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Review

Feasibility of Aerosolized Alpha-1-Antitrypsin as a Therapeutic Option

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Abstract

Inhalation therapy is integral in the management of patients with chronic obstructive pulmonary disease (COPD). Specifically, intravenous augmentation therapy is available to patients with alpha-1 antitrypsin deficiency (AATD), although there is insufficient alpha-1 antitrypsin (AAT) delivery to the lungs to modify airways inflammation. In contrast, the inhaled route allows replacement therapy to reach the target site of action and with higher AAT levels. Patients certainly support the inhalation route as an alternative to intravenous injections, obviating repetitive needle insertion and allowing treatment empowerment rather than dependency on traveling to specialized units. The difficulty with inhalation has been the ability to target the formulation to the pathophysiological site of disease: the emphysematous lung parenchyma of the small alveolated airways. Recent advances have suggested nebulizers as being able to deliver an adequate dose, consistently and reproducibly, and, coupled with developments in formulation science, allowed replacement therapy to reach the epithelial lining fluid of the small airways. The bench science has been translated to the first randomized, placebo-controlled clinical trial to study the effects of nebulized AAT, which, although not meeting the primary endpoint of prolonging time to first exacerbation, showed this treatment modality was safe and achievable in a large patient cohort. Indeed, learning from this trial suggests the importance of choosing the right clinical endpoints, and recent key advances in lung physiology indices allow better assessment of the "silent zone" of small airways disease. Knowledge from other respiratory diseases will complement treating patients with AATD, where there is considerable innovation in aerosol science and inhalation medicine directed at utilizing the inhaled route. Indeed, it could be postulated that the inhaled route may not only achieve local pulmonary therapeutic benefit, but through systemic absorption and controlled pharmacokinetic profiling, the formulation may reach and treat liver disease.

Abbreviations: chronic obstructive pulmonary disease, **COPD**; alpha-1 antitrypsin deficiency, **AATD**; alpha-1 antitrypsin, **AAT**; pressurized metered dose inhalers, **pMDIs**; dry powder inhalers, **DPIs**; soft mist inhaler, **SMI**; diffusing capacity of the lung for carbon monoxide, **DLCO**; forced expiratory volume in 1 second, **FEV_1**; computed tomography, **CT**; COPD Assessment Test, **CAT**; functional small airways disease, **fSAD**

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Introduction

From ancient civilizations to modern day practice, the inhaled route has been the foundation and cornerstone in the treatment for patients with respiratory disease, including those with chronic obstructive pulmonary disease (COPD).[1] With the availability of a variety of inhaler devices, aerosolized medication is delivered directly to the site of action to achieve a therapeutic benefit for the patient, thereby minimizing adverse side-effects as compared to the parenteral route. Recent years have seen focused research leading to critical developments in the inhalation route to improve the efficiency of drug delivery systems to target the airways, but also to investigate the inhalation route as a conduit for systemic drug delivery.[2]

Patients with alpha-1 antitrypsin deficiency (AATD) are at an increased risk of developing COPD and pulmonary emphysema and it is the emphysematous lung parenchyma of the small alveolated airways that is primarily associated with AATD and its potential treatment. Management of patients with AATD centers on the general treatment of the underlying COPD and preventing disease exacerbations with inhaled therapy, pulmonary rehabilitation and oxygen therapy. Specific therapy with intravenous AAT augmentation therapy, which is only approved in certain countries,[3] is designed to protect against the inflammatory destruction of the lung parenchyma and attenuate the development of pulmonary emphysema.[4] However, 3 randomized, controlled trials have not demonstrated a significant decrease in the rate or the severity of disease exacerbations,[5] and it has been suggested that the intravenous route does not allow sufficient AAT delivery to the airway epithelium in order to modify airways inflammation.

In this respect, the inhaled route of delivery of AAT seems appealing as it gives the opportunity to deliver AAT directly to the site of disease in the lungs. Data show much higher local AAT levels in the airway epithelial lining fluid have been achieved with the inhaled route compared to delivery with the intravenous route.[6,7] This paper reflects on some of the potential advantages, challenges and key considerations in the feasibility of aerosolized AAT as an alternative approach to intravenous alpha-1 augmentation therapy in the management of patients with AATD.

What Matters to Patients?

As end users, the presumption that patients with AATD receiving intravenous augmentation therapy are content, is not consistently borne out. A study by the Alpha-1 Foundation Research Registry undertaken to gauge patient interest in the potential of AAT therapy delivered by the inhaled route, recorded high levels of acceptability.[8] The survey was conducted in the United States on PiZZ genotype patients, where approximately two-thirds of patients were taking regular inhalation treatment (inhaled bronchodilators and corticosteroids) and all were receiving intravenous augmentation therapy (approximately 85% weekly with 89% for over a year and 17% for over 10 years). Of 107 respondents (age range 31–92 years) asked "what are the most important attributes of any new alpha-1 antitrypsin therapy," 78% specified "better ability to reduce my symptoms," 50% stated "new therapy should not be intravenous" and 51% expressed "lower cost."

This patient-centric study highlights the problems with current intravenous augmentation therapy and the willingness to consider alternative modes of therapeutic delivery. Indeed, many patients with AATD are already familiar with the inhalation route of treatment and this route is therefore readily and naturally acceptable to them. When asked about the advantages of inhaled therapy, the following were cited: flexibility and ability to travel, needle aversion, avoiding repetitive intravenous access, and independence from the health care provider to administer. In contrast, relative disadvantages of the inhaled route cited were increased frequency of administration, unproven benefit, and difficulty in inhaling deeply. When posed with a hypothetical scenario of 2 new alpha-1 augmentation treatments that could be delivered by the inhaled route (one a nebulizer and the other a dry-powder inhaler), with similar efficacy to their current therapy, approximately 2/3 of patients were highly and extremely interested in both inhaled routes of delivery and only 7% were not interested in either. Further analysis of the patient responses observed those patients on regular inhaled bronchodilators were more interested in the inhaled route than those not on inhaled therapy and overall, more patients were interested in the dry powder inhaler device (71%) compared to the nebulizer device (64%).

There was less interest from those patients who were receiving intravenous alpha-1 augmentation therapy for the longest duration and financial considerations were a concern, as those who paid more than $100 per month out of pocket for intravenous alpha-1 augmentation therapy felt lower cost an important attribute of a new treatment.

Where Do We Need to Target?

With the recognition that the inhaled route may offer several advantages over the intravenous route, formulation scientists and device engineers have been challenged to deliver an effective and clinically efficacious lung dose to the airways.[9] Indeed, the ability to specifically target the inhaled therapeutic drug to the site of pathophysiological disease has recently seen great research impetus in patients with COPD.[10] COPD is a disease of the small airways, with the hallmarks of hyperinflation, air-trapping, parenchymal destruction and bullae.[11] The small airways are physiologically the major site of airflow limitation,[12,13] and pathologically the structural damage that causes narrowing of the peripheral airways leads to an insidious trajectory of physical deconditioning, dyspnea, exercise limitation and increasing disability. As the pathophysiological site of disease in AATD is the emphysematous lung parenchyma of the small alveolated airways, it seems logical, if not a necessity, that inhaled treatment should target the disease pathophysiology in the distal lung regions.

How Do We Get There with the Device?

There are a variety of inhaler devices used in respiratory medicine including pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), soft mist inhalers (SMIs) and nebulizers.[2] The challenge is to find an appropriate aerosol system with features that will provide a beneficial aerosol for patients with AATD. The nominal dose emitted from pMDIs and DPIs is small and these devices may need to be used repetitively to be able to achieve adequate dosing to the airways for effective anti-protease activity in patients with AATD. Within the nebulizer category, ultrasonic nebulizers generate a high frictional force that can destabilize proteins such as AAT and are not suitable delivery systems. The alternative nebulizer systems are jet nebulizers and vibrating mesh nebulizers, where the latter achieves greater efficiency in drug delivery to the lungs, but are more expensive and have limited availability for an aerosol fine enough to target the very distal respiratory bronchioles and the alveoli. Aerosol science has shown that the important factors to achieve efficient drug deposition in the lungs and effective delivery to the distal lung regions are drug particle size and inhalation flow.[14] It has been shown, using monodisperse aerosols that can accurately assess the airway distribution of inhaled particles,[15] that a smaller drug particle size (< 3 microns) inhaled at a slow inhalation flow (30 litres / min) achieves better total lung deposition and peripheral drug distribution than larger drug particles in patients with COPD and asthma.[16,17] Devices that control breathing patterns, which are optimized for each patient individually, certainly, are an advance, where targeting of aerosols to the peripheral lung regions may be achieved with controlled delivery methods.[18] A number of radiolabelled imaging studies designed to specifically look at aerosol treatment in patients with AATD with controlled delivery methods have shown high total lung deposition[19] and the ability of the alpha-1-protease inhibitor to penetrate to the lung periphery.[20] An appreciation of these studies shows that there are different approaches between laboratories used to assess and determine aerosol deposition in the lungs, and radiolabelled imaging studies should report a complete mass balance in order to calculate device efficiency and lung penetration of the aerosol.[21] For this very reason, a consensus statement to standardize the methodology to facilitate data comparison between laboratories has been published.[22]

It is clear that AATD affects the distal lung region and that any replacement therapy needs to reach the epithelial lining fluid of this region, and this poses important considerations for the formulation.[23]

What Are the Challenges for Formulation Science?

There are many barriers that an inhaled formulation for the treatment of AAT disease needs to overcome in order to have a biochemical effect in reaching and maintaining protective AAT levels in lung tissue

and blood.[24] Not only does the anatomy of the oropharynx, upper airways and distorted branching airway divisions in disease impede efficient drug deposition in the distal lung, other factors such as the presence of mucus may impede the aerosol reaching its intended site of action and once there, the epithelial thickness, alveolar integrity, and interstitial thickness will also affect aerosol retention within the airways. Characteristics of the protein such as particle size, density, lipophilicity, and charge need to be optimized to achieve stability of the formulation, and then tested with a suitable drug delivery system to achieve dosing consistency, in order to provide an opportunity for the inhaled AAT to have a biochemical effect in reaching and maintaining protective AAT levels in lung tissue.

Recently, the first randomized placebo-controlled clinical trial to study the effects of inhaled nebulized AAT for 50 weeks in 168 COPD patients with AATD-ZZ with a high risk for exacerbations, showed on the primary endpoint that inhalation did not prolong the time to the first event-based exacerbation after randomization.[25] However, it was observed that those patients receiving inhaled AAT had a significant reduction in more symptomatic Anthonisen type I exacerbations, and a tendency towards a better forced expiratory volume in 1 second (FEV_1), although this was only evaluated as a safety parameter and not an efficacy outcome. The accompanying editorial reflected on aspects that may have affected the outcomes including the study population (heterogeneity in exacerbation frequency was observed with some patients not meeting the description of a "frequent exacerbator"), study design (as patients learned how to use their delivery system, there was an improvement in how the patients dispensed their medication within the trial duration, which may have improved the overall efficacy of the intervention if optimized at the beginning of the study) and the choice of trial endpoints.[26]

Which Outcomes/Endpoints to Measure Success?

The importance of suitable clinical trial design, including a relevant study population and appropriate endpoints to guide clinical practice, is paramount for any therapeutic medication, including those for AATD.[27] A variety of endpoints have been used to indicate success of treatment including a change in patient symptoms, medication utilization, disease exacerbations, lung physiology markers, and imaging indices. In patients with AATD, where the disease is predominant in the small alveolated airways, markers of distal airway disease are noticeably important[28]; a decline in transfer factor—diffusing capacity of the lungs for carbon monoxide (DLCO)—has been shown to occur before changes in FEV_1,[29] and DLCO and lung computed tomography (CT) lung density demonstrate parenchyma loss even in severe AAT disease where FEV_1 may be stable.[30] CT lung density is the best predictor of mortality in AATD patients and superior to lung function markers.[31] Most recently, specialized physiological techniques such as oscillometry have evolved that allow a specific assessment of the small airways and these have been utilized in patients with AATD.[32,33] Oscillometry indices of small airways disease have been shown to be present in the majority of COPD patients, and increase progressively with patient symptoms and corelate with the COPD Assessment Test (CAT) score.[34] Lung imaging has also provided advanced techniques for assessing functional small airways disease (fSAD) using CT and parametric response mapping methodology,[35] where recently it has been shown that the ratio of FEV_3/FEV_6 and worsening DLCO both strongly correlate to fSAD indices.[36,37] These techniques will allow better characterization of the disease in patients with AATD and provide important endpoints to relate treatment intervention with meaningful pathophysiological indices and patient outcomes.

What Can We Learn From Other Diseases?

Presently, there is considerable effort and innovation in aerosol science and inhalation medicine directed at utilizing the inhaled route to treat many respiratory diseases, where advances in formulation chemistry and airway modelling approaches have given insights into targeting drugs directly to the lungs and specifically to the small airways.[38] An inhaled formulation of a small molecule protein inhibitor of $\alpha v\beta 6$ integrin in the treatment of patients with interstitial pulmonary fibrosis is under drug development,[39] where elevated $\alpha v\beta 6$ integrin expression has been shown to be associated with fibrosis.[40] Specifically

in tuberculosis, inhaled anti-tuberculous therapy is under exploration, where treatment needs to target deep lung alveolar macrophages that harbor the microorganisms, and progressive formulation engineering approaches are being applied in order to achieve high drug concentrations at the infection site in the lung.[41,42] Aerosolized medications have long been standard treatments for cystic fibrosis and there is considerable interest in the utility of inhaled viral gene vectors,[43] where recent findings provide ongoing insight into understanding the interaction between the molecular immuno-biology of the vector and in overcoming barriers to inhaled drug penetration.[44]

Can We Treat the Lung and the Liver by the Inhaled Route?

AATD is the most common genetic cause of liver disease in children, where insoluble mutant antitrypsin " Z" allele proteins are retained in the endoplasmic reticulum of hepatocytes and the accumulation leads to inflammation, fibrosis, cirrhosis, and an augmented risk of hepatocellular carcinoma. At this time, the only approved therapy for AATD-associated liver disease is orthotopic liver transplantation, which is curative. Autophagy is specifically activated by accumulation of AAT-Z in the endoplasmic reticulum and plays a significant role in the disposal of this mutant protein.[45] Enhancement of autophagy has been considered as a potential alternative to liver transplantation using autophagy enhancing drugs such as carbamazepine.[46] In macrophages infected with *Mycobacterium tuberculosis*, an inhalable formulation of rapamycin drug particles has shown to induce autophagy[47] and is undergoing preclinical evaluation.[48]

It is tempting, indeed " blue skies" thinking, to postulate that in the future an inhaled autophagy-enhancing agent could produce not only local pulmonary therapeutic benefit, but through systemic absorption and controlled pharmacokinetic profiling, the formulation may reach and treat liver disease in AATD patients. Nanoparticle therapies may be more advantageous than micrometer aerosols and nanoparticle formulations may overcome the poor solubility and poor bioavailability and achieve controlled-released drug systems on principles similar to what is used for ventilation scanning and currently being investigated as potential chemotherapeutic oncological agents.[49] With the significant research to understand aspects of airway pathophysiology, drug formulation composition, and device engineering, the future holds promise for inhaled therapeutics.[50,51]

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