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EDITORIAL

Elastin Degradation Products as Biomarkers in Alpha-1 Antitrypsin Deficiency: Lastin' Impact?

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Biomarkers for emphysema and specifically for alpha-1 antitrypsin deficiency (AATD)-related emphysema have been investigated vigorously because biomarkers offer the promise of important benefits such as assessing disease status, monitoring disease progression, assessing the effects of therapy, and providing important outcome measures for research. Because of these promising benefits, the appetite to identify validated biomarkers for emphysema is now greater than ever. Among the many biomarkers for emphysema that have been considered to date (e.g., radiographic measures, biochemical tests, patient-centered instrument-based assessments, etc.), desmosine and isodesmosine have held longstanding appeal because of a compelling model by which they should reflect emphysema progression. As pointed out by Ma et al. (1) in the accompanying article, desmosine and isodesmosine (DI) occur as amino acid cross-links only in mature elastin, a major (though not exclusive) source of which is the lung. The underlying model has been that, as emphysema progresses, elastin is degraded, and its degradation products, DI, will appear in increased amounts in various fluids such as plasma, urine, and bronchoalveolar fluid (BALF). Interest in DI as a biomarker in AATD has been steady, with multiple available studies spanning almost two decades (2–5).

As appealing as the elastin degradation product (EDP) concept has been for emphysema in general and for AATD in particular, results regarding whether EDPs decrease with augmentation therapy in AATD have been largely disappointing to date (3, 4). Specifically, the few available studies assessing the impact of alpha-1 antitrypsin augmentation therapy on EDPs have largely shown no significant changes in DI levels before vs. after administering augmentation therapy, thereby challenging their value as biomarkers of emphysema progression. Understandably, this experience had somewhat dampened enthusiasm about DI as a biomarker in AATD – at least until now.

The current study by Ma et al. (1) lends a spark of enthusiasm for the role of DI as a biomarker for assessing treatment of AATD. In a study of diverse patients who received different augmentation therapy interventions (i.e., intravenous augmentation in conventional doses and recombinant inhaled augmentation therapy) and from whom different specimens were collected (i.e., plasma, urine, and BALF), their findings restore an appetite for value of DI as a biomarker in emphysema. Briefly, the key findings of the current study were:

1. In 11 patients receiving augmentation therapy, plasma levels of desmosine and isodesmosine (DI) significantly decreased from before to both 12 and 24 weeks after therapy began;
2. Similarly, in 10 patients in which BALF was available before and after intravenous augmentation therapy, although levels of DI rose after therapy in 2 patients, DI levels fell after therapy in the other 8, with a net statistically significant decline.

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3. In 12 patients receiving aerosolized augmentation therapy, 9 demonstrated a decline in plasma DI after therapy and 3 an increase, with a net effect of no significant change after augmentation therapy.
4. In 8 of these patients who underwent bronchoalveolar lavage before and after aerosolized augmentation therapy, BALF levels of DI significantly decreased after 8 weeks of therapy.
5. In 5 of these subjects in whom urine specimens were available before vs. after aerosolized augmentation therapy, total DI excretion increased in 3 post-therapy and decreased in 2, with the net change not achieving statistical significance; also, the free component of DI increased in 1 subject and decreased in 4.
6. Levels of DI in BALF and plasma correlated modestly ($r^2 = 0.40$) but significantly in 10 patients 12 weeks after receiving intravenous augmentation.
7. Increasing plasma levels of DI were significantly but slightly ($r^2 = 0.17$) correlated with age in normal subjects and in those with AATD, both receiving ($r^2 = 0.30$) and not receiving ($r^2 = 0.26$) intravenous augmentation therapy, and
8. Plasma levels of DI were significantly elevated above normal in 50 AATD subjects receiving intravenous augmentation therapy compared with 47 normal controls.

Taken together, these findings show clear promise for the potential role of DI as a biomarker of emphysema in AATD. Yet, in the context of negative previous studies and some variability of the results regarding DI within the different cohorts and studies reported by Ma et al. (1), it seems unlikely that these results will be regarded as fully satisfying the community's appetite or definitively establishing the role of DI as a biomarker for emphysema in AATD.

Indeed, important questions remain unanswered. For example, how do we adjudicate the discordant studies to date? Why do the results of Ma et al. (1) show declines in DI after intravenous augmentation therapy, whereas some prior studies did not? Does this difference in outcomes relate to the assay, to modifications of the internal standard used (i.e., to introduction of an acetylated pyridinoline internal standard as the authors imply), to other features of the populations studied (e.g., the variable inclusion of smokers and the measurement of smoking effects in different series), or to other, currently unrecognized factors? How do the findings regarding DI levels and trends relate to other clinical measures of emphysema progression such as spirometry, diffusing capacity, oxygenation, patient-centered outcomes, and perhaps most importantly in the emerging era of ECLIPSE (6), EXACTLE (7), the preliminarily reported RAPID trial (8), and the forthcoming analysis of the QUANTUM-1 study (9), to CT densitometric measures of emphysema progression?

In the end, our appetite for useful biomarkers in emphysema remains strong and that for understanding the role of DI in AATD has been importantly whetted by the work of Ma et al. (1) This hunger is justified by the potentially game-changing benefits of having validated biomarkers for emphysema. At the same time, rigorously understanding and demonstrating the role of DI as a biomarker will likely require multiple concordant, prospective studies conducted over long durations with larger numbers of patients and with comprehensive outcome assessments against which to compare DI. For DI in AATD, it seems that the "meal" that has been served to date has been a varied mixture of appetizers but that the main course is yet to come.

Declaration of Interest Statement

The author alone is responsible for the content and writing of the paper.

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