•. 2026 Dec 21;6(4

Analysis from Phase II clinical trial, Alvelestat, NE (neutrophil elastase) inhibitor in AATD-LD: Correlation between biomarker response (Desmosine and Aa-Val^{360}) and Clinical Outcome (SGRQ)

J. Parkin[1], S. Rabbie[1], I. Black[1], J. Inshaw[2]

[1]Mereo BioPharma - London (United Kingdom), [2] Exploristics -Belfast

Rationale

AATD-LD (Alpha-1 antitrypsin deficiency-associated lung disease) is a genetic disorder that can lead to emphysema, driven by disproportionate NE activity.

There is a need for more effective and convenient therapies in AATD-LD to improve patient outcomes. However, development of new therapies is challenging because it is impractical to deliver feasible powered studies to demonstrate benefit with the conventional clinical outcomes in this rare disease.

Therefore, it is important to identify a surrogate biomarker end point with a link to a clinical measure to enable an effective clinical trial design for new therapies.

Introduction

Alvelestat, a potent, reversible, selective, oral inhibitor of neutrophil elastase, with lung penetration, was investigated in patients with AATD-LD to evaluate the mechanistic effect (NE activity inhibition and on disease activity markers Aα-val^{360} and desmosine) up to 12 weeks in a PhII trial ("ASTRAEUS" NCT03636347). St. Georges Respiratory Questionnaire (SGRQ was an exploratory clinical outcome measure.

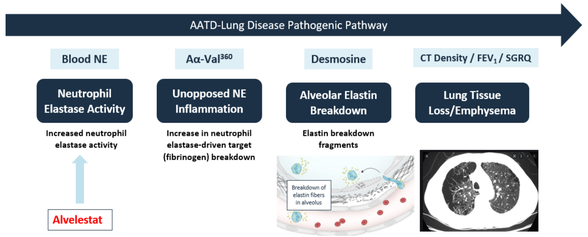
SGRQ is a efficacy assessment in COPD. Total score is calculated from three weighted domains Activity, Impacts, Symptoms. In AATD-LD, the Activity Domain is most affected, potentially reflecting exercise intolerance which patients report as most challenging feature (1).

In ASTRAEUS a statistically significant reduction in biomarkers of disease activity (Aα-val^{360} and desmosine) was demonstrated by week 12 ($p<0.05$). A post-hoc analysis explored the association with changes in SGRQ-Activity domain score.

The research was supported by Mereo BioPharma Plc. Authors relevant interests – JP, SB, IB were employees of Mereo BioPharma Plc during conduct of the research

Aim

To identify potential associations between the response of 2 blood disease activity biomarkers associated with the pathogenic pathway of AATD-LD (2,3) and a clinical outcome (SGRQ-Activity domain).



Methods

Biomarker responders in those completing 12 weeks study drug treatment were defined as follows, with increasing stringency, to test the association between biomarker response and reduction in SGRQ-Activity:

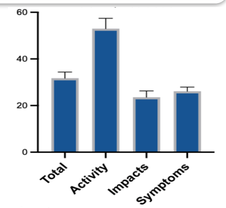
1. Any reduction (>0%) from baseline in both desmosine and Aα-val^{360}
2. > 5% reduction from baseline in both desmosine and Aα-val^{360}.

Requirement for reduction in both biomarkers defined those in whom alvelestat consistently suppressed markers of the NE-driven pathogenic pathway.

An association of reduction (i.e., improvement) in SGRQ-Activity domain with biomarker response was examined by fitting linear mixed effects models, with change in SGRQ-Activity domain as the outcome, and visit, treatment arm (alvelestat or placebo), biomarker responder status, and their interactions as covariates, as well as baseline SGRQ-Activity domain score and a random effect for subject.

Results

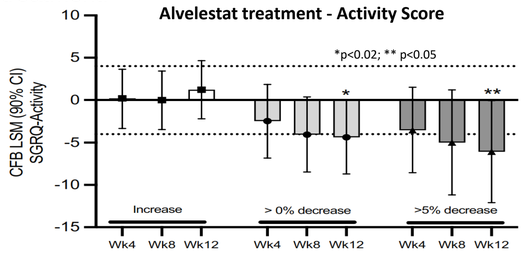
Baseline data demonstrated predominance of SGRQ-Activity Domain as anticipated in this population with AATD-LD. Higher score showing greater impairment (Mean/SE)



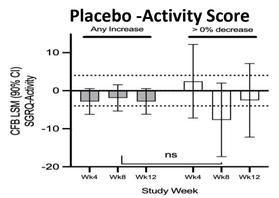
A statistically significant association between biomarker responder status and change in SGRQ-Activity domain was observed.

The effect size increased with:

- Magnitude of biomarker reduction: Greater SGRQ-Activity domain improvement with more stringent biomarker reduction threshold (>5%).
- Duration of alvelestat treatment: Greater SGRQ-Activity domain improvement with longer alvelestat treatment.



No clear biomarker association was observed in the placebo group.



Similar pattern of changes in Impacts domain and Total Score was observed, though not with the Symptoms Domain. The Symptoms domain predominantly reflects symptoms of cough, which is relatively less a feature of importance (1).

Discussion

The association between a reduction in disease-activity biomarker responses and a clinically-relevant measure (SGRQ), is an important finding particularly in the Activity domain, which appears the most relevant for patients with AATD-LD.

The association of SGRQ-Activity domain with biomarker response was only observed in alvelestat-treated subjects, not in placebo, supporting that the findings are relevant to the NE inhibition mechanism of alvelestat, potentially reflecting pathophysiology.

In ASTRAEUS, progressive reduction in disease activity biomarkers was demonstrated over 12 weeks and further deepening of the response is expected with more prolonged treatment.

The FDA Guidance for Industry for SGRQ in assessment for drug approvals, includes the use of one or more domains as measure of efficacy (4). A clinically meaningful difference of 4-points has been determined for COPD, further validation in AATD-associated lung disease will be required.

Conclusion

An association between reduction in Aα-val^{360} and desmosine with SGRQ-Activity domain improvement, demonstrated a potential link between disease-activity biomarkers and a clinical measure in response to alvelestat. This association can guide selection of primary end points and design of future Phase 3 trial.

References

1) Barrecheguren et al, 2020; ERJ Open Research 6: 523-2020
2) Carter et al, 2011; Thorax 66:686-691
3) Ma et al, 2017; Chronic Obstr Pulm Dis. 4: 34–44.
4) FDA. Chronic Obstructive Pulmonary Disease: Use of the St. George's Respiratory Questionnaire as a PRO Assessment Tool Guidance for Industry March 2018

Thank you to the patients and investigators participating in the ASTRAEUS study and to The Alpha-1 Foundation's The Alpha-1 Project (TAP) for their funding contribution