year follow-up". "An increase in Fleischner emphysema grade on sequential CT scans using an automated deep learning algorithm was associated with increased functional impairment and increased risk of mortality" (Ash S.Y. et al. *Radiology*. 299: 222-231). More details: Emphysema Progression at CT by Deep Learning Predicts Functional Impairment and Mortality: Results from the COPDGene Study | Radiology (rsna.org)
- Lung CTs do not require the use of contrast "unless looking at blood vessels".
- Fewer airway branches predict mortality.
- Mucus plugs predict mortality.

Alpha-1 Liver Tests / Imaging (presented by Jeff Teckman)

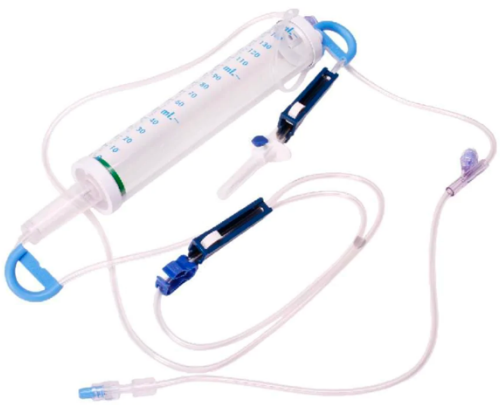
- No one test is adequate to monitor liver damage.
- ZZ and SZ phenotypes should have a baseline liver scan and when there is a change in symptoms.
- If cirrhosis has been diagnosed, six-monthly scans are required to monitor for liver cancer, as early surgery can lead to a cure.
- Ultrasound is only modestly good at finding liver damage. However, CAT Scans are good at finding liver damage.
- Elastography (e.g., Fibroscan) is good at detecting no cirrhosis and liver stiffness but is not so good with 'mid-range' results.
- As Alpha-1 Antitrypsin Deficiency tends to affect all the liver, a liver biopsy is useful. However, there could be a 15% difference between two samples.

Clinical Trials / Inhalers / Liver disease (presented by Mark Brantly)

- Patients should be self-empowered. Keep a book and record what happens with different treatments e.g., it is trial and error to see which inhaler works best for each individual.
- If a patient participates in a gene therapy clinical trial, then they will be ineligible for future studies.
- If you have liver disease, then the advice is 'no alcohol'.
- Alpha-1 can have a fatty liver component.

Emerging Therapies (presented by companies)

- *Bean Therapeutics* – Uses base editing to correct the PiZ mutation and convert *A-to-T* to *G-to-C* base pairs. The treatment aims to reduce liver globules by the correction of base pairs, a treatment from *BioMarin Pharmaceutical* – Targeting liver disease only. Stops new polymer and clears the liver. Injection – effect lasts about one month. Not yet in clinical trial.
- *BioMarin Pharmaceutical* – Targeting liver disease only. Stops new polymer and clears the liver of polymer. Injection – effect lasts about one month. Not yet in clinical trial.
- *Belcesiran* – Goal is to reverse liver disease. In clinical trial now using injections. The treatment stops the production of all antitrypsin so this would disadvantage MZs who tend to have enough protective antitrypsin, therefore they are excluded. [In Australia currently – St Vincents Melbourne].
- *Novo Nordisk* – Goal is to reverse liver disease using gene therapy. However, no permanent change. Going to clinical trial later in 2023. The treatment stops the production of all antitrypsin so this would disadvantage MZs who tend to have enough protective antitrypsin, therefore they are excluded.
- *Inhibrx* – Recombinant Alpha-1 Antitrypsin (AAT) protein. INBRX-101 study. Dosing every three to four weeks. [Should be in clinical trial in some Australian States soon e.g., Victoria. No NSW site has been enrolled].
- *Vertex* – Aims to restore normal folding of Z protein. Currently in trial.
- *Wave Life Sciences* – Uses RNA editing. Not using nanoparticles or viruses. No permanent change. Aims to restore functional wild-type AAT protein and reduce Z-AAT protein aggregation. Clinical trial later in 2023.



A1OA Survey Findings

A1OA recently completed its first survey of members, which was designed to help us ensure our limited resources are focussed on delivering the maximum benefit to members. Thank you to those of you who took the time to respond and provide your input.

The key findings of the survey were:

The majority who responded are ZZ and lung affected, although responses were also received from members with rare alleles and those who are liver affected.

The majority of responders consider the current mission of A1OA to be appropriate, although some felt the focus on supporting research into a cure could be broadened to also support research into the management of symptoms.

The most used and useful communication channels were:

- Facebook page/group
- Monthly peer support group meetings
- Webpage
- Newsletter
- YouTube channel

The least used communication channels were:

- LinkedIn page
- Pinterest boards
- Twitter - Alpha-1 Organisation Australia Inc
- Instagram

Among the ideas of how we could better support alphas were:

- An Australian register of Alphas
- More information regarding specific management of symptoms
- More positive stories of people living a normal life with Alpha 1
- More information on research
- Advocate for clean air

Again, thank you to those who provided this feedback which we will use to better direct our efforts to support members in future.

Would you like to have your Alpha-1 Chronic Obstructive Pulmonary Disease (COPD) research ideas heard and considered by Australian researchers?

You can, as we are helping Australian COPD researchers with COPD patient research priority setting!
Australian COPD researchers are interested in identifying **research priorities that are important to people with Alpha-1 COPD** and general COPD, including emphysema and chronic bronchitis.
We are keen to hear from all Alpha-1 patients with COPD regardless of phenotype, caregivers, and family members also welcome to contribute their ideas too.

Question:
What are the two most important problems for people with Alpha-1 COPD that you feel should be addressed by research?

Please email your answers (and any questions) to contactus.a1oa@gmail.com by **31 August 2023** and we will compile them and pass deidentified answers onto the research group.

Alveoli and emphysema

Your lungs contain around 500 million tiny air sacs called alveoli that pull oxygen from the air you breathe and release carbon dioxide when you exhale.

In people with alpha-1 antitrypsin deficiency, damage occurs due to lack of protection from neutrophil and eosinophil attack during infection, such as Covid 19 and influenza.

This leads to emphysema, meaning the walls of the alveoli are damaged causing the small airways in your lungs to collapse when you breathe out, thus making it hard for air to flow into your lungs and even harder for it to flow out. The damage also makes the alveoli become bigger and less elastic.

The damage to the alveoli and airways makes it harder to exchange carbon dioxide and oxygen during each breath. Decreased levels of oxygen in the blood and increased levels of carbon dioxide cause the breathing muscles to contract harder and faster.

Alveoli can sometimes self-repair over time though the extent to which this can happen varies from person to person. The rate of repair needs to exceed the rate of destruction for the area to recover.

COPD and Alpha-1

According to the World Health Organisation, Chronic Obstructive Pulmonary disease (COPD) is the third leading cause of death worldwide.

COPD is a common lung disease causing restricted airflow and breathing problems. It is sometimes called emphysema or chronic bronchitis.

In people with COPD, the lungs can get damaged or clogged with phlegm. Symptoms include cough, sometimes with phlegm, difficulty breathing, wheezing and tiredness.

As medical professionals and Alphas who are lung affected know, these symptoms of COPD are common in the Alpha-1 community. We struggle with breathing, chronic cough (usually with phlegm) and feeling tired.

COPD symptoms can get worse quickly. These are called flare-ups. These usually last for a few days and often require additional medicine.

People with COPD also have a higher risk for other health problems. These include:

- lung infections, like the flu or pneumonia
- lung cancer
- heart problems
- weak muscles and brittle bones
- depression and anxiety.

COPD symptoms usually start in mid-life as damage is cumulative and worsens over time.

An exciting development for Australian Alphas is the work being undertaken by Professor Philip Hansbro, a leading respiratory researcher, and his team. They are asking for input from patients on research questions. If you have questions about COPD that you think would be useful as research questions send them to president@a1oa.org.au to be forwarded to the research team.

Update on Grifols *Sparta* trial.

The recruitment target has now been met.

Alpha-1 Organisation Australia, A1OA, now has a number of video resources available for viewing on our YouTube channel.

A1OA YouTube channel
https://www.youtube.com/@alpha-1organisationaustral421

Estrella Clinical Research Study

This is a clinical research study being run by Dicerna to test the efficacy of a treatment to silence the abnormal AAT gene, thus preventing build-up in the liver, potentially causing damage.

If you are a ZZ Alpha who is liver affected, you may be interested in taking part in the Estrella study, which, in Australia is being conducted at St Vincent's Hospital in Melbourne.

You can find more information on this video:

Estrella Australian Captioned Animation

https://www.youtube.com/watch?v=NN03Uc-iqcA

Note: St Vincent's has temporarily put a hold on screening for this trial.

Artist's impression of lungs and liver affected by Alpha-1 Antitrypsin Deficiency.

Aunty Alpha

Dear Aunty Alpha,
I am a ZZ Alpha. I've read that Alphas have a 40% chance of liver damage. Is that true?

Regards
Shannon

Dear Shannon,
It is correct that Alphas are at risk of liver damage. Talk to your GP, who will examine you, and get a referral to a liver specialist for more specific testing if you think you might be affected or to get a base level for your liver. Dr Jeffery Teckman, who spoke at the recent Alpha-1 Foundation 2023 Alpha-1 National Conference, is recognized as the leading authority on Alpha-1 liver. He recommends several tests, including blood test for ALT, AST, and bilirubin, as well as ultrasound, fibroscan, and liver biopsy. These are important as one test does not tell the full story and a patient can have normal blood enzyme levels but still have fibrosis, which can lead to cirrhosis and liver failure.

Regards
Aunty

If you have a question about any of the issues raised

write to Aunty Alpha, who is always happy to answer your questions, or contact the A1OA through contactus.a1oa@gmail.com

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