Alvelestat: An Investigational Oral Neutrophil Elastase Inhibitor for the Treatment of Alpha-1 Antitrypsin Deficiency-associated Emphysema

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Professor Stockley is Professor of Medicine at the University of Birmingham and established the Lung Immunobiochemical Research Group in the 1980s to study the cell biology and biochemistry of chronic obstructive pulmonary disease (COPD). He has a longstanding interest in COPD phenotypes with particular reference to airway inflammation, proteinases and anti-proteinases, and especially the role of the neutrophil, bacteria and exacerbations, which he lectures widely on. He acts as an advisor to many pharmaceutical companies on the design and delivery of phase II and phase III clinical trials, and has been the principle investigator for several large multinational COPD trials. Professor Stockley organized a comprehensive alpha-1 antitrypsin deficiency (AATD) database and the ADAPT programme for clinical management and research in AATD in the 1990s. This database includes over 1,000 patients and has documented the natural history of the disease for almost 20 years. He also established the Alpha One International Registry (AIR). He has coordinated multicentre trials of augmentation therapy and alveolar regeneration in these patients, and continues to act as an advisor to several companies exploring new therapies for AATD. He has published more than 450 peer reviewed papers, reviews and chapters, edited eight books, supervised 47 higher degree theses in clinical and basic science and been a member of the editorial board of more than 15 journals. He has been a member of the Executive Committee and is currently a member of the Scientific Committee of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). He initiated and established the International meeting on COPD held every 2 years in Birmingham. UK since 1998.

Keywords

Alpha-1 antitrypsin deficiency, alpha-1 antitrypsin deficiency-related lung disease, alvelestat, ASTRAEUS, emphysema, Fast Track designation, lung diseases, neutrophil elastase inhibitor

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Alpha-1 antitrypsin deficiency (AATD)-lung disease (LD) is a rare genetic disease caused by a deficiency of the alpha-1 antitrypsin (AAT) protein in the blood and lungs. Loss of the AAT protein reduces inhibition of the proteases, specifically neutrophil elastase, which digests connective tissue in the lungs.[1]

AATD is associated with a predisposition for developing emphysema, with this risk further increased in smokers.[2] AATD often remains undiagnosed, with heterogeneity in the presentation of LD, and the World Health Organization (WHO) recommends testing all patients with chronic obstructive pulmonary disease (COPD) or adult-onset asthma for AATD.[3,4]

Alvelestat (Mereo BioPharma, London, UK), is an oral neutrophil elastase inhibitor currently being investigated in the phase II ASTRAEUS study (ClinicalTrials.gov identifier: NCT03636347) in patients with severe AATD-associated emphysema.[5] In an expert interview, Prof. Robert Stockley discusses the unmet needs for new therapies to treat AATD-LD, the difficulties in conducting clinical trials in rare diseases, and what the Fast Track designation of alvelestat will mean for clinical development.[6]

Q. What is the link between alpha-1 antitrypsin deficiency and emphysema and why is a diagnosis of alpha-1 antitrypsin deficiency-related lung disease often overlooked?

The issue is that firstly, people are not aware of the WHO remit that, although the first cases were very clear and people thought that they were relatively straightforward (young people with minimal smoking history and lower zone emphysema), usual emphysema tends to be located in the upper lobe and is observed most frequently in middle age, and in heavy smokers.[7] Unlike these initial cases, few patients present at a young age with minimal smoking history and emphysema in the lower zone of the lung. This has led to a lack of testing in patients. The WHO highlighted that assumptions about presentation were being made, which was leading to an under-represented testing population. Research has been conducted to show that AATD has a heterogenous presentation. Patients can present late in life or early in life, with emphysema at the top of the lung or at the bottom of the lung, and also with other issues in the lungs. Due to the simplicity of the testing, the WHO suggested testing to be conducted for AATD in all patients with COPD, which is a broad term as not every patient with COPD has emphysema. This change will hopefully instil a change in thinking in physicians, as many do not see the value in testing, especially due to the

lack of treatment options in some countries for an AATD diagnosis. This is a negative mindset that is particularly prominent in the UK and is a blinkered view towards any medical condition, creating a diagnostic and management blind spot. There are physicians becoming more aware and in turn testing more. But the reality is, the vast majority of patients with AATD go through life perfectly well. Therefore, there is an assumption that all subjects with AATD had a high risk of developing COPD and emphysema, which is unlikely to be true.

Q. What are the difficulties in developing new therapies to address alpha-1 antitrypsin deficiency-related lung disease?

The first issue to be addressed is identifying a patient who is believed to have AATD. As AATD is related to low alpha-1 antitrypsin (AAT) level, in the 1980s it was believed that a resolution to the issue would be to replace the AAT. Almost 30–50 years later, a clinical trial that was sufficiently powered to show the effect of adding AAT has been delivered.[8] Attempts at a successful clinical trial have proven difficult due to the rare nature of the disease. The incidence in Europe is between 1 in 1,600 to 1 in 2–4,000, depending on geographical location, and if only a subset of these individuals develop AATD-LD, this significantly reduces the potential sample size for classical clinical trials.[9]

A pilot study was conducted with the aim of investigating the usual methods of assessing how patients progressed, which are relatively insensitive as everyone ages and lung function declines even without LD.[10] A successful study therefore needs to demonstrate that intervention improves the rate of decline that is additional to your average decline caused by age, which is a difficult trial to complete as it requires too many patients. The intervention and assessment is not as simple as a study where antibiotics are prescribed and the primary endpoint is cure of the infection or improved survival. In this study, to pinpoint and measure the emphysema accurately, lung scans were used, which enabled a study assessing the efficacy of AAT replacement to be powered in a smaller sample of patients.[10] The first such study involved a couple of centres with 36 patients and showed some benefit, however, this was not statistically significant. This indicated that to conduct a properly powered study using the scanning method, the sample size needed to be at least doubled. Eventually, this was achieved and published a few years ago.[8]

We are now at a point in the literature where it has been demonstrated that AAT replacement has an effect on AATD-LD. However, agencies such as the United States Food and Drug Administration (FDA) have queried what this means for patients. It has been shown that the more emphysema a patient has, the worse they feel, the worse the lung function, the worse the exercise capability and the less chance of survival. But the FDA want to know what this really means as the data have not shown to have an effect on any of those factors. Then we reviewed these papers showing that even if you give the AAT, you do not actually stop the emphysema, you slow it down and that, again, creates a problem as there needs to be an explanation for why it cannot be stopped. Therefore, there are multiple reasons why the trials cannot be conducted and interpreted like a conventional trial, which causes the agencies that review the trials, such as the FDA, to be reluctant to say yes the treatments are approved.

Q. What is the mechanism of action and rationale for investigating alvelestat in alpha-1 antitrypsin deficiency-related lung disease?

The function of AAT in the human body is to protect tissues that get inflamed. When tissues get inflamed, the white blood cells (WBCs), which are one of the main defence cells in your blood, move to the area of inflammation. To get there, the WBCs have to move out of the blood vascular system, which they achieve by releasing high concentrations of discrete enzymes. The enzyme that people concentrate most on is neutrophil elastase. It was the first enzyme that demonstrated the ability to produce emphysema and it digests lung connective tissue, particularly elastin.[11] WBCs have to release neutrophil elastase when they go into the lungs, therefore, in every person when these cells move into the lungs, albeit in extremely small numbers, on a daily basis some damage occurs, which may be the cause of the aging-related decline. When you smoke, larger numbers move across meaning more cells and more elastase. When you have a chest infection, you also get more elastase released due to increased numbers of WBCs. The AAT then moves into the tissues, allows the WBCs to get into the lungs, and then the AAT mops up these enzymes before they cause too much damage. If a patient has AATD, more damage occurs for every cell that moves, and this forms the rationale for AAT treatment. If neutrophil elastase is the agent that causes that damage, then developing a drug that functions in the same manner as AAT by inhibiting elastase enables mass production compared with the difficulties and limitation of purifying it from plasma. It also offers the option of consumption via tablet, rather than requiring injections every week to uphold anti-elastase defences. Therefore, the rationale is a sensible one. It is a better method for patient consumption, it is more specific, and you can administer a reasonable dose that will cover the missing functional capacity of AAT.

Q. What were the aims and design of the phase II proof-of-concept ASTRAEUS trial and what were the topline findings?

I advise pharmaceutical companies with novel agents and the first piece of advice for companies is to demonstrate that the compound does what it claims to before spending millions on conducting a large clinical trial. For example, a drug like alvelestat, which is an anti-elastase, should be able to show that it restricts elastase production and release or damage when given to patients. Firstly, a phase II trial should demonstrate that the drug administered does not have serious side effects. Next, a target patient group should be selected in whom you are likely to see signs of elastase causing damage, then when the drug that inhibits elastase is administered, that signal should be reduced if not wiped out. That should be the protocol for all phase II studies with a novel drug. A large study spanning a 12-month period was initiated in patients with AATD, however, the coronavirus disease 2019 pandemic occurred, which resulted in difficulties with recruitment and patients not wanting to attend face-to-face hospital appointments to have the required tests.[5] At this point, the sample size had reached 100 patients, and this ended up being the final sample size due to recruitment issues. Mereo BioPharma were conducting an array of safety tests, assessing the effect on lung function, how patients felt, as well as using specific markers of elastase activity.[6] These markers decreased in patients receiving the drug but did not decrease in patients receiving placebo. As the signals decreased in patients receiving the drug, there were additional signals that indicated efficacy, and patients also claimed to be more active. However, these data were clearly and statistically split between the two arms, (the patients receiving a placebo and those receiving the active drug). From that point of view, it clearly achieves what it claims to be able to. There were a few other surprising findings, particularly the activity side, which can now start to be included as an outcome while moving forward to a more traditional type of clinical trial, which will include measuring the amount of emphysema. Though, to achieve an analysable signal, those trials need to run for two or three years.

Q. What will be the next steps for alvelestat following the topline efficacy and safety data from ASTRAEUS?

The next step for Mereo BioPharma is taking the preliminary data and using it to convince the European Medicines Agency and the FDA that they are going to conduct a sensible trial. This is currently underway and further information will be sought from the two agencies in Europe and the USA. In response to the application, these agencies can modify the trial or ask for other things to be included. They can try and change the statistics and the way the statistics are applied. However, these agencies have to be slightly more realistic than they have been previously as the traditional trials in COPD have been conducted with up to 18,000 patients. A trial in this indication will not have a sample size of that magnitude. The COPD trials assess the effect of an inhaler, which is a treatment that can make a patient feel better within days. Whereas, in AATD-LD, the trials are looking at a treatment that prevents a patient from getting worse as time goes by and given the fact that humans are continuously declining with age, this treatment is a more difficult one to assess as it has to differ from natural decline.

Q. How has Fast Track designation by the United States Food and Drug Administration impacted the development of alvelestat?

The FDA has been approached on many occasions with requests of simpler outcomes and methods to validate the efficacy of such drugs. Therefore, data can be submitted with a note that if this methodology is used and the treatments proposed show benefits, it would be seen in a trial of this alternative design. Almost every time the FDA is approached, the first thing they ask is how it is going to affect lung function. With new updates, a letter of intent will be written to the FDA asking for the proposed alternative method to be accepted by the FDA. One thing that has been requested is for computed tomography scans to be accepted by the FDA, as then drugs can be fast tracked, however, this request has continuously been declined. If patients have an inhaler, which is a bronchodilator, lung improvement upon use will be noticed within days, with patients suddenly feeling better. If patients have multiple chest infections over a year or two, they will get less chest infections if the drug works. There are ways of assessing efficacy by asking how the patient feels, and those are also accepted to reflect efficacy if the health of the patient has changed by improving or declining. However, when you are assessing a population with a chronic disease, where the factors being investigated are decreasing anyway, the difference in decrease needs to be compared with the decline in patients without the disease. This is a much more difficult feat to achieve unless a long study with a very large number of patients is conducted, and unless a novel approach is adopted. ❑

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