Response to:

Inhaled Corticosteroids and Long-Acting β2 Receptor Agonists for Preterm-1 born Children: New Insights but Still Many Questions – Authors Response

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To the Editor,

We thank Bonadies and colleagues for their interest in our study (1). We agree that this is the only evidence-based data to aid the management of children with contemporary prematurity-associated lung disease (PLD). They suggest that chronic pulmonary inflammation is important in PLD, although the evidence-base to support this is poor. This is most likely due to the poorly constructed phenotypes that are used to investigate PLD. Most focus has been on children who had bronchopulmonary dysplasia (BPD) in infancy, but BPD is now recognised as a poor predictor of PLD. Indeed, we recently reported that gestation and intrauterine growth restriction are better predictors of decreased future lung function than BPD (2). Although our systematic review did not show differences for FE_{NO} between preterm groups (3), we believe this is due to poorly defined phenotypes of lung disease – especially given the poor predictability of BPD to predict future lung disease. Indeed, in this study FE_{NO} decreased in both arms including inhaled corticosteroids (ICS) suggesting that pulmonary inflammation is ongoing (1). Given the evidence base and recommendations against the use of single agent bronchodilators, a trial arm of long-acting bronchodilator agonists (LABA) alone was not considered ethical (4). However, addition of LABA to ICS resulted in an impressive additive response suggesting strong structural dysfunction in the underlying disease process.

Bonadies *et al* question why we did not use symptoms as our outcome: symptoms are unfortunately often overly subjective especially when physical activity is habitually decreased (exercise-induced symptoms are unlikely). We, therefore, used objectively measured lung function for two reasons: firstly, improved $\%FEV_1$ is likely to improve well-being beyond respiratory symptoms; but equally importantly, the decreased lung function is increasingly recognised as a significant predictor of long-term morbidity and mortality thus interventions that improve lung function (irrespective of symptoms) are important. As we discuss, whether instituting treatment at an earlier age results in improvements in long-term lung function is unknown and will require longer-term assessment. It is for this reason that we chose an improvement of 10% in $\%FEV_1$ rather than the largely adult asthma-based improvements of 12% recommended by ERS/ATS consensus guidelines. We questioned (as reported in the article) whether absolute or relative improvements were preferable; after much discussion with national/international

experts, we settled on absolute improvements of 10% in $\%FEV_1$. Indeed, a larger effect size would require a smaller study population (39 and 53 for 12% and 10% improvement respectively). Regardless, combined therapy improved $\%FEV_1$ by >14%.

Our evidence-based findings are thus timely and important; and cannot be discarded given the conclusions by the ERS (4) and ATS (5) of evidence-free zones for the management of prematurity-associated lung disease. We suggested using our conclusions pragmatically by instituting combined ICS/LABA treatment in children with respiratory symptoms or decreased lung function and objectively evaluating response after 12-weeks to determine if treatment should be continued. Our aspiration is that our findings promote further studies so that robust evidence-based, rather than opinion-based, clinical guidelines can be developed for children with PLD.

References:

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