








Research priorities in α_1 -antitrypsin deficiency: results of a patients' and healthcare providers' international survey from the EARCO Clinical Research Collaboration

Miriam Barrecheguren¹, Karen O'Hara², Marion Wilkens³, Jeanette Boyd⁴, Ewa Kolda⁵, Beatriz Lara ⁶, Joanna Chorostowska-Wynimko⁷, Ilaria Ferrarotti ⁸, Jan Chlumský⁹, Christian Clarenbach ¹⁰, Timm Greulich ¹¹, Marc Miravittles ¹ and Maria Sucena¹², on behalf of EARCO

ABSTRACT α_1 -antitrypsin deficiency (AATD) is a rare and under-recognised genetic condition. Owing to its low prevalence, international initiatives are key for conducting high-quality research in the field.

From July 2018 to December 2019, the European Alpha-1 Research Collaboration (EARCO) developed and conducted two surveys, one for healthcare providers and one for patients and caregivers, aiming to identify research priorities and barriers in access to treatment for AATD.

A survey on 164 research questions was electronically sent to 230 AATD experts in Europe, and 94 completed surveys from 24 countries were received. The top research areas identified by healthcare providers were causes of variable progression and poor outcomes, improvement in diagnosis, initiation and optimal dosing of augmentation therapy and effectiveness of self-management interventions. During the same period, 438 surveys were completed by patients and caregivers from 26 countries. The top research areas identified were improving knowledge about AATD, in particular among general practitioners, access to AATD specialised centres and access to reliable, easy to understand information about living with AATD. Regarding barriers to treatment, participants from countries where augmentation therapy was reimbursed prioritised improving knowledge in AATD, while respondents in non-reimbursed countries regarded access to AATD augmentation therapy and to specialised centres as the most relevant.

The main research and management priorities identified by healthcare providers and patients included understanding the natural history of AATD, improving information to physicians, improving access to specialised reference centres, personalising treatment and having equal opportunities for access to existing therapies.



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Surveys for patients and healthcare providers on research priorities in AATD, developed by the @EuroRespSoc CRC EARCO, show that international collaboration and engagement with patients are key development strategies needed for improvement <https://bit.ly/2ItIzaW>

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Introduction

α_1 -antitrypsin deficiency (AATD) is an under-recognised genetic condition that affects ~1 in 2000 to 1 in 5000 individuals and predisposes to early-onset emphysema and liver disease [1]. Owing to its low prevalence, AATD is considered a rare disease. Because of the variety in its clinical manifestation, many patients may remain undiagnosed until they develop a severe respiratory or liver disease.

A recent statement on AATD by the European Respiratory Society (ERS) [2] recommended organising the care of patients in reference centres because of the low prevalence of the disease. Reference centres must establish a registry of their activity that enables them to share data concerning the clinical characteristics and natural history of patients, nationally and internationally. In this context, the European Alpha-1 Research Collaboration (EARCO) was created in 2018 [3] as a Clinical Research Collaboration (CRC) of the ERS [4], composed of an international group of experienced and new researchers in the field of AATD committed to promoting research in different aspects of the disease: epidemiology, genetics, physiopathology, clinical management and prognosis of lung disease. The ultimate goal is to improve the quality of life of patients with AATD.

One of the initial objectives of EARCO was to build a network of patients' representatives, researchers and clinical investigators to identify research needs and establish an agenda for AATD research [3]. The involvement of patients' representatives and organisations is essential to conduct patient-centred quality research. To reach this goal, a task force of EARCO developed and conducted two surveys, one for healthcare providers and the second for patients and caregivers to better understand the key research needs and barriers to management in the field of AATD. In this report we present the development, results and implications of these surveys, which will guide the future research of EARCO.

Method

A working group comprising six EARCO members (four respirologists and two patient representatives) from five European countries and representatives of the European Lung Foundation (ELF) was established to develop two surveys: one for healthcare providers and another for patients and caregivers (figure 1).

Healthcare providers' survey

From June to August 2018 the working group analysed the research needs indicated in the recent ERS statement on lung disease in AATD (table 1) [2] and systematically evaluated the literature published after this statement to identify potential new areas of research. After this revision, 180 research questions were drafted and sent to an advisory group formed by five EARCO members for a final check. A final list of 164 research questions was defined, divided into eight research categories (epidemiology and natural course of the disease (n=25); diagnostic and screening (n=16); awareness and education for healthcare providers and for patients and registries (n=13); clinical manifestations (n=23); outcomes and monitoring (n=38); augmentation therapy (n=23); other treatments/AATD therapies (n=8); other non-pharmacological interventions (n=18)). From March 29 to May 1, 2019, an online survey was sent to AATD experts around Europe who were asked to grade each research question anonymously using a five-point scale (1=unimportant to 5=very important). Time for completion of the survey was estimated to be 20–30 min. The complete survey is shown in supplementary material S1.

Patients' survey

During the same period, a survey for patients and caregivers was developed. The survey was designed by the same working group of members of EARCO, including patient representatives and representatives of the ELF. The draft was reviewed by an advisory group of four expert patients with AATD from four

Affiliations: ¹Pneumology Dept, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain. ²Alpha-1 UK Support Group, Droitwich, UK. ³Alpha1 Deutschland e.V, Gernsheim, Germany. ⁴European Lung Foundation, Sheffield, UK. ⁵Dept of Respiratory Medicine, Allergology and Pulmonary Oncology, Poznań University of Medical Sciences, Poznan, Poland. ⁶Dept of Respiratory Medicine, University Hospitals of Coventry and Warwickshire, Coventry, UK. ⁷Dept of Genetics and Clinical Immunology, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland. ⁸Dept of Internal Medicine and Therapeutics, Pneumology Unit, IRCCS San Matteo Hospital Foundation, University of Pavia, Pavia, Italy. ⁹Dept of Pneumology, Thomayer Hospital, First Faculty of Medicine, Charles University, Prague, Czech Republic. ¹⁰Division of Pulmonology, University Hospital Zurich, Zurich, Switzerland. ¹¹Dept of Medicine, Pulmonary and Critical Care Medicine, University Medical Centre Giessen and Marburg, Philipps-University, Member of the German Centre for Lung Research (DZL), Marburg, Germany. ¹²Pulmonology Dept, Centro Hospitalar do Porto, Porto, Portugal.

Correspondence: Marc Miravittles, Pneumology Dept, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Passeig Vall d'Hebron 119–129, 08035 Barcelona, Spain. E-mail: marcmm@separ.es

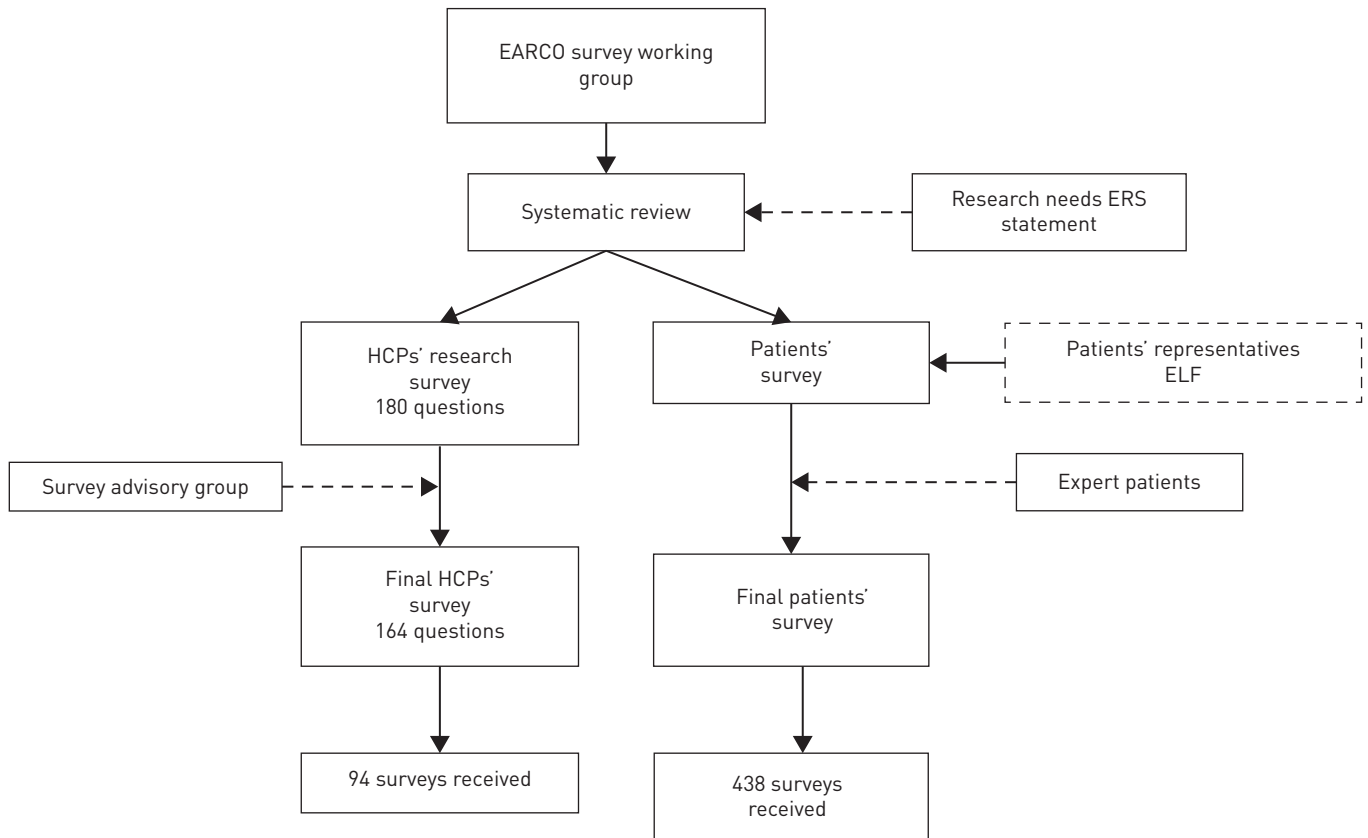


FIGURE 1 Development of surveys for healthcare providers (HCPs) and patients and caregivers by the European Alpha-1 Research Collaboration (EARCO) survey working group. ERS: European Respiratory Society; ELF: European Lung Foundation.

European countries, and revised to ensure that it met the needs of the project and would be relevant, interesting and accessible for patients and caregivers.

The survey was provided in nine languages: English, Dutch, French, German, Italian, Polish, Portuguese, Serbian and Spanish. The survey was online for 6 weeks from November 2018 to January 2019 and promoted through the networks and social media of Alpha-1 Global, Alpha-1 patient organisations and groups, ELF, ERS and members of the CRC.

After collecting demographic data from the participants, the survey was divided into two parts: A) questions about the most challenging aspects of managing the disease and barriers to treatment and B) research needs. For part A, patients and caregivers were asked to rate the challenges and barriers using a four-point scale (1=very difficult, 2=difficult, 3=not very difficult, 4=not an issue). For part B, research need questions were divided into six categories: symptoms and burden of the disease, areas of research,

TABLE 1 Research priorities identified by the European Respiratory Society task force on pulmonary disease in AATD [2]

1. Biomarkers of emphysema progression in AATD
2. Biomarkers of response to augmentation therapy
3. Research on the minimum clinically important difference in rate of decline in lung density
4. Personalised augmentation therapy, with individualised selection of therapeutic regimen according to the patient needs
5. Development of genetic and regenerative therapies
6. Other types of treatment, e.g. biochemical inhibitors of neutrophil proteinases
7. Development of specific patient-reported outcomes for patients with emphysema associated with AATD
8. Efficacy of augmentation therapy after lung transplant in AATD patients

AATD: α_1 -antitrypsin deficiency.

TABLE 2 Most-rated research questions by respiratory specialists

Research question	Score [#]
What are the causes of fast progression and poor outcome in patients with AATD?	4.60
How can we improve early and accurate diagnosis in AATD?	4.52
When should augmentation therapy be initiated?	4.51
Are self-management interventions effective in AATD patients?	4.49
What is the optimal dose regimen (dose and frequency of administration) of augmentation therapy?	4.38
What is the clinically valid definition of a fast decliner, what is the advisable observation period?	4.33
How should the severity of an exacerbation, in AATD patients, be assessed and what is its impact on long-term outcomes?	4.31
How can awareness of AATD, among physicians, be improved?	4.27
What is the prevalence of emphysema among never-smokers PiZZ?	4.27
What is the impact that the delay of diagnosis has in the prognosis of the disease?	4.25
What are the risk factors, other than cigarette smoking, for the development of lung disease in AATD?	4.25
How can delay in diagnosis be reduced?	4.24
Does an early referral to a specialist in AATD change outcome in patients?	4.24
Which are the best lung function tests for the follow-up of pulmonary disease in AATD patients?	4.23
What is the relation between bronchiectasis and AATD?	4.20
What is the most appropriate AAT blood concentration to consider severe and intermediate AATD?	4.19
Could augmentation therapy be effective in other phenotypes/genotypes with low levels such as SZ?	4.19
Should the laboratory diagnosis algorithm be standardised in Europe?	4.18
What is the therapeutic efficacy of aerosol AAT preparation?	4.18
What is the role of augmentation therapy for reduction of exacerbations frequency and severity?	4.17

AATD: α_1 -antitrypsin deficiency; AAT: α_1 -antitrypsin. #: scores range from 1=unimportant to 5=very important; answers are ranked by mean score.

diagnosis and awareness of the disease, treatment, treatment burden, and self-management and education. Participants were asked to rate each research priority question by order of importance (unimportant, not very important, important, very important, no opinion). Data are presented as the percentage of responders that rated each item as either important or very important. The complete survey is presented in supplementary material S2.

Statistical analysis

Because the survey was exploratory and there was no *a priori* hypothesis, no contrasts of hypothesis were performed. Data are presented as descriptive statistics only with mean values or percentages, when appropriate.

Results

Healthcare providers' survey

The survey was sent electronically to 230 AATD experts in Europe and we received 94 complete surveys (response rate 41%) from 24 countries. The majority (76.6%) of the participants in the healthcare providers' survey were aged between 40 and 60 years old. Most responders (58.5%) had 5–20 years' experience in following and treating patients with AATD, while 71% visited more than five patients with severe deficiency per year. Most of the responders (92.6%) were pulmonologists.

Table 2 shows the 20 highest-rated research priorities. The top five areas identified by healthcare providers were causes of variable progression and poor outcomes (mean score 4.6 out of 5), improvement of early and accurate diagnosis (4.52), initiation of augmentation therapy (4.51), effectiveness of self-management interventions (4.49) and optimal dose regimen for augmentation therapy (4.38). Other questions considered relevant addressed the definition of a fast decliner, severity and impact of exacerbations and improvement in awareness. The complete list of responses is shown in supplementary material S3.

TABLE 3 Patients' demographics and clinical characteristics

Variable	From non-reimbursed countries	From reimbursed countries	Total
Participants n	124	239	438 [#]
Patient	107 (86)	194 (81)	368 (84)
Parent, relative or caregiver	17 (14)	45 (19)	70 (16)
Age years	54	52	50
Female sex	78 (63)	132 (55)	254 (58)
Smoking			
Active	4 (3)	5 (2)	9 (2)
Former	78 (66)	126 (56)	272 (62)
Alcohol	69 (58)	113 (51)	241 (55)
Environmental exposure	36 (30)	69 (31)	127 (29)
Lung transplant recipient	1 (1)	3 (1)	18 (4)
Liver transplant recipient	2 (2)	3 (1)	5 (1)
Diagnosis made by			
Pulmonologist	56 (47)	125 (58)	245 (56)
GP	38 (32)	29 (14)	79 (18)
Gastro/hepatologist	7 (6)	19 (9)	31 (7)
Paediatrician	5 (4)	14 (7)	26 (6)
Other	13 (11)	27 (12)	61 (14)
Reason for diagnosis			
COPD	31 (26)	68 (30)	140 (32)
Family testing	25 (21)	45 (20)	74 (17)
Asthma	14 (12)	19 (8)	39 (9)
Liver disease	7 (6)	19 (8)	26 (6)
Panniculitis	2 (2)	5 (2)	4 (1)
Other	41 (33)	76 (32)	153 (35)
AATD phenotype			
ZZ	75 (63)	161 (72)	306 (70)
SZ	16 (13)	19 (8)	39 (9)
MZ	7 (6)	31 (13)	44 (10)
MS	2 (2)	2 (1)	4 (1)
Unknown	16 (13)	2 (1)	26 (6)
Other	4 (3)	12 (5)	18 (4)
Time since diagnosis years	10	11	12

Data are presented as n (%) or mean, unless otherwise indicated. GP: general practitioner; COPD: chronic obstructive pulmonary disease; AATD: α_1 -antitrypsin deficiency. [#]: there were 75 participants from countries with partial reimbursement who were not included in either of the two subgroups.

Patients, family members and caregivers' survey

Characteristics of respondents

A total of 438 surveys from 26 countries were completed. 84% of respondent were individuals diagnosed with AATD and 16% were parents, relatives or caregivers. Among the individuals diagnosed with AATD, 70% had the PI*ZZ genotype. More than half of respondents were diagnosed by a respiratory specialist (56%), with the most likely cause for diagnosis being chronic obstructive pulmonary disease (COPD) (32%), followed by family testing (17%). Almost two thirds of respondents were former smokers (62%) (table 3).

Among the survey responses, 124 (28%) were from people living in one of the countries where augmentation therapy is not currently reimbursed (Australia, Denmark, Finland, Ireland, Norway, Sweden and the UK) and 239 (55%) from people living in countries where augmentation is reimbursed (Argentina, Austria, France, Germany, Italy, Portugal, Spain, Switzerland and the USA). 75 surveys (17%) were from respondents from countries where reimbursement was only partial or had an unclear status. The characteristics of the respondents were similar in both groups (table 3).

Most challenging aspects to manage and barriers for treatment

Figure 2 shows the aspects of the disease considered most challenging by patients and caregivers. Decreased exercise tolerance and shortness of breath were the most difficult aspects identified by patients, followed by not feeling fit or having the strength to do daily activities, tiredness and fatigue.

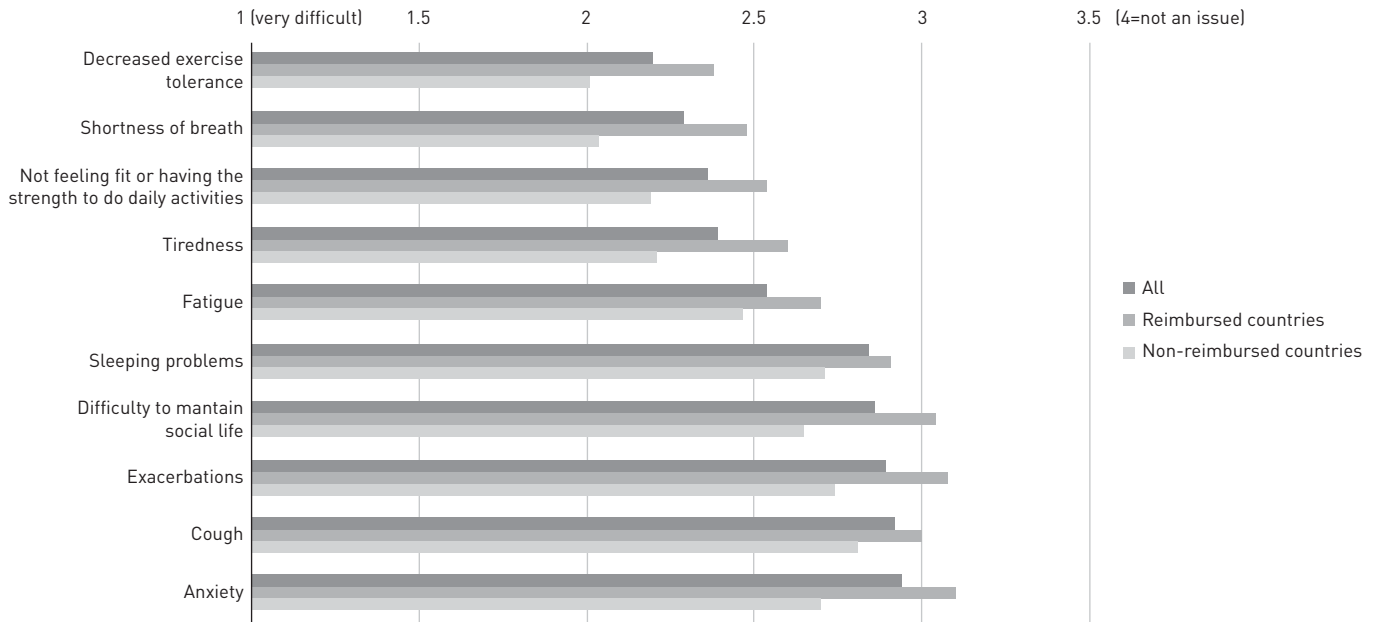


FIGURE 2 Most challenging aspects to manage for patients. The scale used is 1=very difficult, 2=difficult, 3=not very difficult, 4=not an issue.

Among the most challenging aspects/barriers for treatment, the three considered most important were access issues to augmentation therapy, professional implications of the diagnosis of AATD and access to maintenance classes or using fitness centres after rehabilitation for regular exercise (figure 3).

There were important differences between reimbursed and non-reimbursed countries. Respondents in non-reimbursed countries identified all aspects related to augmentation therapy as the most challenging barriers for treatment: access issues to augmentation therapy in their healthcare system, hospital administration of augmentation therapy and time consumed in augmentation therapy. By contrast, individuals in reimbursed countries identified access to maintenance classes or fitness centres to maintain fitness after rehabilitation, access to pulmonary rehabilitation and the impact of transplant on patients and their families as the most challenging barriers (figure 3).

Research prioritisation by patients and caregivers

Almost all respondents (99%) considered improving knowledge of AATD to be a priority, in particular in general practitioners (GPs). Other top research areas identified were access to AATD specialised centres (97%),

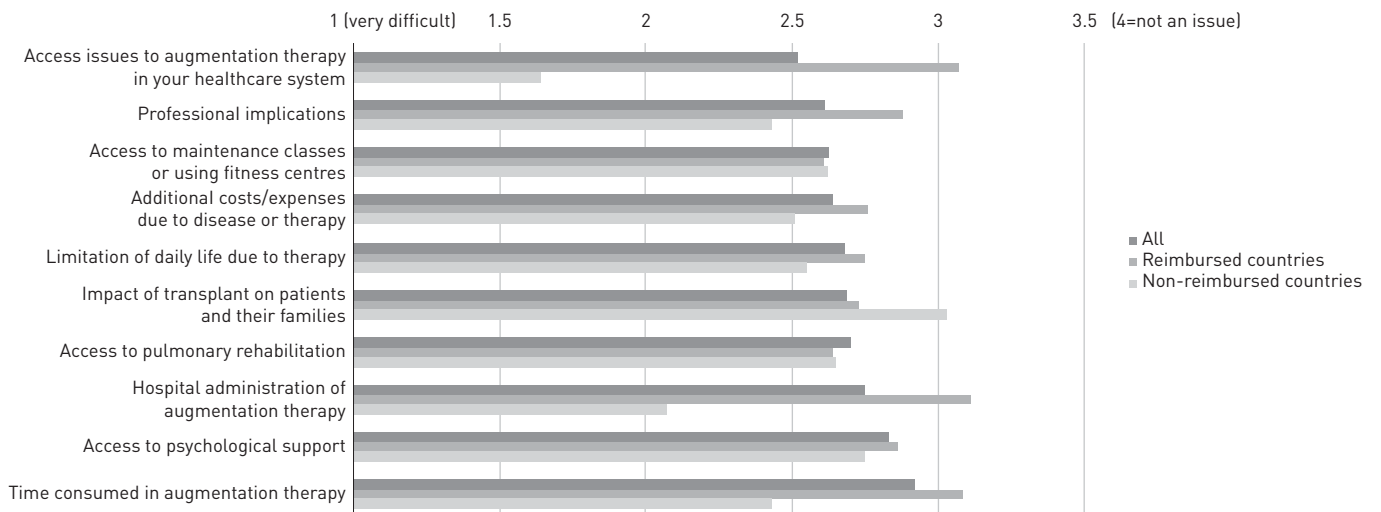


FIGURE 3 Most challenging aspects/barriers for treatment. The scale used is 1=very difficult, 2=difficult, 3=not very difficult, 4=not an issue.

TABLE 4 Most important research areas as rated by patients and caregivers

Research area	Total	Non-reimbursed countries	Reimbursed countries
Improving knowledge of AATD, in particular among general practitioners	99	99	99
Access to AATD specialised centres	97	99	96
Access to reliable, easy to understand information about living with AATD	97	99	96
Being able to recognise an exacerbation	97	98	97
Targeted screening programmes: COPD and asthma patients	96	94	99
Having an action plan for exacerbations and easy access to healthcare during episodes	96	99	95
A personalised integrated care plan including therapeutic physical activity	95	91	98
Education for physicians on diagnostic techniques, algorithm, interpretation of results	95	95	97
Regular communication between healthcare professional team and AATD patient	94	94	97
Having access to pulmonary rehabilitation and being taught the techniques and how to use the equipment at home	93	95	93
Diagnosis in liver disease patients (children and adults)	93	92	95
Educational programmes regarding regional/national resources to diagnose and refer AATD patients	93	96	95
Smoking cessation	93	88	96
Develop better ways of teaching people to use their medicines e.g. inhalers, oxygen	92	90	94
Diagnosis of non-respiratory diseases associated with AATD	91	90	95
Develop other aspects of integral care (e.g. physical activity, caregiver support, maintaining work or schooling, nutrition, psychological care, sex life, daily life)	91	85	94
Role of pulmonary rehabilitation	91	89	95
Availability of organ (lung and/or liver) donation	90	91	92
Role of nutrition	90	91	93
Use of vaccines to prevent exacerbations	90	93	90
Relationship between AATD and other diseases	90	94	89
More evidence on effectiveness of augmentation therapy	90	94	92
Different evolution of the disease among patients	89	91	91
Synthetic AAT production to cover the demand	89	91	88
Evidence on the effect of augmentation therapy on reducing exacerbations	89	92	90
Development of an international AATD registry	89	91	89
Alternatives to IV augmentation therapy (e.g. inhaled augmentation therapy)	89	89	94

Data are presented as the % of participants that considered each item to be important or very important. AATD: α_1 -antitrypsin deficiency; COPD: chronic obstructive pulmonary disease; AAT: α_1 -antitrypsin; IV: intravenous.

access to reliable, easy to understand information about living with AATD (97%), being able to recognise an exacerbation (97%), targeted screening programmes for COPD and asthma patients (96%), and having an action plan for exacerbations and easy access to healthcare during episodes (96%) (table 4). The complete survey results by section are shown in supplementary material S4.

Differences in research prioritisation between countries according to reimbursement of therapy

Top research priorities identified by respondents in reimbursed and non-reimbursed countries are shown in table 4. For both groups, top research priorities included more evidence on effectiveness of

augmentation therapy, education for physicians on diagnostic techniques, algorithms for treatment and interpretation of results, and improving knowledge of AATD in particular among GPs. Respondents in non-reimbursed countries considered access to AATD specialised centres and to reliable, easy to understand information about AATD a priority, as well as having an action plan for exacerbations. For individuals in reimbursed countries, a personalised integrated care plan including physical activity, targeted screening programmes for COPD and asthma patients, and being able to recognise an exacerbation were also relevant, among others. Research on alternatives to intravenous augmentation therapy was also considered relevant for these participants. The complete survey results by type of country are shown in supplementary material S5.

Discussion

International collaboration is crucial to develop strategies for improving patient care and research in the field of rare diseases. Although research in AATD has been conducted for more than 50 years [5], there are still several areas of uncertainty. This is a result of the limited number of patients affected by the disease, which is a hurdle for large epidemiological studies [6] or sufficiently powered clinical trials [7], and the reduced investment in research into rare diseases generally. These two challenges provide motivation to join forces and direct research to the aspects that are considered more relevant by researchers and, more importantly, by the patients themselves.

In this context, the ERS endorsed the creation of EARCO [3, 4], aimed at establishing a collaborative effort to advance understanding through research and to improve the quality of life of patients with the disease. The first objective of EARCO was to design and implement a prospective, international registry of patients with AATD to better understand the natural history of the disease and to investigate the impact of different therapies, including augmentation therapy, on the disease course [8]. This registry is already open and recruiting (information available at www.earco.eu/registry). Beyond the registry, or in addition to it, EARCO wants to establish a research agenda for AATD; to develop this agenda, a working group designed and conducted the current survey of unmet needs and challenging aspects to management and research in AATD for healthcare providers and patients.

Healthcare providers' research priorities

The main research priorities that healthcare providers focused on was understanding the evolution of the disease and the risk factors for poor outcomes and, consequently, identifying the best candidates, the best regimens and the right time to initiate augmentation therapy. The first prospective studies of cohorts of AATD patients indicated the large variability in rates of lung function decline, in particular between index and non-index cases and between smokers and never-smokers [9, 10]. However, these factors do not completely explain the variability in the natural history of lung disease in AATD [11, 12]. Although individual cases may have poor evolution, it is recognised that the majority of never-smoker, non-index patients with AATD have the same survival as the general population and therefore may not require any specific treatment [13]. However, early identification of at-risk individuals is crucial because treatment only slows down the evolution of emphysema, it does not restore the damaged lung [14].

Indications for and regimens of augmentation therapy have remained unchanged for >30 years [15], but evidence has accumulated suggesting that treatment needs may be different for different patients [16]. Only recently, the biochemical efficacy of double doses of AAT was tested in a pilot study [17] and a clinical trial comparing different doses is ongoing [18]; different routes of administration, such as inhaled AAT, have also been explored [19]. It is clear that more research is needed on identifying the right therapeutic regimen in a more personalised approach to augmentation therapy [16]. Interestingly, the research priorities identified by the survey matched very well with those proposed by the ERS task force on AATD (table 1) [2].

Other research priorities that were selected by both healthcare providers and patients were the need for early and accurate diagnosis and the design of targeted screening programmes. Because both lung and liver AATD-associated diseases are irreversible, early identification is crucial to stop the evolution of the disease at mild initial stages [20, 21]. Studies conducted in the 1990s showed that, on average, patients with AATD had a delay in diagnosis of around 8 years and >20% of patients had visited four or more physicians before the diagnosis was established [22]. Moreover, this finding refers to those who were diagnosed, but epidemiological studies have indicated that despite several information campaigns and detection programmes, the majority of patients remain undiagnosed and do not receive appropriate care [1, 6]. It is not surprising that early diagnosis and the development of effective screening programmes were selected as top priorities by patients and healthcare providers.

Patients' and caregivers' research priorities

Dissemination of information about the disease is a necessary first step to improve early and accurate diagnosis of AATD. One of the first priorities for patients was improving knowledge about AATD among GPs. Different surveys in European countries have demonstrated the gaps in knowledge about AATD among different specialists, and in particular among GPs [23, 24]. This is relevant because in many countries GPs attend the majority of patients with COPD and they are the first contact for these patients with the health system; therefore, if early diagnosis is the goal, improving knowledge and awareness among GPs must be a priority action.

One of the top priorities for patients and caregivers was access to specialised, reference centres for AATD care. Owing to the low prevalence of AATD, it is almost impossible for a single clinician or department to accumulate enough expertise in its diagnosis and management; therefore, care for patients with AATD is best organised in reference centres that can provide the highest standard of care and advice to the individuals affected and their families while also contributing to knowledge accumulation. This is in line with the recommendations of the European Commission on management of rare diseases [25]. The recent ERS statement on AATD included a description of the optimised format of service provision by a reference centre for AATD [2]. These reference centres must establish a registry of their activity and collect information on the natural history of the patients prospectively. The development of registries is crucial because it is the only way to successfully accumulate knowledge about the clinical characteristics, evolution, natural history and response to treatment of patients with rare diseases such as AATD.

The next priority for patients was access to reliable information. This is very relevant in an era of misleading information, and it is important for patients to be able to identify reliable sources of medical information, e.g. information from scientific societies and patients' associations. Examples of reliable sources of patient information and support for the AATD community are ELF (www.europeanlung.org), Alpha-1 Global (www.alpha1-global.org), the Alpha-1 Foundation (www.alpha1.org) and several national Alpha-1 patients' associations, including the Alpha-1 UK Support Group (www.alpha1.org.uk) and Alpha1 Deutschland (www.alpha1-detschland.org).

Finally, among the top priorities for patients was the need to recognise an exacerbation and some aspects related to exercise and rehabilitation. These are medical aspects relating to self-management that can potentially improve the quality of life of the patients, but, interestingly, they were ranked just below some other organisational aspects of the disease.

Challenging aspects to manage for patients and barriers for treatment

Patients identified problems related to decreased exercise tolerance and shortness of breath as the most difficult to manage, followed by other similar concepts such as tiredness and fatigue. Other respiratory symptoms, such as cough or even exacerbations, were not perceived as so difficult to manage. This is related to the finding that access to pulmonary rehabilitation, to maintenance exercise classes and to fitness centres were among the most challenging barriers for treatment mentioned by patients. Strategies to provide adequate access to pulmonary rehabilitation and for maintaining adequate levels of physical activity must be encouraged.

Professional implications and additional costs due to the disease or therapy were also very high in the ranking of barriers for treatment. Patients with lung disease associated with AATD are younger than patients with usual COPD and in most cases professionally active. The disease may, therefore, have a huge impact on their professional lives and economic status.

Differences between patients living in countries where augmentation is reimbursed or not

The ERS statement on AATD [2] highlighted the differences in access to specialised care and specific treatments for patients in Europe. Regarding augmentation therapy, there are inequalities of access across different European countries [25, 26], which were confirmed in a recent European survey [27]. Even in countries where augmentation is available and reimbursed, there are differences in prescribing habits between regions, cities and even centres in the same city depending on personal views of attending physicians about efficacy of treatment [27]. These differences in access to treatment have an impact beyond the direct effect of therapy. In our survey, we observed worse scores in all challenging aspects of management in patients living in countries where augmentation is not reimbursed. It is likely that patients living in countries where augmentation is reimbursed may have more frequent contact with healthcare providers and better knowledge about their disease. This is a new and unexpected finding of our survey that requires corrective actions in countries without augmentation therapy available.

Not surprisingly, the most challenging barrier for treatment for patients in non-reimbursed countries was, by far, access issues to augmentation therapy, while patients in reimbursed countries indicated that

maintenance of physical activity was the most challenging barrier for treatment. Again, in the majority of items, patients in non-reimbursed countries gave a lower (worse) score than patients in reimbursed countries.

Conclusions

The main research and management priorities identified by healthcare providers and patients included 1) markers of prognosis of the disease and understanding the natural history of AATD; 2) personalised treatment: when, which regimen and to whom; 3) improve information to physicians, including GPs, and improve early and accurate diagnosis; 4) access to specialised, reference centres and to reliable information for patients; 5) equal opportunities for accessing existing therapies: augmentation, pulmonary rehabilitation and maintenance of physical activity.

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