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Response to: risk of lung disease with the Pi*SS genotype of alpha-1 antitrypsin: the evidence in context

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To the Editor,

We appreciate the interest demonstrated by O'Brien et al. in our manuscript and while, in general, we agree with their comments, we wish to clarify some of the points raised.

The definition of severe AATD is based on serum AAT levels falling below the putative protective threshold of 57 mg/dL [1]. In the case of PI*SZ, only a minority of cases (less than 10%) may exhibit such low levels [1]; nevertheless, this is why most authors classify PI*SZ as severe deficiency, which does not necessarily imply severe clinical manifestations.

We agree with O'Brien et al. that there is a comparable risk of lung disease between PI*MZ and PI*SZ, and PI*SS and PI*MM genotypes. Our study also observed a similar risk between the PI*SZ and PI*SS genotypes, and they all have a significantly lower risk of lung disease compared to the PI*ZZ genotype. This was our main finding, as indicated in the conclusions of our article [2].

To complement the information provided by O'Brien et al. in their letter, not only EARCO is funded by companies that produce AT, but, as transparently disclosed in the publication, most of the authors of the article also have professional relationships with these companies. Nonetheless, this does not prevent us from having a very similar, almost identical, approach to the indication of AT as that of the unconflicted authors of the letter. We did not suggest intravenous AT as a treatment option for SS individuals and we believe that it might only be considered in very few (if any) cases of PI*SZ. In contrast, we strongly support AT for Pi*ZZ subjects with progressive emphysema, although unfortunately after more than 35 years of AT, patients in some European countries still don't have access to this treatment, that potentially increases survival [3].

Indeed, in the Discussion we speculated about the indication of AT in genotypes other than the PI*ZZ, but the text read (textually): "*However, similar to PI*SZ, there is no evidence about the efficacy of AT in this population and the great majority (if not all) of subjects with the PI*SS genotype have serum levels above those considered to be protective. In any case, if our results showing a similar risk of lung disease for PI*SS and PI*SZ are confirmed in larger series, this could justify the inclusion of PI*SS subjects in clinical trials of other future preventive treatments under development, such as oral or inhaled elastase inhibitors.*" However, if our position about the indication of AT is still not clear, interested readers can read two of our recent publications about this topic [4, 5].

In conclusion, the risk of lung disease in PI*SS and PI*SZ appears to be similar and significantly less than that of PI*ZZ. There is no indication for AT in PI*SS subjects, but this genotype, in addition to PI*MZ and PI*SZ, should be further investigated for potential preventive approaches rather than be dismissed. We appreciate the opportunity to clarify these points and look forward to

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further constructive dialogue on this nuanced and evolving area of research.

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