alpha-1
ORGANISATION AUSTRALIA INC

Position Paper

Alpha-1 Antitrypsin Deficiency: Preventing Harm and Saving Lives

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Contents

Acronyms and abbreviations

α1	Alpha-1
A1OA	Alpha-1 Organisation Australia Incorporated
AAT	Alpha-1 Antitrypsin
A1AD	Antitrypsin deficiency / α1-antitrypsin deficiency
ADMAPP	Alpha-1 Disease Management and Prevention Program
AFBP	Adipocyte fatty acid-binding protein
AT	Augmentation therapy (for A1AD)
BODE	Body mass index, airflow obstruction, dyspnea and exercise capacity
COPD	Chronic obstructive pulmonary disease
COPD-X	Chronic obstructive pulmonary disease guidelines
CRP	C-reactive protein
CT	Computed tomography
D_{LCO}	Decreased diffusing capacity of the lung for carbon monoxide
EARCO	The European Alpha-1 Research Collaboration
ERS	European Respiratory Society
EXACTLE	Exacerbations and computed tomography scan as lung end-points
FEV_1	Forced expiratory volume in one second
GOLD	Global initiative for chronic obstructive lung disease
HDCT	High density computed tomography
HRQoL	Health Related Quality of Life
KCO	Carbon monoxide transfer coefficient
MSAC	Medical Services Advisory Committee (an independent non-statutory committee) established by the Australian Government for Health)
NHLBI	National heart, lung and blood institute
NTM	Non-tuberculosis mycobacterium
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International prospective register of systematic reviews
PA	Plasminogen activator
RAPID-RCT	Randomised, placebo-controlled trial of augmentation therapy in alpha-1 proteinase inhibitor deviancy randomised controlled trial
RAPID-OLE	RAPID open label extension
RCT	Randomised control trial
SGRQ	St George's respiratory questionnaire
TGA	Therapeutic Goods Administration
USA	United States of America
WHO	World Health Organisation

1 Executive Summary

Lung-affected individuals with the genetic disorder known as alpha-1 antitrypsin deficiency (A1AD) have no access to government subsidised treatment known as augmentation therapy which is known to slow the progression of lung decline and improve survival in A1AD. Peer reviewed evidence, published in reputable international journals, on the use of augmentation therapy in lung affected A1AD patients, supports subsidised augmentation therapy while patients wait for a cure - expected within the next five to ten years. Without augmentation therapy, patients with A1AD related respiratory disease face a poor quality of life, an expensive traumatic double-lung transplant – if eligible – or an early death, as standard inhaled medication such as corticosteroids does not slow lung decline caused by genetic emphysema.

A1AD lung affected patients typically go undiagnosed until damage presents in early adulthood. This paper argues that A1AD needs to be included in newborn screening in each state and territory, arming parents with the knowledge of the need to minimise exposure to cigarette smoke, household and environmental pollutants and dust, saving young lungs from cumulative damage and preventing a life-time of unnecessary suffering and medical costs.

Many lung-affected A1AD individuals routinely practise social isolation to protect their lungs from further damage. The need to maintain this approach has been exacerbated by COVID19, as research shows that antitrypsin plays a role in COVID19 survival.

The evidence presented in this paper overwhelmingly supports government subsidised augmentation therapy, despite advice from the Medical Services Advisory Committee (MSAC), which claimed that the cost and lack of evidence does not support treatment. There has been an international call from Alpha-1 experts to update the narrow A1AD Cochrane review which overlooks various levels of evidence and has historically led several countries, including Australia, to deny access to subsidised treatment when patients in Europe and North America benefit from augmentation therapy.

The immediate subsidisation of augmentation therapy by the Australian Government should be implemented for severely deficient lung affected Australians, reflecting “Rule of Rescue” principles. Factors supporting subsidised treatment include:

a) the Thoracic Society of Australia and New Zealand’s (TSANZ) 2020 position statement and their updated COPD-X Guidelines which state that augmentation therapy could be given to non-smokers;
b) Ireland’s reinstatement of augmentation therapy to severely deficient individuals, based on McElvaney et al.’s 2020 study, which shows the life-saving, anti-inflammatory benefits of augmentation therapy and hospital savings.
c) Denmark’s recent announced that it supports augmentation therapy, having reviewed and accepted the results from the A1AD Rapid-RCT; [(1)]
d) the 2020 research study by McElvaney which shows that augmentation therapy improves survival, provides hospital savings and has anti-inflammatory benefits; [(2)]
e) other statistically significant scientific evidence exists, that shows that augmentation therapy rebuilds lung density, restores the protease/antiprotease balance required for lung health; is essential for a healthy immune system and inflammation control; improves survival in severely deficient individuals with D_{LCO} values <60%, independent of FEV_1;

f) CT lung density is a clinically meaningful measure associated with lung disease, including A1AD and shouldn't be dismissed by government advisors;
g) augmentation therapy is essential to survive COVID19; [3]
h) A1AD patients are immunocompromised and without augmentation therapy are at increased risk of dying from COVID19, emphysema and bacterial lung infections e.g. non-tuberculosis mycobacterium – typically with five-years of infection;
i) viruses rapidly turn into serious lung infections in damaged lungs, which in turn cause further irreversible lung destruction;
j) under the *International Covenant on Economic Social and Cultural Rights* individuals with A1AD have a right to health, a right work, and the right to a family life and participation in cultural life;
k) the 2016 A1AD Cochrane Review is flawed due to its narrow focus on RCTs which does not reflect Cochrane's Handbook on mandatory inclusion of other levels of research when undertaking a systematic review;
l) MSAC has overlooked critical evidence when making its recommendation not to support government subsided augmentation therapy;
m) treating lung affected patients will reduce the burden of COPD, the burden on the healthcare system and provide savings in bed days and overall costs.

This paper questions how the statistically significant findings published in peer reviewed studies by A1AD experts, who demonstrate the life prolonging effect of augmentation therapy and the importance of early intervention to slow disease progression, can be overlooked by Australian Government advisors and the Minister for Health. The study of rare disorders and policy related research reviews require a broad methodological approach, or individuals with rare disease will continue to be disadvantaged, be excluded from essential medical treatment and be a burden on the healthcare system.

Augmentation therapy is an evidence-based solution that will improve patient outcomes and reduce lung disease. Subsidised augmentation therapy, provided until the anticipated cure arrives, can occur by diverting funds from many non-life saving government activities to save A1AD patients.

2 Background

2.1 The Essential Protein Known as Antitrypsin

AAT is an essential potent anti-inflammatory, anti-infective, immunomodulating protein, required for normal lung health. [4; 5; 6] The genetic condition known as alpha-1 antitrypsin deficiency (A1AD) predisposes individuals to early onset hereditary emphysema, sometimes as early as age 20, loss of lung elastin, [7; 8] bronchiectasis and life-threatening lung infections, such as non-tuberculosis mycobacterium (NTM) [9] trapped in 63% of damaged lungs killed 27% of patients within five-years despite 18 months of triple antibiotic therapy. [10; 11; 12] A1AD is a chronic progressive disease and many patients are rapid decliners. If left untreated, individuals face a greatly reduced life expectancy [13; 14] as their lungs, including the lung alveoli and supporting structures, are destroyed from proteases, due to the lack of inhibitory antiprotease (i.e. antitrypsin).

Inhaled corticosteroids do not contain the essential protein (antitrypsin) required to protect individuals' lungs. Augmentation therapy is the only treatment that resolves lung inflammation via neutrophil apoptosis and can fight NTM and COVID19 infections. Without antitrypsin, patients also face systemic vasculitis, necrotizing panniculitis, aneurysms and a variety of inflammatory and neoplastic diseases [5; 15] and an early death with only 16% alive at 60 years of age. [16]

Damage to lungs is cumulative, starting in young children. Newborn screening is a cost-effective blood test that can be used to detect A1AD. Knowing who is at risk of lung damage will empower parents to protect children from household chemicals, cigarette smoke, dust, environmental pollutants and lung infections. Testing for A1AD is only required once as one's genotype determines the level of antitrypsin. A standardised national approach to screening for A1AD is required. Bloodspot screening offers huge benefits for families, children and government i.e. a coherent management strategy to prevent lung damage, COPD and associated morbidity. [17]

2.2 Treatment for A1AD

The only treatment to stop genetic emphysema and to slow lung function loss is augmentation therapy [18] - a weekly infusion of the missing protein known as alpha-1 antitrypsin (AAT). AAT has biochemical efficacy at a dose of 60 mg/kg, raising serum levels to a protective threshold. [6] Treatment takes life expectancy from less than 60 to over 80. [13; 14] Treatment improves survival in A1AD patients with low FEV_1 (< 65% predicted) and independently in patients with low gas exchange (D_{LCO} <60% predicted). Augmentation therapy is registered for use by the Therapeutic Goods Administration (TGA) but treatment is not subsidised. The Medical Services Advisory Committee (MSAC) claims that there is not enough evidence to support subsidised therapy and that the treatment cost is too high. Non-subsidised treatment remains unaffordable to most patients at approximately $100,000 per annum for life (depending on body weight).

Research synthesis supports A1AD treatment but Australian regulators tend to focus on level 1 evidence, reflecting the narrow Cochrane review of augmentation therapy. This focus occurs at the expense of other compelling synthesised evidence, leading to treatment denial in Australia, as patients can't afford treatment. When making recommendations to the Minister for Health, advisors need to consider all significant evidence, as when fully considered, augmentation therapy

is found to improve A1AD patient survival, reduce exacerbations and associated hospital costs, build lung density, maintain pulmonary health, improve quality of life, reduce comorbidities such as inflammatory bowel disease [19] and improve the likelihood of surviving a COVID19 infection. [3]

2.3 Evidence and Ethics

MSAC's Public Summary document released in response to Application No. 1530 for subsidised augmentation therapy, [20] indicates that MSAC overlooked pooled evidence that shows the clinical efficacy of CT densitometry, survival predictions and its superiority to FEV_1, in A1AD. [21]

This position paper presents results that need to be considered by the Australian Government as research shows that CT lung densitometry is proven to determine A1AD treatment impact and lung decline, and that it is clinically relevant. Research indicates that augmentation therapy:

a) results in less severe exacerbations, fewer hospital admissions and hospital savings;
b) improves respiratory function and risk of respiratory failure;
c) improves quality of life;
d) controls damaging proteases;
e) controls inflammatory biomarkers and C-reactive protein and lactate; and
f) improves survival.

Australia is party to international law and supports the right to health - both physical and mental. Australian A1AD patients are a vulnerable group requiring "essential" therapy. [22] Based on the evidence, the Rule of Rescue [23] should be applied to lung affected A1AD patients as a moral, socially just, clinical and scientific response, giving patients an opportunity to extend their lives.

The incorporated charity known as Alpha-1 Organisation Australia (A1OA), believes that it is unethical to leave patients with no access to affordable treatment, when augmentation therapy has been saving lives internationally and treatment is registered with the TGA. Treatment denial has unfairly arisen due to the narrow examination of evidence by the MSAC, with important evidence (including survival data and the clinical role of CT densitometry) dismissed. This paper examines the range of issues associated with A1AD treatment denial and presents evidence that needs to be considered which supports government subsidised treatment.

3 Discussion

There is no debate that the biochemical evidence supports augmentation therapy as serum antitrypsin levels are raised to a protective level. [24] Augmentation therapy is required to reduce inflammation, to restore the lung protease-antiprotease balance for lung protection [24] and it is the only specific therapy available for lung affected patients.

Choate's (2016) research explains why treated A1AD patients are living to 80.4 years [2; 13] while McElvaney et al. reinforce the dramatic benefits of therapy, made possible as a consequence of the abrupt cessation of augmentation therapy in Ireland. The results from the drug wash-out study were presented to Irish governmental policymakers. The overwhelming results led to severely deficient A1AD patients, who had been denied therapy, being provided with augmentation therapy at a discounted price. The study shows that lack of augmentation therapy

is linked to respiratory failure, that exacerbations and hospitalisations increase when denied AAT, and that clinical benefits including the control of elastase and multiple inflammatory biomarkers.

3.1 Augmentation Therapy Stops Genetic Emphysema

Augmentation therapy has been shown to reduce elastin degradation [25] and to limit widespread destruction of lung parenchyma. [21] A1AD is a slow progressive disease [6] making change hard to detect in short-term randomised control trials (RCTs). Clinical trials and international patient registry studies show augmentation therapy to be disease-modifying with sustained change following therapeutic intervention. [13] This is why augmentation therapy should be subsidised by government as it treats the deficiency and permits patients to lead normal long lives and to engage in normal activities including family life and employment.

3.2 MSAC Rejected the Application for Subsidised Treatment

On 22-23 November 2018 MSAC considered an application for government subsidised augmentation therapy. [20] The Committee's Public Summary Document and advice to the Minister for Health indicates that MSAC rejected the application based on cost and perception of limited strength of evidence, claiming that no statistically significant differences were found between antitrypsin and placebo in relation to mortality, exacerbations, hospitalisation due to exacerbations, quality of life, respiratory function (FEV_1), exercise capacity or carbon monoxide diffusion capacity (D_{LCO}). MSAC also claimed that there was weak evidence to suggest that changes in CT density predicts clinically meaningful health outcomes. [20]

This paper presents evidence overlooked by MSAC that shows treatment:

- slows lung emphysema decline
- reduces lung infections (exacerbations)
- improves survival
- reduces lung elastin degradation
- slows emphysema progression
- reduces the severity and frequency of exacerbations
- improves quality of life
- provides hospital savings from reduced patient admissions, and that
- CT density predicts clinically meaningful health outcomes. [13; 18; 21; 26; 27; 28]

3.3 The Value of CT Densitometry as a Surrogate

CT densitometry is a sensitive outcome measure for assessing disease progression, is linear and more consistent than traditional endpoints. It measures destruction of alveolar walls, loss of lung tissues, lung disease progression, augmentation treatment effects and increased survival. [27] CT density is the most sensitive measure, followed by diffusing capacity of the lungs for carbon monoxide (D_{LCO}).

Early studies used the gold standard FEV_1 as a marker for monitoring disease progression, however, changes in FEV_1 occur slowly and FEV_1 lacks sensitivity. This means that RCTs using FEV_1 require large patient numbers which is difficult to obtain with rare disease.

Mascalchi et al. raise five reasons why CT lung densitometry should be the main tool to monitor lung disease: (I) improved reproducibility; (II) complete *vs.* discrete assessment of the lung tissue; (III) shorter computation times; (IV) better correlation with pathology quantification of pulmonary emphysema; and, (V) better or equal correlation with pulmonary function tests (PFT). [29]

$FEV_1$is a measure of both airway wall thickening and collapse of the small airways. CT lung density measures airspace enlargement such as in alveolar destruction found in emphysema. FEV_1 doesn't discriminate between emphysema and airway disease. CT density is better at identifying emphysema. CT densitometry is a robust tool with reproducible results. It is a valid, reliable indicator in lung disease identification, emphysema and treatment impact. [18; 27; 28; 30]

MSAC has not accepted that CT-lung density as a surrogate for the effects of augmentation therapy on clinical outcomes e.g. respiratory function, quality of life, survival, or quality-adjusted life-years. [20] MSAC's comments indicate that the following evidence has been overlooked.

3.4 Overlooked Evidence

3.4.1 Reduction in Exacerbations

a) McElvaney et al. (2020) found that withdrawal of augmentation therapy was linked to respiratory failure during exacerbations and increased hospitalisations. [2]
b) Campos et al. (2018) reported that augmentation therapy reduces exacerbations by 36.1% in a cohort analysis and in overall savings due to fewer and shorter hospitalisations. [31]
c) Barros-Tizon et al. (2012) found a reduction of severe exacerbations and hospitalization-derived costs in A1AD patients treated with alpha-1-antitrypsin augmentation therapy. [32]
d) Kohnlein et al. (2010) reported that patients receiving augmentation therapy had a significantly lower exacerbation frequency and severity compared to placebo. [33]
e) Dirksen et al. (2009) found that patients treated with augmentation therapy had less severe exacerbations compared to placebo. [34]
f) Lieberman (2000) found that augmentation therapy was associated with a marked reduction in the frequency and severity of lung infections. [35]

3.4.2 Respiratory Function

a) McElvaney et al. (2020) prove that patients denied augmentation therapy can suffer from respiratory failure. [2]
b) Chapman et al. (2015) reported slower lung density decline in augmentation therapy individuals, compared to placebo. [1]
c) Barros-Tizon et al. (2012) found that the rate of lung decline was more marked prior to augmentation therapy compared to control subjects. Augmentation therapy is able to sustain lung function equivalent to that of a normal population. [32]

d) Tonelli (2009) found that A1AD patients receiving augmentation therapy had better lung function and they did significantly better than the non-treatment group. [36]
e) Chapman et al. (2009) reported that augmentation slows lung function decline in FEV_1 in the moderate sub-group 30-65% FEV_1% predicted. [37]
f) Wencker et al. (2001) reported FEV_1 declines more slowly in the treatment group with pre- and post-augmentation were 49.2 vs 34.2 ml/year respectively. [38]
g) Wencher et al. [39] (1998) reported the rate of decline in FEV_1 in augmentation treated patients (~57 ml/year) was approximately half that reported for untreated controls.
h) Seerholm et al. (1997) reported a significant difference in annual FEV_1 decline with an increase in FEV_1 over 2 years compared to comparator group. [40]

3.4.3 Augmentation Treatment and Survival

a) McElvaney et al. (2020) reported when augmentation therapy was withdrawn patients died from heart failure. [2]
b) Rahaghi et al. (2014) reported that augmentation therapy improves FEV_1, D_{LCO} and assists individuals with air trapping from hyperinflated lungs. [26]
c) Sclar et al. (2012) found that augmentation therapy was associated with a significant increase in years of life gained (more than 10 years gained in non-smokers). [41]
d) Choate et al. (2016) reported normal life expectancy from augmentation therapy (median survival 80.4 years) in severely deficient patients with A1AD. [13]
e) The NHLBI (1998) reported higher survival in the augmentation arm of a study. [42]

3.4.4 CT Lung Density and Survival

a) Green et al. (2016) reported that augmentation slows lung-density decline and the rate of change in lung densitometry predicts survival. Decline in KCO and D_{LCO} had a higher sensitivity than FEV_1 decline to predict CT density decline in non-treated patients. [27]
b) Stockley et al. (2010) [43] reported significant change in lung density in the treatment group over 2.5 years. 60 treated /59 non treated. (Clinical trial data from 5 centres)
c) Dirksen et al. (2009) reported that in patients treated with augmentation therapy that CT was a more sensitive outcome measure than physiology and health status. [34]
d) Green et al.'s (2016) study of CT densitometry reveals that it is linked to survival with CT density shown to be the most sensitive measure and can predict CT density decline. [27]
e) Annual deterioration in lung density is less on augmentation therapy (EXACTLE study). [18]
f) Dirksen et al. [34] (1999) reported CT densitometry is correlated to FEV_1. Reduced decline of lung tissue and beneficial effect of augmentation therapy assessed by CT.

3.4.5 CT Lung Density and Respiratory Function & HRQoL

a) Ma et al. [25] (2017) reported augmentation therapy reduces elastin degradation, including pulmonary elastin. Results show a correlation between biomarkers of elastin degradation and CT lung density.

b) McElvaney et al. (2015) reported that annual CT lung density decline in the first 2 years was less by 0.75 g/L/year in the first cohort and that decline was reduced to -1.26 after 4 years; and a 34% reduction in lung density decline compared to placebo. [44]
c) Dirksen et al. (2009) found that CT densitometry is more sensitive than other measures in measuring emphysema progress but CT density and FEV_1 are correlated. [34]
d) Dowson et al. (2001) note that CT density is related to lung function and health status. [45]
e) CT density use in emphysema is validated against pathology, lung function and health status and is useful in clinical management. [18; 31]

3.4.6 HRQoL

a) McElvaney et al. (2020) reported the clinical benefits of augmentation therapy e.g. controlling elastase, C-reactive protein, lactate and multiple inflammatory biomarkers (interleukin-1β, interleukin-6, interleukin-8, soluble tumour necrosis factor receptor). [2]
b) Dowson et al. (2001) found that CT scans are well correlated with the HRQoL and pulmonary physiology. [45]
c) Gelmont et al. (2009) reported significant improvements in HRQoL mental functioning over two years while on augmentation therapy. [46]

3.4.7 Hospital Costs due to COPD Exacerbations

a) Barros-Tizon et al. (2012) confirmed a reduction in the incidence and severity of exacerbations, lower hospitalization rates and admission costs and fewer medications. [32]
b) Kohnlein et al. (2010) demonstrated patients receiving augmentation therapy had a significantly lower severity of exacerbations and hospitalisation compared to placebo. [33]
c) Gildea et al. (2003) found that augmentation therapy is cost effective for patients with severe A1AD. (Markov-based decision analytical model) [47]

Possible reasons for MSAC overlooking compelling evidence include:

a) acceptance of the methodologically flawed A1AD Cochrane Reviews;
b) using narrow literature reviews and overlooking non-RCT data;
c) the assumption that mortality is a good RCT outcome indicator when it is difficult to measure in short-term trials and ignoring survival data;
d) a lack of understanding of the need to use the best available evidence when studying rare diseases as RCTs will generally be underpowered; and
e) not appreciating that FEV_1 is not sensitive to change in the short term.

3.5 Methodological Issues in Rare Diseases

Narrow literature reviews that don't meet review standards diminish their value. A systematic review should be exhaustive and include different levels of evidence [48] including clinical trials,

cohort studies, patient registry studies and subgroup analyses. Reviewers need to embrace broader evidence [49] that shows that augmentation therapy reduces lung loss and mortality.

Augmentation therapy has been used for decades in North America and publications from its patient registry show life-years gained - raised from 54.5 years (not treated) to a median survival of 80.4 years. [13] Understanding the needs of rare disease research is presented below.

Rare disease research faces challenges not shared with common diseases. [50] Green et al. (2016) note that mortality difference may not be observed in clinical trials as Kaplan Meir plots show that deaths occur in the longer term. [27] The Rapid Study and the Rapid Extension did manage, however, to show that lung density decline can be measured with CT and that augmentation therapy slows lung decline. [37; 51] Edgar's 2017 systematic review came to the same conclusion. [18] The importance of the RAPID study and the RAPID Extension study and augmentation therapy treatment is echoed by others as therapy slows disease progression. [44]

Non-RCT and adaptive designs e.g. natural history studies, crossover designs, patient registry data, clinical trials and continuous outcomes are required for the study of A1AD. [50; 49] The limitations of using RCTs in rare disease research has been explained to regulators, therefore, other levels of evidence and pooled analysis need to be embraced. [49; 52; 21; 6; 53; 50]

In their 2019 paper on the current state of evidence, Brantly et al. present the positive impact of augmentation therapy including survival improvement. [6] They raise the importance of registry data, the need for longitudinal studies and that the majority of A1AD deaths occur after 4 to 9 years follow-up. Registry data reveals treatment effect on survival with a statistically lower mortality rate in patients receiving augmentation therapy compared to those not treated. Brantly et al. present evidence that augmentation therapy is useful for early and late stage disease. [6]

The compelling life-years gained argument is supported by historical survival observations based on longitudinal patient registry data. [13; 21; 27] The A1OA believes that registry data should be incorporated into therapy considerations and government advisors and regulators need to be able to explain subsidised treatment denial when evidence exists to support subsidisation.

The flawed, poorly designed 2016 Cochrane review [54] ignores patient registry data and downplays the importance of subgroup analysis with statistically significant results. The Cochrane review states that "studies should be large enough to detect a possible effect on mortality". Such data exists, i.e. pooled analysis shows improved survival from augmentation therapy.

The Cochrane findings have been brought into question by the North American Alpha-1 Foundation in an open letter [55] and results have been widely criticized [18] as the reviews overlook the issues raised in this position paper. This oversight, and restricted analysis by the Cochrane reviewers, have resulted in treatment denial which is unethical and is an international inequity. A1AD deficient patients are living with distress from a debilitating disease knowing that augmentation therapy could extend and save vulnerable lives. [56]

3.6 The Broader Context of Augmentation Therapy

3.6.1 Treatment Guidelines

Within Australia, A1AD is bundled with COPD despite A1AD being a treatable disease with augmentation therapy. In 2020 the TSANZ published a position statement indicating that

augmentation could be given to lung-affected non-smoking patients. Their Guidelines for the Management of Chronic Obstructive Pulmonary Disease (COPD-X Guidelines) have been updated reflecting the position statement.

While low FEV_1 is the focus in international A1AD treatment guidelines, low D_{LCO} and air trapping have been overlooked due to regulators familiarity with FEV_1, leaving patients with poor gas exchange excluded from clinical trials and more likely to die prematurely if not considered for augmentation therapy. Therefore, three groups of patients need to be included in treatment guidelines:

a) Individuals with lower than predicted FEV_1;
b) Individuals with poor gas exchange (D_{LCO}); and
c) Individuals with both poor D_{LCO} and FEV_1 (as there is no correlation between them)

A personalized approach to treatment is required due to differing rates of lung function decline in A1AD patients. [57] This is important, as FEV_1 has been privileged over gas exchange, despite gas exchange being an earlier and better indicator of emphysema. [58; 59] The TSANZ acknowledge the importance of gas exchange in its position statement on A1AD [19] Augmentation guidelines need to include gas exchange.

The USA and Canada support augmentation therapy as do many countries in Europe. A cohort analysis from the USA's Alpha-Net patient registry database shows the **median survival age of 80.4 years** (95% CI: 78.1 – 82.7), showing normal life expectancy. [13]

The European Respiratory Society notes that CT lung density decline relates well to A1AD clinical outcomes, such as mortality and HRQoL. The ERS statement supports the use of augmentation therapy as part of an integrated management program for A1AD. The ERS notes that FEV_1 is a poor surrogate measure for emphysema and that FEV_1 decline reflects a late physiological change in the disease process whereas gas transfer is reduced much earlier indicating that gas exchange may be a more sensitive and specific test of emphysema development [16]. This suggests that the earliest change is a decline in gas transfer, independent of and faster than FEV_1 decline.

3.7 A Right to Health

MSAC's recommendation to not subsidise A1AD treatment is scientifically, morally and socially unjust as the evidence shows that treatment is related to survival, less severe exacerbations, improved quality of life, hospital savings and that CT lung density is relevant in lung disease identification and patient management. Likewise, bloodspot screening for A1AD needs to be introduced so that children can be protected from triggers causing COPD and bronchiectasis. The following issues need to be considered by the Australian Government:

a) The TSANZ has updated its recommendation on the use of augmentation therapy, indicating that it could be given to A1AD patients.
b) Australian A1AD patients have the right to enjoy the highest attainable standard of health under *The International Covenant on Economic, Social and Cultural Rights.* [22]

c) The annual cost of A1AD treatment was considered high by MSAC. However, the real cost to the Australian Government needs to be included in costing studies including comorbidities and treatment saving offset effects.
d) The cost effectiveness ratio of A1AD is similar to many currently subsidised treatments such as haemodialysis. [47]
e) Treatment cost effectiveness should be considered in the context of augmentation therapy being the only available treatment. [47]
f) The Australian Disability Discrimination Act 1992 defines disability as a total or partial loss of the person's bodily or mental functions that limits one or more major life activities Treatment denial is associated with a profound economic toll. Costs include lost wages, physical and mental suffering, disability costs, exacerbations (GP visits, antibiotics, corticosteroids, hospitalisation), oxygen therapy, comorbidity treatment costs, and lung transplants. Mortality costs of future earnings lost through premature death need to be included. Augmentation treatment should not be denied to A1AD patients who are disabled with lung disease. The number of lung-affected patients requiring immediate treatment is small as the majority are yet to be diagnosed however estimates suggest approximately 4,126 in the highly deficient category.
g) Since 1946 international law has supported a right to health. Australia is a party to seven core international human rights treaties. As noted on the Australian Government Attorney-General's Department website, the right to health is the right to the enjoyment of the highest attainable standard of physical and mental health [22] and alpha-1 patients are a "vulnerable" group requiring "essential" therapy.
h) MSAC identified that the claim for therapy met three of the four criteria for warranting Rule of Rescue but all four are met as there is the literature supports the clinical effectiveness of CT density in the detection of emphysema and other lung diseases and in their clinical management. The Rule of Rescue should be applied to A1AD in Australia as: a) no treatment alternative exists in Australia; 2) A1AD is a severe, progressive disease expected to lead to premature death; 3) a small number of patients require treatment; 4) the broad evidence shows that treatment will provide a clinical improvement with lung density stabilised and a normal life expectancy possible from treatment.
i) Patients and their carers are the main stakeholders of this orphan disease and a patient-centred management approach needs to be adopted.
j) Waiting for A1AD adults to present with genetic emphysema is unacceptable when bloodspot screening could assist parents in preventing early lung disease in their children.
k) The World Health Organisation (WHO) supports social justice in health [60] and endorses the use of augmentation therapy. [61]
l) The over-reliance on level 1 evidence in the study of rare diseases, denies Australian A1AD patients' access to life-saving treatment.

4 Conclusion

Until such times as a cure is available for A1AD, individuals with A1AD need early identification of the disorder so a management plan to avoid risk factors for lung disease can be put in place as early as possible. Bloodspot screening supports this need.

Treatment (augmentation therapy) for lung disease prevention in A1AD is available but not subsidised by the Australian Government due to a narrow interpretation of the evidence by government advisors. Augmentation therapy has been proven to reduce inflammation and save lives in A1AD. It is also known that augmentation therapy maintains lung density, slows emphysema decline, reduces the severity and frequency of exacerbations, improves quality of life, leads to a normal life expectancy and saves hospital costs. The literature on CT densitometry in lung disease confirms its clinical effectiveness in A1AD patients and shouldn't be dismissed.

A1AD patients are a vulnerable group, made more vulnerable in a COVID19 environment, and have a right to health and treatment which has been proven. Overlooking evidence allows A1AD patients to die prematurely and unfairly when a treatment option exists for genetic emphysema.

MSAC's recommendation to the Minister for Health to not approve subsidised treatment is scientifically, morally and socially unjust based on the breadth of peer review evidence supporting treatment. MSAC's questioning of the suitability of CT density indicates that broad evidence on the use and suitability of CT densitometry use in pulmonary disease has been overlooked. The CT lung density evidence is appropriate, accurate, reliable, clinically meaningful, supporting the application of Rule of Rescue by the Australian Government to vulnerable A1AD patients. As all four Rule of Rescue factors are concurrently present, the Australian Government could immediately apply the Rule of Rescue criteria to save the lives of patients who are severely deficient in antitrypsin.

A1OA opposes the withholding of subsidised augmentation therapy in Australia, when conclusive evidence exists for the effectiveness of the therapy and the Rule of Rescue applies.

5 References

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