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Expert Perspectives on the Management of Alpha 1-Antitrypsin Deficiency

Perspetivas dos Especialistas na Gestão da Deficiência de Alfa 1-Antitripsina

Bebiana CONDE[1,2], Filipa COSTA[3], Joana GOMES[4], António Paulo LOPES[3], Maria Alexandra MINEIRO[5], Orlando RODRIGUES[6], Cristina SANTOS[7], Luísa SEMEDO[5], Maria SUCENA[4], Catarina GUIMARÃES✉[8]
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ABSTRACT

Alpha 1-antitrypsin deficiency is an inherited autosomal codominant disorder, which predisposes patients to lung and/or liver disease. Even though it is considered rare, it is one of the most frequent genetic disorders worldwide, albeit remaining underdiagnosed. Several organizations and societies, including the Portuguese Society of Pulmonology have been elaborating guidelines and recommendations for the diagnosis and management of alpha 1-antitrypsin deficiency. Nevertheless, some important matters are yet to be included in those, mainly due to lack of robust scientific evidence, and continue to represent a point of discussion. This article reviews some important scientific publications and expresses the perspectives of a group of Portuguese experts regarding the management of alpha 1-antitrypsin deficiency, namely in terms of the pre and neonatal diagnosis, the impact of the COVID-19 pandemic, the validity of replacement therapy in lung transplant-receiving, and finally, alternative strategies of alpha 1-antitrypsin deficiency treatment to improve the patients' quality of life.
Keywords: alpha 1-Antitrypsin; alpha 1-Antitrypsin Deficiency

RESUMO

A deficiência de alfa 1-antitripsina é uma doença hereditária autossómica codominante que aumenta a predisposição para o desenvolvimento de doença pulmonar e/ou hepática. Esta doença, embora seja considerada rara, é um dos distúrbios genéticos mais comuns em todo o mundo. Contudo, atualmente ainda constitui uma doença subdiagnosticada. Várias organizações e sociedades, incluindo a Sociedade Portuguesa de Pneumologia, elaboraram recomendações e diretrizes para o diagnóstico e gestão da deficiência de alfa 1-antitripsina. Porém, estes documentos ainda não abordam alguns temas relevantes associados à gestão da deficiência de alfa 1-antitripsina, principalmente devido à falta de robustez na evidência científica, que continuam a representar um ponto de discussão entre a comunidade médica. Neste artigo é feita a revisão de publicações científicas relevantes acerca da deficiência de alfa 1-antitripsina, e são descritas as perspetivas de especialistas portugueses sobre a gestão da deficiência de alfa 1-antitripsina, nomeadamente ao nível do diagnóstico pré e neonatal, do impacto da pandemia COVID-19, da validação da terapêutica de aumento em doentes que receberam um transplante pulmonar e, por fim, estratégias alternativas para a melhoria do tratamento da deficiência de alfa 1-antitripsina de modo a promover a qualidade de vida dos doentes.
Palavras-chave: alfa 1-Antitripsina; Deficiência de alfa 1-Antitripsina

INTRODUCTION

Alpha 1-antitrypsin (AAT), otherwise known as alpha-1-proteinase inhibitor, is the most prevalent protease inhibitor in the human serum, which belongs to the supergene family of serpins (serine protease inhibitors), encoded by the *SERPINA1* gene, located on chromosome 14.[1-3] This 52 kDa glycoprotein is primarily synthesised by the liver (around 80%) and to a lower extent by mononuclear cells, neutrophils, broncho-alveolar and corneal epithelium, colonocytes and endocrine pancreatic cells.[1,2] As an acute phase protein, AAT responds to inflammation by neutralizing neutrophilic elastase, and therefore supressing pulmonary associated damage. This glycoprotein develops an additional important role, considering that it also behaves as a tissue repair inducer.[1,2,4]

AAT deficiency (AATD) is an inherited autosomal codominant disorder, which remains underdiagnosed.[2,5] This condition may result from various point mutations that can cause either a deficit of AAT or a loss of anti-proteolytic and anti-inflammatory function, which are associated with the development of pulmonary emphysema, hepatic disease, severe asthma, bronchiectasis, granulomatosis with polyangiitis, and less frequently, skin disorders such as panniculitis.[2-4,6-10] From a clinical perspective, AATD is a very heterogeneous condition, considering that its symptoms may appear earlier or later in life, or even never develop at all. This diversity may result not only from the individual genotype, but also from damage in the liver or lungs caused by infections or toxic agents.[2,3]

1. Centro Hospitalar Trás-os-Montes e Alto Douro. Vila Real. Portugal.
2. Universidade de Trás-os-Montes e Alto Douro. Vila Real. Portugal.
3. Serviço de Pneumologia. Centro Hospitalar e Universitário de Coimbra. Coimbra. Portugal.
4. Serviço de Pneumologia. Centro Hospitalar e Universitário do Porto. Porto. Portugal.
5. Serviço de Pneumologia. Centro Hospitalar Universitário Lisboa Central. Lisboa. Portugal.
6. Serviço de Genética Médica. Hospital Pediátrico do Centro Hospitalar e Universitário de Coimbra. Coimbra. Portugal.
7. Serviço de Pneumologia. Centro Hospitalar e Universitário Lisboa Norte. Lisboa. Portugal.
8. Serviço de Pneumologia. Hospital Senhora da Oliveira. Guimarães. Portugal.
✉ **Autor correspondente:** Catarina Guimarães. catarina.guimaraes11@gmail.com
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As for the prevalence of AATD, this condition is estimated to represent up to 5% of COPD cases.[11] Importantly, although epidemiological data are scarce in both Europe and the United States, the prevalence of AATD can be compared with that of cystic fibrosis, impacting 1:2000 to 1:5000 people.[3-5,12] Nevertheless, and in order to contribute to a better awareness of AATD and to accurately record the real impact of this genetic disorder, efforts are being made and the Portuguese medical community is currently registering their patients on the pan-European Alpha-1 Research Collaboration platform (EARCO),[13] which is supported by the European Respiratory Society and the Portuguese Society of Pulmonology.

Guidelines concerning the management of AATD have been proposed by different societies and organizations.[14-17] In Portugal, a consensus document was published in 2018 and included an extensive literature review and recommendations for the diagnosis and management of AATD.[4] However, in light of the new scientific evidence and of the current pandemic situation, the AATD patient association, as well as the medical community, felt the need to debate a few important topics. To this end, an advisory board meeting was arranged, during which a group of experts discussed the appropriateness of implementing pre and neonatal diagnosis, the impact of the coronavirus disease 2019 (COVID-19) pandemic, the importance of maintaining the augmentation therapy in patients receiving a lung transplant, and finally, strategies to improve the patient quality of life as far as AAT administration is concerned.

This article provides an overview of some important scientific publications about AATD and summarizes the perspectives of a group of Portuguese experts (all the authors) in AATD diagnosis and management, specifically their opinion about scientific publications taking into consideration their clinical expertise about AATD. Briefly, data on the new scientific evidence about ATTD and strategies that can improve AAT administration was presented at this meeting (17th September 2021) and, afterwards, the experts debated about AATD diagnosis and management according to the scientific evidence and their clinical expertise.

EXPERT PERSPECTIVES

Pre or neonatal diagnosis of AATD

Even though AATD is the most frequent genetic lung disease in the Caucasian population, it remains underdiagnosed and only a modest proportion of patients are detected with this condition.[18]

The relevance of early diagnosis, pre or neonatally, has been a matter of discussion. Even though it is acknowledged that early identification of AATD enables those individuals to implement preventive therapeutic or lifestyle measures which may protect lung and/or liver damage, thus delaying the onset of disease, some ethical concerns may be raised.[4,11,19]

Prenatal diagnosis may be performed by means of an amniocentesis or chorion villi biopsy, which subsequently undergo a DNA analysis (genotyping).[19] Importantly, the collection of either of these samples is invasive and may put the viability of approximately 1% of pregnancies at risk.[20] Neonatal diagnosis, on the other hand, does not imply a mortality risk, as it can be done by drawing blood from the newborn, after which the serum levels and genotype can be assessed.[4,6] Nonetheless, the common diagnostic method of DNA analysis either by Sanger or next generation sequencing (NGS) only allows the identification of the most frequent AAT pathogenic variants, and consequently does not guarantee the detection of all pathogenic variants.[4] Even though DNA sequencing analysis of exon-intron and promoter regions is a method which allows the identification of all mutations, it cannot be used as a universal screening tool due to its costs and technological requirements.[4] Therefore, this analysis is only performed when the phenotype/genotype diverge from the biochemical analysis or from clinical manifestations.[4]

In view of the limitations and risks that the aforementioned methods imply, as well as its costs, the Portuguese experts foresee some ethical concerns regarding the implementation of a universal prenatal or neonatal screening. Firstly, the detection of AATD implies the identification of a predisposition for the development of a disease rather than the diagnosis of a disease.[3] As such, it does not mean that the individual will ever develop clinical symptoms. As previously reported by other authors, a diagnosis without the presence of symptoms may increase the psychosocial stress of those families and raise financial, social, insurance and employability uncertainties.[21] Additionally, a negative result through the currently used DNA sequencing approaches, that only identify the most common pathogenic variants, may lull the parents into a false sense of security.

Nevertheless, the group of experts recommends referring couples with a family history of severe AATD to genetic counselling, so that they can be informed about the risks and benefits of screening. For patients who have experienced a neonatal death due to AATD associated liver disease, prenatal diagnosis may be considered.

Additionally, the early detection of AATD allows the implementation of preventive measures, namely avoidance of smoking and of environmental risks, compliance with vaccination, physical exercise, adequate follow-up and eventual treatment in the early stages of the disease, which are widely recognized as being of particular importance to prevent and/or avoid the progression of pulmonary disease.[3,4,11,21] Therefore, and because non-invasive methods are available, the experts also recommend neonatal diagnosis for

those individuals who descend from couples where both parents carry an AAT pathogenic variant.

Impact of COVID-19 on AATD patients

AATD has been proposed as a risk factor for COVID-19, not only because it may facilitate the entry of the virus into host cells, but also due to an increased likelihood of lung injury and to a possible risk of developing a coagulation disorder.[22,23] In fact, 67 countries have reported a positive correlation between AATD (specifically, the genotype SZ) and COVID-19 associated mortality.[22]

In Portugal, however, the group of experts did not observe that same trend. On the contrary, most of their patients did not develop COVID-19 and, interestingly, the majority of those that became infected did not show severe disease.[24] Similarly, a survey conducted in Germany by BREATH – Member of the German Center for Lung Research (DZL) has shown that among 208 participants with AATD only six were infected with COVID-19 virus, of which none had to undergo mechanical ventilation.[25]

Several reasons may be presented to justify these observations. The lockdown, social distancing and the use of personal protective equipment are likely to have contributed to a lower exposure to the virus, hence reducing the incidence of cases in this population. In fact, during 2020, these experts observed a reduction in the frequency of COPD and asthma exacerbations, and therefore a decrease in the number of hospitalizations, indicating that all patients with respiratory diseases benefited from these preventive measures.[26]

Additionally, doctors have stressed to their patients since the beginning of the COVID-19 pandemic, the importance of adhering to their treatment regimens. As such, most AATD patients retained their treatment adherence and continued receiving augmentation therapy, even if altered to a biweekly scheme, in order to prevent lung function deterioration, which may have contributed to some kind of protection against COVID-19-associated severe disease.

Replacement treatment in transplant receiving patients

Replacement therapy with AAT has an important role in reducing lung density decline[27,28] and postponing lung transplantation, as a result of its clinical benefits in preserving lung tissue integrity.[29] Whether transplant recipients should receive exogenous AAT has been a matter of debate, due to insufficient evidence.[3,4]

A few studies have reported that patients who were not under replacement treatment prior to lung transplant showed a longer survival after lung transplant, when compared with those that had received AAT intravenously.[30,31] However, it has also been speculated that the discontinuation of AAT treatment may be associated with a rebound phenomenon, characterized by a pro-inflammatory state in the post-transplant period, which may negatively impact the outcome of those transplanted patients.[29-31] In fact, AATD patients who suffer from infections during the post-transplant period or transplant rejection present excessive inflammation and neutrophil activity.[29]

Similar post-transplant survival rates have been described between patients who received and didn't receive replacement therapy immediately after transplantation.[32] Of note, a small study showed that the reintroduction of AAT therapy immediately after lung transplantation seems safe and may have a stabilizing effect on the forced expiratory volume in one second.[33]

The validity of implementing augmentation therapy post-lung transplantation, can be further supported by AAT's immunomodulatory properties. AAT has been shown to lead to a reduction in the levels of pro-inflammatory mediators, namely tumour necrosis factor (TNF)-α and interleukin (IL)-1β, while increasing those of anti-inflammatory cytokines, thus promoting immunological tolerance.[34-36] Additionally, it also decreases neutrophil chemotaxis and adhesion, prevents cell death, and also participates in the regulation of fibrinolysis.[34-36]

Recurrence of emphysema after lung transplantation is rare and has only been described in patients who have resumed smoking.[37] In light of the current knowledge, it is appealing to think that there is benefit in continuing augmentation treatment after lung transplantation, at least in some subgroups of patients, during the peri-transplant period or during periods of clinical worsening,[38,39] in order to reduce the risk of inflammatory complications after the procedure and to prevent a decline in the pulmonary function in the healthy lungs. Presently, the role of replacement therapy in the post-transplant period is under discussion.

Improvements on the administration of AAT

The current treatment for AATD consists in the intravenous infusion of human purified AAT, administered on a weekly basis.[4] The augmentation therapy has been reported as a therapeutic strategy that is effective in slowing the progression of emphysema and safe, with a low adverse event rate.[15,27,28] Although this treatment is of major importance for the patient's well-being, it is a burden for both patients and healthcare institutions. For the hospitals and healthcare professionals, AAT administration requires a considerable amount of time for preparation and perfusion, and the outpatient clinics are often overbooked as they usually cover a wide geographical area.[40-42] Concerning the burden for patients, the frequent visits to the hospital may represent several problems, namely a threat to their health (due to exposure to viral and bacterial infections), costs due to travelling and workdays lost and impossibility to spend more than

a few days away from hospital, thus affecting holidays and travel plans.[40-42] Considering the current disadvantages to AAT administration, the group of experts discussed the existence and implementation of patient-centred alternatives with the objective of improving the patient's quality of life and adherence to treatment:

- A bi-weekly dosing strategy (120 mg/kg) has been shown to be an interesting and convenient therapeutic option, as it appears to be safe, presenting a tolerability profile similar to that of a weekly administration of 60 mg/kg,[43] and seems to be sufficient to obtain protective serum levels of AAT (> 57 mg/dL) in ZZ patients.[44] In fact, many clinicians have been considering and implementing this therapeutic regimen, and although it seems to have biochemical efficacy, there is lack of evidence concerning the long-term impact on the progression of the disease.[41,42] Indeed, since the start of the pandemic until now, some of the experts included in this group implemented a bi-weekly dosing strategy, in order to reduce contact with the hospital environment, hence protecting their patients from exposure of hospital infections. Additionally, this therapeutic scheme entails several advantages, which include higher convenience for full-time employees, reduced travel costs and the possibility of enjoying longer vacations.[41,42] Care should be taken when using this regimen in null patients (i.e. with absence of AAT levels) as though protective concentrations may not be achieved.
- Self-administration is a safe alternative commonly used in other diseases, namely haemophilia, primary immunodeficiency and hereditary angioedema,[45-47] where it has demonstrated to be well tolerated, cost-effective and to improve patients' quality of life, independence and well-being. In AATD, it has been shown that patients who self-administer AAT therapy are very satisfied, have improved independence and require limited training to self-administer independently.[48] Although the experts consider that this strategy would not suit all of their patients, it may represent a valuable option for those who are younger and still working.[49]
- Home therapy is a strategy already available in a few countries.[41,42] Alpha-1 Global initiative, a collaborative global network of Alpha 1 patient leaders, physicians, and researchers, has appealed to all European Union (EU) Member States to make this option available, with the objective of reducing the risk of AATD patients developing COVID-19.[50] The results obtained where this option was implemented revealed a positive impact, as patients felt less stressed, not only because it increased their independence relatively to a caregiver, but also because it reduced the impact of treatment on their personal and professional lives.[42] Although this strategy is currently not implemented in Portugal, the experts foresee the advantages and agree that this option would be valuable to many patients.
- Treatment provided by community health centres close to the patients' home may also be an interesting option, as it would reduce the inflow of patients into hospitals and the burden to hospital healthcare professionals. Therefore, the experts consider that this strategy could represent a feasible alternative, whilst also having a positive impact on patients, who would not have to travel long distances to their treatment centre, hence reducing costs and saving time.
- The upcoming new presentations of 4 g and 5 g vials of AAT concentrate may also improve the convenience of treatment either at the hospital setting, at home or during a self-administration approach. Considering that it will allow, in most cases, the preparation and infusion of a single vial, this alternative will certainly reduce the time and costs of preparation, as well as facilitate the administration handling.

CONCLUSION

The advisory board meeting organized for this group of experts to discuss recent scientific evidence and concerns raised by the Portuguese association of AATD patients resulted in a compilation of important suggestions for the improvement of diagnosis and management of AATD. The group of experts considers that their clinical experience and their perspectives explained in this article may help other colleagues and, more importantly, may have a significant impact on preventing a decline in the pulmonary function of AATD patients and improve their quality of life.

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AUTHOR CONTRIBUTIONS

CG: Project coordination. Conception, design and drafting of the manuscript.

BC, FC, JG, APL, MAM, OR, CS, LS, MS: Design and drafting of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

COMPETING INTERESTS

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