Perspective

Designing Clinical Trials in “Regular” COPD Versus Alpha-1 Antitrypsin Deficiency-Associated COPD: “More Alike Than Unalike?”

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Abstract

Alpha-1 antitrypsin deficiency (AATD) predisposes to emphysema, liver disease, and panniculitis. This emphysema risk naturally invites a comparison between “regular” chronic obstructive pulmonary disease (COPD) (i.e., unrelated to AATD) and AATD-associated emphysema.

Several features characterize both conditions. Both can be life-limiting and highly debilitating. Both are highly under-recognized.

An important corollary of this comparison between “regular” COPD and AATD-associated COPD is whether both should be treated similarly and whether clinical trials to assess new therapies can be conducted similarly in both. Here, the distinctions between “regular” COPD and AATD-associated COPD are quite pronounced. Therapeutically, sparse available data suggest that lung volume reduction surgery confers less improvement in forced expiratory volume in 1 second (FEV1) in AATD and that such benefits are shorter-lived. Perhaps the most striking contrast between the 2 conditions is that clinical trial designs and conduct are necessarily very different. The relative scarcity of diagnosed individuals with AATD hampers recruitment to trials. Furthermore, primary outcome measures in trials of “regular” COPD must differ markedly from those of AATD-associated emphysema. Specifically, power calculations show that FEV1 and exacerbation frequency, which are amply represented as endpoints in large COPD trials, are infeasible in studies of AATD-associated emphysema. Rather, in the 3 available randomized controlled trials of intravenous augmentation therapy, the rate of emphysema progression based on serial computed tomography densitometry measurements has been the only feasible primary outcome measure.

These considerations underscore the distinctive challenges and needs of conducting treatment trials in AATD-associated emphysema and emphasize that, with regard to clinical study design, the 2 conditions are “more unalike than alike.”

Abbreviations: alpha-1 antitrypsin deficiency, AATD; forced expiratory volume in 1 second, FEV1; Efficacy and Safety of Triple Therapy in Obstructive Lung Disease study, ETHOS; Body-mass index-airflow Obstruction-Dyspnea-Exercise capacity, BODE; National Heart, Lung and Blood Institute, NHLBI; computed tomography, CT; Long-term Oxygen Treatment Trial, LOTT; randomized controlled trials, RCTs; long-volume reduction surgery, LVRS; relative risk, RR; salmeterol, SAL; fluticasone propionate, FP; hazard rate, HR; tiotropium, TIO; azithromycin, AZITHRO; oxygen, O2; fluticasone furoate, FF; vilanteral, VII; glycopyrrolate, GLYCO; Intravenous Augmentation Treatment in Severe Alpha-1 Antitrypsin Deficiency, RAPID; Towards a Revolution in COPD Health, TORCH; Understanding Long-term Impact on Function with Tiotropium, UPLIFT; St George’s Respiratory Questionnaire, SGRQ; total lung capacity, TLC

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Trial Design in “Regular” COPD versus AATD

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Introduction

Alpha-1 antitrypsin deficiency (AATD) predisposes to chronic obstructive pulmonary disease (COPD), which naturally prompts the question about “lumping” versus “splitting” the 2 entities: COPD associated with AATD versus “regular” (i.e., alpha-1 antitrypsin-replete) COPD. Do the 2 conditions have different clinical implications? Should they be treated differently? Should clinical trials in both conditions be conducted similarly? These issues have been especially topical in the ongoing dialog between the patient and clinical/scientific communities and regulatory agencies regarding endpoints for registrational trials of new therapies for AATD.

In this context, the current perspective considers the common and discordant features of both conditions, with a special focus on issues regarding clinical trial design. In her poem, Human Family, Maya Angelou, the Pulitzer Prize-nominated poet, states: “I note the obvious differences between each sort and type. But we are more alike my friends then we are unalike.” The question here is whether regular COPD and AATD-associated COPD are “more alike than unalike,” especially regarding the design of clinical trials to assess treatment.

Common Features of Regular COPD and COPD Associated with Alpha-1 Antitrypsin Deficiency

Regular COPD and AATD-associated COPD bear important similarities. Both conditions are life-threatening. Regular COPD is currently the fourth leading cause of death in the United States with 38.2 deaths per 100,000. Similarly, data from the recent Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) trial in regular COPD show a 1-year mortality rate of 2.5% in study participants. Also, regular COPD individuals with the highest body mass index-airflow obstruction-dyspnea-exercise capacity (BODE) index quartile (BODE 4) demonstrated only a 20% 1-year survival rate. In AATD, data from the National Heart Lung and Blood Institute (NHLBI) Registry for Individuals with Severe Deficiency of Alpha-1 Antitrypsin showed a similar 18.6% mortality rate at 5 years or approximately 3% year mortality rate.

Another similarity is that both conditions are severely debilitating. Combining death and disability, regular COPD is the fourth leading cause in the United States. Based on data from the NHLBI AATD Registry, 30% of participants whose mean age was 46 years reported being retired or medically unemployed, a reminder of the disability burden associated with AATD.

Similarly, both regular COPD and AATD are severely under-recognized. Specifically, 2020 estimates suggest that >25 million Americans have regular COPD, of whom 12 million are currently undiagnosed. Regarding AATD, estimates suggest that there are approximately 100,000 severely deficient Americans, of whom the vast majority – perhaps ~90,000 – are currently unrecognized. Under-recognition of AATD has regrettably been longstanding. In a 1989 study sampling 20,000 St. Louis blood bank specimens, Silverman et al identified 7 PI*Z genotype individuals, for a prevalence of 1 in 2900. Reasoning that donated blood bank specimens were representative of the overall population of St. Louis (2 million), this prevalence estimate predicted 700 PI*Z St. Louis individuals. However, when the investigators subsequently polled all the pulmonary practices in St. Louis, only 28 (4%) of the expected 700 individuals were reported.

More recently but similarly, an analysis of 458,164 participants in the U.K. Biobank showed that only 6.4% of the 140 PI*ZZ genotype individuals in the Biobank had been previously identified as having AATD. These observations show that AATD is persistently and severely under-recognized.

Further evidence of under-recognition of AATD is the long diagnostic delay commonly experienced by
AATD individuals. A 1994 survey of 300 self-reported severely AAT-deficient individuals showed that the mean age of onset of lung symptoms, most frequently dyspnea, was 35 years but that individuals reported a mean 7.2-year interval between first onset of dyspnea and first diagnosis of AATD. Furthermore, when asked about the number of physicians they saw between first symptom and first diagnosis of AATD, 25% reported having the diagnosis made on the first physician visit but 12.5% reported seeing 6–10 physicians before initial diagnosis; 44% reported seeing >3 physicians before the initial diagnosis of AATD.

This prolonged diagnostic delay interval has persisted over time (Table 1), i.e., was estimated to be 6 years in 2019 versus 7 years in 1994. The inescapable conclusion is that, like regular COPD, AATD remains severely under-recognized currently.

### Table 1. Diagnostic Delay Interval Estimates for Alpha-1 Antitrypsin Deficiency

| Authors and Reference | Publication Year | Country | Diagnostic Delay (Years±SD) |
|-----------------------|------------------|---------|----------------------------|
| Stoller et al⁹         | 1994             | USA     | 7.2 years±8.3               |
| Stoller et al¹⁰        | 2005             | USA     | 5.6 years±8.5               |
| Campos et al¹⁴         | 2005             | USA     | 8.3 years±6.9               |
| Kohnlein et al¹⁵       | 2010             | Germany | 6 years                     |
| Greulich et al¹⁶       | 2013             | Germany | 7 years (0–73, IQR 13)      |
|                        |                  | Italy   | 6 years (0–40, IQR 11)      |
| Tejwani et al¹⁷        | 2019             | USA     | Median 6 years              |

SD=standard deviation; CI=confidence interval

### Discordant Features of Regular COPD and COPD Associated with Alpha-1 Antitrypsin Deficiency

Notwithstanding these considerable similarities between both regular COPD and AATD-associated COPD, there are substantial differences. First, regular COPD demonstrates polygenic inheritance with a strong environmental/lifestyle component. In contrast, AATD is inherited as an autosomal codominant condition where the risk is also amplified by smoking and occupational exposures. AATD is also a distinctive endotype of COPD, with different pathogenesis than regular COPD, a characteristically different distribution of emphysema, and a markedly higher prevalence of associated bronchiectasis. Pathogenetically, McDonough et al proposed that inflammation and subsequent disappearance of small airways leads to the loss of alveolar walls in regular COPD. In contrast, in AATD, emphysema results from unopposed proteolytic damage to lung matrix like elastin, causing the destruction of alveolar walls and resultant emphysema.

Radiographically, the craniocaudal distribution of emphysema between regular COPD and AATD differs markedly; lower lobe predominance is more frequent in AATD, and homogeneous or upper lobe emphysema is more prevalent in regular COPD. Specifically, in PI*ZZ genotype individuals, 96% demonstrated lower lobe predominant COPD in contrast to individuals with regular COPD, in whom homogeneous or upper lobe emphysema was evident in 84%. Data from Parr et al confirm the distinctively lower lobe predominance of emphysema in AATD; specifically, 64% of 102 PI*ZZ genotype individuals undergoing computed tomography (CT) chest scans demonstrated predominantly basilar hyperlucency.

The prevalence of bronchiectasis associated with COPD can also differentiate the 2 entities. The frequency of bronchiectasis in regular COPD ranged from 4% to 69% with a mean of 38.5% in 16 available studies. While prevalence estimates of bronchiectasis in AATD vary, one series showed that 95% of PI*ZZ genotype individuals had radiographic evidence of bronchiectasis, with 31% of individuals demonstrating clinical bronchiectasis, e.g., copious phlegm, with exacerbations, hemoptysis, etc. In the UK Biobank study, though only 4.3% of AATD participants carried the clinical diagnosis of bronchiectasis, the odds ratio for having bronchiectasis in PI*ZZ genotype AATD compared with AAT-replete participants was 7.3.

Treatment differences also underscore the distinctiveness of these 2 entities. Absent specific studies in AATD, mainstay treatment of COPD in both conditions – e.g., bronchodilators, supplemental oxygen, rehabilitation – is often similar. Yet, when AATD has been specifically studied, important
treatment differences are noteworthy. For example, in a subset analysis from the National Emphysema Treatment Trial, lung volume reduction surgery conferred smaller and shorter improvements in FEV1 in individuals with AATD-associated COPD than with regular COPD. Similarly, in a subset analysis from the Long-term Oxygen Treatment Trial (LOTT), individuals with AATD-associated COPD demonstrated earlier and more profound desaturation than matched individuals with regular COPD.

Perhaps the most important dissimilarity between the 2 conditions involves the feasibility and conduct of clinical trials regarding treatments. While regular COPD is common, allowing large-scale recruitment for a large number of clinical trials of various treatments (Table 2), relatively few randomized controlled trials (RCTs) in AATD are available. For example, only 3 published RCTs have examined the efficacy of intravenous augmentation therapy, and 1 each has examined the efficacy of inhaled AAT and the efficacy of the retinoid agonist, palovarotene. The largest of the available RCTs of augmentation therapy in AATD, called RAPID for “Intravenous Augmentation Treatment in Severe Alpha-1 Antitrypsin Deficiency,” recruited a total of only 180 individuals. Notably, recruitment of these 180 individuals took 56 months in 28 centers across 13 countries and actually even longer from study inception to recruitment close (approximately 7 years). The number of participants in the palovarotene and inhaled AAT RCTs were 262 and 168 respectively, underscoring the challenge of recruiting large numbers of participants in RCTs regarding AATD.

In contrast to the experience with AATD, sample sizes from some of the many recent RCTs in regular COPD are summarized in Table 2 and indicate large-scale recruitment success. In some instances, the number of participants was over 1200 for some of the trials.

### Table 2. Summary of Selected Key Trials in “Regular” COPD

| Trial/Author (Reference and Date) | Intervention | Primary Outcome | Number of Participants | Summary of Results |
|----------------------------------|--------------|-----------------|------------------------|--------------------|
| NETT25 (2003)                    | LVRS vs. Usual Care | Survival | N=1218 (of 3777 assessed) | Long-term survival with LVRS > usual care, RR death with LVRS 0.85 (p=0.02) |
| TORCH27 (2007)                   | Salmeterol (SAL)+Fluticasone Propionate (FP) vs. Placebo or Single Agents | Time to death over 3 years | N=6184 (of 8555 recruited) | 2.6% reduction in death risk with SAL+FP, HR 0.825, p=0.052 |
| UPLIFT28 (2008)                  | Tiotropium vs. Placebo | Rate of FEV1 decline over 4 years | N=5993 (N=2987 TIO vs. N=3006 Placebo) | No difference in FEV1 slope after 30 days (2ml/yr, p=0.21) |
| Calverley et al29 (2009)         | Roflumilast vs. Placebo | Time to first COPD exacerbation | N=3296 (2 trials combined, individually N=1525 and 1571) | Roflumilast better than placebo, HR 0.89, p=0.0185 |
| Albert et al30 (2011)            | Azithromycin vs. Placebo | Time to first exacerbation | N=1142 | Longer time to 1st exacerbation with AZITHRO, p<0.0001 |
| POET31 (2011)                    | Tiotropium vs. Salmeterol | COPD exacerbation | N=7376 | TIO>SAL, HR 0.72, p<0.001 |
| LOTT32 (2016)                    | Supplemental O2 vs. No Supplemental O2 | Death and/or time to first hospitalization (any cause) | N=738 | No effect, HR 0.94, p=0.52 |
| IMPACT33 (2018)                  | Fluticasone Furoate (FF)+Vilanterol (VII)+Umeclidinium vs. Double vs. Placebo | Annual rate of mod/severe COPD exacerbation | N=10,355 | Triple vs. FF+VII, rate ratio 0.85, p<0.001 |
| ETHOS5 (2020)                    | Budesonide/Glycopyrrolate (GLYCO)/Fluticasone Furoate vs. Double vs. Placebo | Annual rate of mod/severe COPD exacerbation | N=8572 | Triple vs. GLYCO+FF, rate ratio 0.76, p<0.001 |

LVRS=lung volume reduction surgery; RR=relative risk; SAL=salmeterol; FP=fluticasone propionate; HR=hazard rate; TIO=tiotropium; FEV1=forced expiratory volume in 1 second; AZITHRO=azithromycin; O2=oxygen; FF=fluticasone furoate; VII=vilanterol; GLYCO=glycopyrrolate
as in the TOwards a Revolution in COPD Health (TORCH) study\textsuperscript{27} and the Understanding Long-term Impact on Function with Tiotropium (UPLIFT) study,\textsuperscript{28} where 6184 and 5993 patients respectively participated, differences between treatment and placebo arms were still inapparent, even in the face of very large numbers of participants. As noted, recruitment experience in studies regarding AATD are orders of magnitude greater given the infrequency of AATD\textsuperscript{1,11} and its under-recognition. In this context, regular COPD and COPD associated with AATD are distinctly “more unalike than alike.”

Compounding this recruitment challenge, sample size estimates for various primary outcome measures in studies regarding AATD suggest the infeasibility of using many of the conventional outcome measures employed in studies of regular COPD, including mortality, spirometry measures, St George’s Respiratory Questionnaire (SGRQ), and exacerbation frequency. For example, Idell and Cohen\textsuperscript{39} estimated the sample size required to detect a reduction in mortality in AATD. The smallest estimated number of participants in a study with mortality as a primary endpoint and an effect size (i.e., mortality benefit) of 50\% in individuals followed over 5 years was 192 patients per treatment arm. For less dramatic reductions in mortality related to augmentation therapy and shorter follow-up (e.g., 30\% mortality reduction studied over 2 years), the estimated number of participants necessary to show power increased (e.g., to 1757 per treatment arm). The infeasibility of such recruitment numbers led to the recommendation to defer an RCT of augmentation therapy and have the NHLBI assemble a registry for individuals with AATD. On the basis of observed mortality data from the resultant NHLBI registry, Schluchter et al\textsuperscript{40} estimated that 208 patients would be required in each treatment arm for an RCT of augmentation therapy showing a 50\% reduction in mortality in the subset of individuals whose FEV\textsubscript{1} was between 35\% and 49\% predicted at baseline. With a smaller effect size, i.e., a 30\% reduction in mortality, the required sample size rose to 648, which is clearly infeasible (Table 3). Power calculations using SGRQ as a possible primary outcome measure in studies of AATD show similar infeasibility. Even using an enriched population with rapid decline in FEV\textsubscript{1}, Stockley et al\textsuperscript{41} estimated that 5039 participants would be needed per treatment arm to show a 25\% decrement in decline. The message is clear. As with mortality and SGRQ as endpoints, recruitment requirements based on these estimates make a trial of therapy for AATD using FEV\textsubscript{1} or exacerbation frequency as a primary outcome measure infeasible. Indeed, none of the 3 available RCTs of intravenous augmentation therapy has shown significant benefits regarding FEV\textsubscript{1} slope or exacerbation frequency.\textsuperscript{34-36} While other endpoints like degree of inflammation in exacerbations or duration of exacerbation could be considered, inexperience with their use as primary outcomes in pivotal trials and the lack of power calculations have blunted enthusiasm for their use. Also, some have advocated using FEV\textsubscript{1}\% predicted or % predicted transfer factor in trials in which the participant pool is enhanced by including participants screened for rapid FEV\textsubscript{1} decline. While the proposed numbers of participants for such trials (86 and 77 per treatment arm, respectively)\textsuperscript{41} have appeal for feasibility, it bears emphasizing that such rapid decliners comprise a small minority of all AATD individuals, which compounds the recruitment challenge by limiting inclusion to a small subset of an already limited population. For example, in the study by Wencker et al,\textsuperscript{42} rapid decliners comprised only 7.3\% of the overall population of 96 AATD participants in that study.

The only primary outcome measure for which recruitment goals for an RCT of augmentation therapy for AATD have proven feasible, to date, is CT densitometry.\textsuperscript{43} Based on the first available RCT,\textsuperscript{34} an observed effect of size of loss of lung density

\begin{table}[h]
\centering
\caption{Sample Size Estimates for Trials of Augmentation Therapy Using Forced Expiratory Volume in 1 Second as Primary Outcome}
\begin{tabular}{|l|c|c|c|}
\hline
Author(s) and Reference & 3 Years & 4 Years & 5 Years \\
\hline
\textsuperscript{a}Idell S and Cohen AM\textsuperscript{39} & 377 & 352 & 344 \\
\textsuperscript{b}Schluchter et al\textsuperscript{40} & 213 & 164 & 143 \\
\textsuperscript{c}Dirksen et al\textsuperscript{34} & 275 & & \\
\hline
\end{tabular}
\begin{tablenotes}
\item[\textsuperscript{a}] For individuals with FEV\textsubscript{1} 30\%-65\% predicted; calculations assume 90\% power, untreated FEV\textsubscript{1} decline -89 ml/yr, and 4 measurements/year.
\item[\textsuperscript{b}] For individuals with FEV\textsubscript{1} 30\%-65\% predicted; calculations assumed one-sided test, 90\% power, \(p=0.05\) with FEV\textsubscript{1}ml/year and treatment effect=24\%.
\item[\textsuperscript{c}] To achieve a 50\% reduction in FEV\textsubscript{1} slope
\end{tablenotes}
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\textsuperscript{2}For individuals with FEV\textsubscript{1} 30\%-65\% predicted; calculations assume 90\% power, untreated FEV\textsubscript{1} decline -89 ml/yr, and 4 measurements/year.
\textsuperscript{3}For individuals with FEV\textsubscript{1} 30\%-65\% predicted; calculations assumed one-sided test, 90\% power, \(p=0.05\) with FEV\textsubscript{1}ml/year and treatment effect=24\%.
\textsuperscript{4}To achieve a 50\% reduction in FEV\textsubscript{1} slope
at 1.07 g/L/year over a 3-year trial estimated the need for 130 total participants in an RCT using CT densitometry as the primary outcome measure. In the subsequent RAPID trial,\textsuperscript{36} although challenging and, as discussed above, requiring protracted recruitment to accrue only 180 participants, the study demonstrated a significant difference between the rate of loss of lung density among augmentation versus placebo recipients over 2 years using CT densitometry at total lung capacity (TLC) (but not either TLC or functional residual capacity) as the outcome measure. The effect size of 0.74 g/L/year using CT densitometry (measured at TLC alone) achieved statistical significance at $p=0.03$. Finally, data from the RAPID trial have been used to estimate sample size requirements for FEV\textsubscript{1} %predicted, exacerbation frequency, and the SGRQ data as primary outcome measures in a randomized trial of augmentation therapy in AATD. As suggested above, these estimates (Table 4) suggest a minimum of 1525 participants per treatment arm, again, clearly infeasible in AATD based on the prevalence estimates and under-recognition challenges noted.

In conclusion, as to applying Maya Angelou’s question of “more alike than unalike” to the entities of regular COPD and COPD associated with AATD the response is while they share commonalities of being under-recognized and very debilitating, they are distinctly unalike in important ways, perhaps most pronouncedly regarding the possibility and needs for clinical trial design. The infeasibility of conducting clinical trials in AATD using conventional outcome measures for regular COPD requires innovative thought and design, especially considering CT densitometry as a primary outcome measure. The appeal of CT densitometry as a primary outcome measure is based on its measuring lung integrity\textsuperscript{43} and, importantly, on the demonstrated feasibility of using it as an outcome in trials regarding treatment of AATD.

### Declaration of Interest

Dr. Stoller serves as a member of the Board of Directors of the Alpha-1 Foundation and as a consultant to: 23andMe, Grifols, Takeda, CSL-Behring, InhibRx, Arrowhead Pharmaceuticals, Dicerna, Insmed, Vertex, 4DMT, Korro, and Bridgebio.

### Table 4. Sample Size Estimates to Show Outcome Differences\textsuperscript{29} Based on the Data from the RAPID Trial\textsuperscript{9}

| Outcome Measure          | Observed Difference Between Aug and Placebo in RAPID at 24 Months | Sample Size (per Group) Needed for Observed Difference to Achieve Statistical Significance |
|--------------------------|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| FEV\textsubscript{1} % Predicted | 0.8% predicted (-3.1% predicted vs. -2.3% predicted), $p=0.21$  | N=3510 per group (Total N=7020)                                                        |
| Exacerbation Frequency   | 0.28 per year (1.70 vs. 1.42 at 24 months)                         | N=1525 –1929 per group (Total N=3050–3858)                                             |
| SGRQ                     | 0.8-unit benefit in August recipients, $p=0.91$                   | N=3191 per group (Total N=6382)                                                        |

\textsuperscript{9}Thanks to Amy Nowacki, PhD

FEV\textsubscript{1}=forced expiratory volume in 1 second; SGRQ=St George’s Respiratory Questionnaire
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