alpha-1
ORGANISATION AUSTRALIA INC

Position Paper

Inequity of testing and treatment for patients with Alpha 1-Antitrypsin Deficiency – time to reconsider

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Abstract

Inequity of care and limited access to affordable treatment for patients with Alpha 1-Antitrypsin Deficiency (Alpha-1) are global health issues and exacerbate chronic illness in Alpha-1 patients where treatment access is an issue. Alpha-1 is an autosomal co-dominant disease caused by SERPINA1 gene mutations, most common in populations of European descent. Reduced life expectancy exists for populations facing augmentation treatment denial, the only treatment that slows progression of genetic emphysema and supports a normal life expectancy. Alpha-1 affects more than 120.5 million people worldwide with at least 235,000 individuals with the severe form associated with early onset emphysema. Alpha-1 testing, and affordable treatment access are essential to improve survival. Despite Alpha-1 recognition over 60 years ago, the only specific treatment - augmentation therapy - is not subsidised in many nations resulting in treatment access inequity. Diagnosis delay and underdiagnosis are concerns in most nations. Lung-affected severely deficient Alpha-1 patients urgently need affordable treatment access due to large unmet needs. Early diagnosis and treatment will optimise patient outcomes and prevent progression of chronic illness associated with this neglected disease. When novel therapeutics emerge, such as RNA and DNA based therapy, treatment equity needs to be addressed, meanwhile it is time to reconsider augmentation therapy for severely deficient Alpha-1 patients to achieve health equity.

Key words: Alpha 1-Antitrypsin deficiency, Chronic Obstructive Pulmonary Disease, Alpha 1-Protease Inhibitor, Survival Rate, Health Equity

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Alpha 1-Antitrypsin Deficiency Disease Treatment Inequity

Inequity of care for patients with Alpha 1-Antitrypsin Deficiency (Alpha-1) is a global issue and exacerbates chronic illness in Alpha-1 patients who can't access affordable treatment. Alpha-1 is an autosomal co-dominant disease caused by mutations in the SERPINA1 gene and is most common in populations of European descent but impoverished health outcomes exist for populations facing alpha 1-Protease Inhibitor treatment denial. Alpha-1 is one of the most common serious hereditary disorders with more than 120.5 million people worldwide having at least one faulty gene[1] and at least 235,000 individuals worldwide with PI*ZZ genotype – the most common severe genotype and associated with early onset genetic emphysema.[2]

Alpha-1 promotion, physician awareness, testing and affordable treatment are essential to slow emphysema and to save lives. Despite recognition of Alpha-1 over 60 years ago, the only specific treatment (alpha 1-protease inhibitor – also known as augmentation therapy / replacement therapy), is not subsidised in many nations including Australia, resulting in treatment access inequity and health inequity. Pi*ZZ prevalence varies across nations while delayed diagnosis puts patients at risk of worse health outcomes as augmentation treatment denial continues despite RCT and real-world data showing that treatment slows emphysema progression[3] and improves survival.[4] The potential for ongoing inequity exists if emerging therapies have high costs and aren't government subsidised (e.g. RNA and DNA treatments which are under clinical trial).

Alpha 1-Protease Inhibitor and Emerging Therapies

Alpha 1-protease inhibitor treatment (augmentation therapy) was approved in the United States of America in 1987.[5] Ironically, the evidence from the same placebo-controlled randomised clinical trials (RCTs)[3] is used to both deny and support subsidised treatment, leading to treatment inequity around the world. In recent times augmentation therapy was accepted as the national treatment in Canada (2023) and in Denmark (2020). Treatment was adopted earlier by Argentina, Austria, Poland, Portugal, Spain and Switzerland.[6] These nations see a reasonable relationship between treatment cost and patient outcomes. However, in other locations e.g. Australia, New Zealand, the UK and Sweden, augmentation therapy is not generally subsidised or reimbursed.

Government and insurers' decisions not to subsidise / reimburse augmentation therapy appear to be influenced by the outdated 2016 Cochrane review[7] where non-RCT information was overlooked, despite well-recognised limitations of the use of RCTs in rare disease research[8] and overlooks the fact that such therapy is not designed to treat symptoms but prolong length of life, by slowing emphysema progression, a very different outcome compared to non-genetic COPD studies that focus on lung function, exacerbations and quality of life.[6] Economic studies have overlooked the cost of lung transplantation and the cost per year-of-life gained as augmentation therapy delays time to double-lung transplant - the only treatment in countries where Alpha-1 therapy is denied.[9] Furthermore the costing of augmentation therapy compares favourably to treatment for primary prevention of coronary artery disease and breast cancer screening.[10] Restricting Alpha-1 treatment access due to cost can have devastating consequences for a patient. Restriction disproportionately affects

those already facing systemic disadvantages, exacerbating existing health inequities. Recognising health gaps and inequities are imperative to advancing medical practice, particularly for disadvantaged, vulnerable populations with a rare genetic condition, where treatment denial exists.

Decisions not to subsidise augmentation therapy, are also based on perceived strength of early RCT evidence regarding clinical effectiveness.[11] However, because Alpha-1 is a rare disease it has not been possible to conduct adequately powered RCTs using clinical outcomes used in non-Alpha-1 COPD studies e.g. exacerbations, quality of life, leaving lung density as the preferred outcome indicator associated with augmentation therapy. Meanwhile, it has been established that CT lung densitometry is more specific and sensitive for identifying the protective effects of augmentation therapy related to Alpha-1 emphysema yet CT densitometry has not been widely accepted by regulatory agencies due its lack of routine use in clinical care[11] resulting in subsidised treatment denial.

Clinical research in rare diseases faces challenges not experienced in research into common diseases. These ideas have been addressed in many publications where authors accept that RCTs are not suitable for rare disease research,[12] hence the move in some quarters to real world data to show treatment effect.[13] In addition, Alpha-1 patients with emphysema and low DLCO but high FEV_1 remained disadvantaged, not qualifying for augmentation clinical trials or recombinant therapy as they typically recruit using $FEV_1 \geq 30\%$ and $\leq 70\%$ or 80%[14] with DLCO overlooked. This occurs despite knowledge that FEV_1 is poorly associated with Alpha-1 emphysema and that low DLCO is linked to chronic illness and COPD mortality risk.[15] Without access to affordable treatment, patients with genetic COPD suffer with worse systematic inflammation, symptoms and chronic illness. Alpha-1 is the only subtype of COPD whose progression can be slowed down significantly by lifelong augmentation therapy.[16]

In severely deficient untreated people with Alpha-1, early evidence indicated that the median survival was 54 yrs (49.4 years in index cases and 69.3 years in non-index cases) with no difference between the survival of smokers and never smokers in the index group.[17] Augmentation treatment can slow the more accelerated lung function decline found in Alpha-1 patients including never-smokers.[18] New real-world evidence demonstrates a significant survival advantage associated with augmentation therapy, and confirms that being a never-smoker does not confer a survival benefit, hence the urgent need for treatment.[5] With diagnostic delay associated with a significantly worse overall survival,[19] earlier diagnosis is important which is amplified by the fact that COPD is an independent risk factor for hospitalisation from SARS-CoV-2 (COVID-19)[20] and low AAT levels are associated with a higher likelihood of developing severe COVID-19.[21]

Alpha 1-Antitrypsin is an important anti-inflammatory, anti-protease with antimicrobial and antiviral properties.[22] There are two well-recognised disease processes i.e., liver *gain-of-function* from deposited mutated misfolded Pi*Z protein in hepatocytes (polymer), creating inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), and a lung *loss-of-function* from reduced circulating antitrypsin, causing a loss of immune homeostasis and digestion of connective tissue from uninhibited elastase activity. This leads to small airways destruction, emphysema, chronic bronchitis, and airflow obstruction. Patients need to be

monitored for both lung and liver disease. Monitoring for liver disease includes the evaluation of broad hepatobiliary health and prevention of cirrhosis. Respiratory system monitoring involves annual lung function tests/spirometry, chest CT scans and sputum tests, with the aim of identifying serious bacterial and fungal infections, and patients at risk of respiratory failure and requiring lung transplant referral. Alpha-1 is also associated with a higher risk of pulmonary embolism with a mortality risk seven times higher than in the general population.[23]

In countries where augmentation therapy has been subsidised, the typical regime is weekly infusions of antitrypsin. Novel therapeutics are under clinical trial which may alleviate chronic Alpha-1 lung and liver disease and should require less frequent treatment. These treatments should prevent the 50-plus diseases now associated with Alpha-1, many stemming from uncontrolled proteases and inflammation, including Alpha-1 related heart failure.[24] Emerging RNA and DNA treatments will need to be affordable to address treatment inequity and save lives.

Current Priorities: Diagnosis, Referral and Treatment

There is an urgent need to diagnose severely deficient Alpha-1 patients, particularly PiZZ phenotype (Glu342Lys / E342K mutation), the most common severe form of Alpha-1 linked to liver and lung disease and the current target of most clinical trials. However, identifying rare "at-risk" phenotypes with low or functionally impaired Alpha-1 is important too as some clinical trials target rare phenotypes.

To improve Alpha-1 adult detection rates, all adults should be tested if they have irreversible asthma, unexplained COPD (particularly in non-smokers), early onset COPD, bronchiectasis, unexplained liver disease and alcoholic fatty liver, and family members of Alpha-1 patients. Typically, pulmonologists and gastroenterologists play a key role in managing Alpha-1 patients, however, multidisciplinary management involving immunologists,(30) allied health professionals and engaging and supporting general practitioners to make the initial diagnosis who are at the forefront of patient diagnosis and management will no doubt yield better outcomes in patients.[25] Referring patients to Alpha-1 patient registries and charities will ensure patients are informed when augmentation therapy and other therapies (emerging from clinical trials) are approved by regulators.

Conclusion

Inequity of care and affordable treatment access for Alpha-1 patients are issues in many countries even though Alpha 1-antitrypsin is proven to be an essential enzyme that slows emphysema and provides a significant survival advantage for Alpha-1 patients. Lung and liver-affected severely-deficient Alpha-1 patients need affordable treatment access as they have large unmet needs and suffer from preventable chronic illness and reduced life expectancy. Early diagnosis and treatment are key to optimise patient outcomes which will prevent health burdens associated with this neglected disease. Until novel therapeutics emerge, it is time to reconsider augmentation therapy for severely-deficient Alpha-1 patients to achieve health equity. In regard to current and emerging treatments, health and treatment equity are crucial.

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