Reviewer’s report

Title: N-acetylcysteine Exposure is Associated with Improved Survival in Anti-nuclear Antibody Seropositive Patients with Usual Interstitial Pneumonia

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Reviewer: Teng Moua

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Oldham and colleagues present single center analytical data supporting the association of NAC exposure with improved survival in selected UIP (IPF and IPAF-UIP) with ANA seropositivity (defined as ANA titer >1:320). They also demonstrate possible association of ANA positivity with greater likelihood of having TOLLIP genotype positivity. There is prior data suggesting a subset of IPF pts with TOLLIP positive findings having favorable survival with NAC. Definitions of specific criteria are presented, statistical analysis overall appears appropriate, and conclusions seem suggestive or at least hypothesis generating as the authors describe. I have several comments below.

1. The title suggests that NAC is associated with improved survival in those with ANA positive UIP, yet only 58 had any NAC exposure (25% of the whole cohort), defined as ongoing exposure at the time of first visit, or at least exposure for 3 months or more (mean duration of exposure about 9 months reported). As IPF is at least a chronically progressing disease, it seems difficult to conclude that such short or limited exposure in and of itself would have long term influence on subsequent survival. Can the authors comment on this, as association or brief exposure cannot reasonably change disease course. Take prior retrospective studies noting exposure to PPI and improved survival in IPF, which later was not as definitive in prospectively assessed trials. When one asks what is meant by PPI exposure, this is not clear (any use, daily use, use of at least 1 or more years as true exposure (?)).

2. In Table 3, univariable predictors of survival for the whole cohort did not find NAC exposure as influencing outcome, probably because only 58 had NAC exposure, but I cannot tell from the text or in the legend of the Table what variables were adjusted for in the adjusted analysis, making NAC suddenly now a predictor?

3. Table 2 suggests that concomitant therapy was also given in addition to NAC (which may or may not have affected TFS other than the anti-fibrotics and should not have been given to identified IPAF, or maybe they were(?)), and based on these numbers, few pts were probably given only NAC alone (58 pts were described as exposed to NAC overall for the whole cohort, but the total of other concomitant treatments in this table was 63 in the NAC exposed group, I suspect because there was overlap of both anti-fibrotics and immunosuppressants in the same pt). If this Table 2 is true, Table 5 is a little confusing to me the way presented as it would seem that pts were not only stratified by ANA titer, but then also adjusted for multiple variables including diagnosis type, immunosuppressant
and anti-fibrotic exposure, and GAP at the same time-- can the authors explain how this adjustment occurred with only 58 pts having NAC exposure, and only 33 of these having seropositivity, and then also concomitantly adjusting for the use of anti-fibrotics and immunosuppressants (which appears according to Table 2 nearly everyone got at some point with NAC).

4. Would put death rate or % mortality in Table 1 so one can see the number of deaths overall, perhaps even delineated by IPF vs IPAF.

5. ANA in this study appears to predict overall survival, in unadjusted and adjusted survival for the cohort as a whole, which has not been previously described in either IPF or IPAF pts. Can the authors explain this finding and its distinction from prior studies?

6. Minor point for those uninitiated in genotype terminology, can the abbreviations or terms CC, CT, and TT be clarified in the Background, Methods, or in the Table legend? This would immediately help in reader appreciation of their significance.

7. TThere were 45 with inconsistent UIP on CT, did all of these have SLBx to prove UIP pathology at least (the authors mention this for the possible UIP subset but not the inconsistent). How many of these were IPAF and IPF (hard to call IPAF-UlP unless bx confirmed when the CT is inconsistent with UIP, may just be non-UlP IPAF).

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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