Supplementary material

European Respiratory Society (ERS) Statement: Diagnosis and treatment of pulmonary disease in alpha-1 antitrypsin Deficiency

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1. Literature searches:

Monitoring of evolution of lung disease

To address the issue of monitoring the progression of lung disease in AATD, a systematic review of the literature was conducted on progression of emphysema using the following electronic databases: MEDLINE (Ovid), MEDLINE In Process (Ovid), EMBASE (Ovid), Cochrane Library (Wiley) CENTRAL, CDSR, HTA, EED and DARE databases . No date or language limits were used. In addition Conference Proceedings Citation Index (CPCI) via Web of Science and British Library's ZETOC were searched for conference proceedings and abstracts and Clinical Trials.gov and WHO ICTRP (International Clinical Trials Registry Platform) were searched for ongoing clinical trials. A similar search for the ATS/ERS statement published in 2003 was conducted with a search up to 1999. Therefore, the current information provided below is from the year 2000 onwards. The search was confined to alpha-1-antitrypsin deficiency of homozygous Z genotype, Null genotype or Null/Z genotype, abbreviated for this document as AATD. Combined text words and index terms used for the search are shown in the online supplement.

Augmentation therapy

In brief MEDLINE, MEDLINE In Process, EMBASE (via Ovid), Cochrane Library (Wiley) CENTRAL, CDSR, HTA, EED and DARE databases were searched, seeking any study of augmentation therapy conducted in patients with an AAT level <14μM and a genotype consistent with such a level (PiZZ, Znull etc). In light of the rarity of AATD we also included studies containing mixed populations, however only if AATD participant data met this criteria and was available separately. In addition Conference Proceedings Citation Index (CPCI) via Web of Science and British Library's ZETOC were searched for conference proceedings and abstracts and ClinicalTrials.gov and

WHO ICTRP for ongoing trials. We sought studies with any clinical outcome measure, including (but not restricted to) mortality, CT scans, lung function and quality of life (QOL). Studies reporting only a biochemical measure (e.g. AAT level) were given lower priority within our synthesis of the evidence. Retrieved titles, abstracts and appropriate full manuscripts were assessed independently by two reviewers. Narrative and tabular evidence synthesis was conducted.

2. Patients' perspective

Many patient organisations noted that they are still struggling to get correct information about AATD out to the health professionals in their countries; this statement was considered an important tool in their information strategies. Patient highlighted the following issues as important from a patient perspective.

Additional topics for inclusion in the current statement

Burden of illness from patient perspective: patients reported that broader recognition of their experience of living with the condition and how it affects all areas of their lives is an important element of any discussion about the condition, and forms the basis of developing management strategies aimed at improving patients' quality of life.

Delay to diagnosis: Patients reflected that the time to diagnosis averages 6 – 8 years and this has an impact on their quality of life.

Non-pulmonary associations with AATD: while patient recognised that the statement's specific focus is on pulmonary disease related to AATD, they believed that the current statement does not include sufficient detail on non-respiratory associations with alpha-1

deficiency, including cardiac disfunction, aortic dissection, aneurysms, panniculitis, and liver function and the effects of the disease (ASAT and ALAT concentrations).

Identifying young patients: the statement should include information on how to recognise the signs of AATD, including in young children: jaundice; increase of bilirubin; poor weight gain; enlargement of the liver and spleen were suggested. Paediatricians should be trained to recognise the signs.

Genetic testing and genetic counselling: there are ethical implications which should be taken into account in familial genetic testing and the importance of informed consent, the right to confidential results and the importance of pre- and post-genetic counselling were highlighted by patients. Patients can experience problems in different areas of their lives (e.g. insurance cover, eligibility for mortgages, etc.) if they have been identified with a genetic condition, irrespective of whether they ever develop clinical manifestation of the condition. While genetic testing is an important element in identifying those at risk of AATD, the potential for negative consequences should be recognised within the statement.

Treatment options: Refers to other treatment options, including pulmonary rehabilitation, physiotherapy, oxygen therapy and inhaled corticosteroid treatment, as well as influenza and pneumonia vaccination, While some patients derive benefit from a variety of treatment options not discussed, they can also experience difficulties in accessing those options.

Self-management guidance: Other self-management strategies which many patients are currently recommended to follow, including weight management (for both over- and under-weight patients), regular exercise and hygiene to manage risk of infection. Depending on the country of residence, these interventions can be delivered via out-

patient services, such as dietary counselling services, physiotherapy clinics or specialised nursing teams and the statement should take into account the diversity of services across Europe.

Side effects of augmentation therapy: Given that many health technology appraisals take into account treatment side effects, it was considered important that this statement outlines the current evidence on adverse events from previous trials.

Environmental exposure to irritants: Although smoking cessation and reducing exposure to second hand smoke are addressed, healthcare professionals treating AATD patients should also be advised to ask about exposure to other irritants, such as dust and gas, in the home and workplace.

Patient choice in agreeing a treatment plan: this was considered particularly important for patients resident in countries where augmentation therapy is not currently reimbursed.

Relocation and reimbursement policies: although outside the scope of the current statement, some patients suggested including details of what to expect if you relocate in order to access augmentation therapy in another country. This should include details of the reimbursement policy of each country for citizens and non-citizens and the costs patients may be expected to fund themselves. Similarly, other patients recommended assessing the underlying reasons for the inequality of access to augmentation therapy, as well as potential strategies to mitigate this situation.

Areas for future research

Patients highlighted a range of topics where more research evidence is required and which would have a large impact on the lives of patients.

Augmentation therapy, definitive trials: Patients feel very strongly about augmentation therapy. Although there is debate about the effectiveness of the therapy, the fact that it is covered under some national health reimbursement policies and not others leads to uncertainty for patients, with many believing that they are denied treatment access due to purely economic rather than clinical reasons. Definitive evidence of the effectiveness of augmentation therapy for respiratory patients is urgently needed, including evidence of which patient populations (according to genetic variant, symptoms, disease progression) will benefit most.

Optimising treatment: evidence-based guidance on optimising current COPD therapy for AATD patients is needed, including inhaled medication.

Timing of intervention and outcome measures for trials: researchers should include preservation, as well as decline in lung function, as outcome measures. It is important to patients to preserve existing lung function, not just to measure the rate of decline. Evidence-based guidance is needed on the optimum time to start patients on augmentation therapy when they have lung disease in order to preserve lung function.

Suggested clinical trial: in response to the following statement on page 22: "there is no evidence to support the use of AAT trough levels to monitor or adjust the dosage and/or frequency of intravenous augmentation therapy ", MM people produce more Alpha-1 to regulate increased neutrophil activity and to check inflammation during periods of infection. They recommend: “a study assessing augmentation therapy in Alpha-1 patients in cases of respiratory infections, surgery or other illness to assess the effectiveness as a treatment for exacerbations. An observation of what would happen when a severe Alpha-1 genetic type patient receives a normal increased amount of

Alpha-1 and whether this helps to maintain lung function and combat infection and inflammation."

Suggested clinical trial: augmentation therapy as a preventative approach to respiratory infection and inflammation: "There is a lot written on inflammatory illness being related to Alpha-1 therefore it would be interesting to see if Alpha-1 people with MM Alpha-1 blood levels, through augmentation, would have less inflammatory illness. It is the case that the body structures make the abnormal Alpha-1 but it should investigated to see if an MM blood level could help to combat the effects of the neutrophil abnormal Alpha-1 attraction."

Suggested clinical trial: trials are needed in treatments that may slow disease progression, such as hyaluronic acid and progesterone [1 – 2].

AATD in heterozygotes: more studies on heterozygotes are needed

Gene therapy: research is needed to develop gene-based therapies to prevent and/or manage the condition at an early stage: "develop AAT therapies using nonviral gene transfer, gammaretrovirus, recombinant adenovirus (rAd), and recombinant adeno-associated virus (rAAV) vectors. Scientific focus on the search for small molecules and chaperones to correct the basic defect in cellular alpha-1 antitrypsin (AAT) trafficking and polymerization, the development of new molecules with anti-elastase activity, and gene/stem cell therapies".

Disease registries: establishing disease registries in AATD would help to monitor the natural history of the condition and also facilitate recruitment into clinical trials.

Areas for future advocacy and education

Patients highlighted a range of campaigning and policy activities which would improve diagnosis and treatment of AATD. There could be a potential role for patient organisations and professionals to collaborate on some of these areas.

Smoking and environmental pollution awareness-raising.

Multi-disciplinary approaches: links to medical societies and specialist centres that deal with alpha-1 liver disease to share learning and good practice. The newly established European Reference Networks could facilitate this.

Awareness-raising of the need to test for Alpha-1 amongst primary care practitioners thorough understanding of the condition: patients highlighted the need for an improved understanding of the condition across all levels of primary and secondary care. A lack of awareness of Alpha-1, coupled with the lack of approved therapies in some countries, can lead to substandard care and poor patient outcomes. Furthermore, clinicians provide expert advice on patients' illness and capabilities which is used to inform access to social service provision (such as financial reimbursement for disability support, income support etc). Without a clear understanding of the disease, some physicians may provide inaccurate information to inform these assessments. Education for health professionals in all aspects of AATD is needed.

Training to recognise the signs of AATD in young children: paediatricians require training to recognise early indications of AATD in order to fast track genetic testing, diagnosis and personalised risk guidance.

Research funding: lobbying is needed to improve financial endowments (from private and public institutions) towards research.

Support groups: healthcare professionals should be encouraged to signpost newly diagnosed patients to local and national support groups as a source of support and information.

Who provided feedback?

ELF contacted patient organisations with an interest in alpha-1 antitrypsin deficiency and invited them to comment on the statement. Feedback was received from a total of 15 individuals and organisations. The following organisations provided feedback on the draft statement:

- Alfa-1 Denmark – staff and individual patients
- Alpha-1 Norway – staff and individual patient
- Alpha-1 Plus (Belgium) – staff and individual patient
- Alpha-1 UK Support Group - Board of Trustees and individual patients
- Organisation for Respiratory Health, Finland – staff
- Alpha-1 Advocacy and Action Coalition (international) – individual patients
- Alpha1 Deutschland – staff and five individual patients
- Alpha One Foundation (Ireland) – staff

References

1. Allegra L, Della Patrona S, Petrigni G. Hyaluronic acid : perspectives in lung diseases. Handb Exp Pharmacol 2012;(207):385-401.
2. Hall O, Limjunyawong N, Vermillion M S, Robinson D P, Wohlgemuth N, Pekosz A, Mitzner W, Klein S L. Progesterone-Based Therapy Protects Against Influenza by Promoting Lung Repair and Recovery in Females. PLoS Pathog 2016 Sep;12(9): e1005840.