Author’s response to reviews

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

Authors:
Justin Oldham (joldham@ucdavis.edu)
Leah Witt (leah.witt@ucsf.edu)
Ayodeji Adegunsoye (Ayodeji.Adegunsoye@uchospitals.edu)
Jonathan Chung (JChung@radiology.bsd.uchicago.edu)
Cathryn Lee (cathryn.lee@uchospitals.edu)
Scully Hsu (shsu@medicine.bsd.uchicago.edu)
Lena Chen (lenawc@uchicago.edu)
Aliya Husain (Aliya.Husain@uchospitals.edu)
Steven Montner (smontner@radiology.bsd.uchicago.edu)
Rekha Vij (rekha.vij@uchospitals.edu)
Mary Strek (mstrek@medicine.bsd.uchicago.edu)
Imre Noth (inoth@medicine.bsd.uchicago.edu)

Version: 1 Date: 08 Dec 2017

Author’s response to reviews:

December 8, 2017

Cecilia Devoto, PhD
Editor-in-Chief

BMC

Dear Drs. Devoto, Moua and Homma,
We thank you for your feedback regarding our submitted manuscript titled “N-acetylcysteine Exposure is Associated with Improved Survival in Anti-nuclear Antibody Seropositive Patients with Usual Interstitial Pneumonia.” We sincerely appreciate the time spent appraising this manuscript and have sought to address each of your comments and incorporate your recommendations into the revised manuscript. A point-by-point explanation of each comment is provided below.

Technical Comments:

C1: Please move the Authors' contributions into the Declarations section.

R1: This has been moved to the Declarations section as requested.

C2: Under Ethics approval and consent to participate, please explain why the need for patient consent was waived, and the name of the ethics committee that granted the exemption.

R2: Thank you for your careful review. All patients who participated in this study signed an informed consent. The sentence stating that a waiver of consent was obtained has been deleted. Additionally, it has been noted in the methods section that consented patients were screened for this study.

C3: Under the Funding heading, please declare the sources of funding for the research reported and the name of the funding body. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should also be declared.

R3: The requested information has been added to the funding section and now reads “This study was funded by a career development award from the National Heart Lung and Blood Institute (K23HL138190), which included salary support for JO, but had no role in the design, data collection, analysis, interpretation of results or writing of the manuscript.”

Teng Moua (Reviewer 1) Comments in general:

C1: 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 (?)).
Thank you for highlighting this important point. We agree that these results should be viewed with caution given the relatively short duration of median exposure relative to overall duration of disease. We have changed our title to indicate NAC exposure (rather than “therapy” which perhaps implies treatment over a more prolonged timeframe) is associated with improved survival in ANA positive patients with UIP. We do specifically highlight the need to view our results with caution in our discussion and suggest that our results be viewed as hypothesis generating. We hope our results will justify the collection of ANA data for patients enrolling in future IPF clinical trials.

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?

Thank you for your thoughtful review. This multi-variable model was constructed using all unadjusted variables. To clarify this, we have added the following language to our results section: “These survival associations remained in a multivariable model adjusted for ANA status, diagnosis, NAC exposure, immunosuppressant exposure, anti-fibrotic exposure and GAP score.”

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-fibotics 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-fibotics 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-fibiotics and immunosuppressants (which appears according to Table 2 nearly everyone got at some point with NAC).

We agree that this is an important point and major limitation of the study. We attempted to address this in a sensitivity analysis contained in our supplement, which showed consistent results after exclusion of patients receiving each of these classes of therapy. Table E3 in particular excludes patients who received an immunosuppressant or anti-fibrotic so assess this association in those receiving NAC monotherapy. Because it is unclear from Table 2 the number of patients who received NAC monotherapy (n=29), we have added an additional row to clarify this. We have also added language to the results section specifically noting that among NAC treated individuals, 15 received an immunosuppressant, 11 received an anti-fibrotic and 3 received both. Additionally, we have revised our limitations to specifically address this issue: “The imbalance in immunosuppressant and anti-fibrotic therapies between NAC exposed and non-exposed cohorts also potentially introduced bias, as did the variability in NAC, immunosuppressants and anti-fibrotic exposure time. We conducted a sensitivity analysis to
explore this limitation and found consistent results after exclusion of patients exposed to an immunosuppressants and/or antifibrotic therapy. (Tables E1-3)."

C4: 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.

R4: These summary statistics have been added to table 1, along with stratification of the cohort by diagnosis, as recommended.

C5: 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?

R5: We agree that this was an unexpected finding given previously published papers on the topic. We do highlight this difference in our discussion, specifically noting the higher percentage of patients with ANA seropositivity in Chicago relative to other centers reporting similar data, suggesting some degree of regional heterogeneity.

C6: 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.

R6: We agree that this is confusing so have removed the genotype letters from the abstract and instead just refer “TOLLIP genotype” associated with improved outcomes in NAC treated individuals.

C7: There 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-UIP unless bx confirmed when the CT is inconsistent with UIP, may just be non-UIP IPAF).

R7: Thank you for highlighting this important point. All but two patients with an HRCT pattern inconsistent with UIP had UIP on SLB. These two patients were considered to have IPF given a strong history of pulmonary fibrosis and therefore likely carried a diagnosis of familial interstitial pneumonia. We have added language to our methods sections indicating this and have updated table 1 to reflect this.

Sakae Homma (Reviewer 2): Comments in general:

C1: In the table 1, baseline characteristics comparing IPF and IPAF-UIP should be evaluated.

R1: We thank you for highlighting this important point, as IPF and IPAF-UIP patients have different characteristics despite similar outcomes. We have updated Table 1 as recommended and now stratify our baseline demographics (and outcomes) by diagnosis along with providing summary statistics for the combined UIP cohort.
C2: In the results, not only TFS but also serial changes in FVC and DLco, the incidence of acute exacerbation as a prognostication in IPF and IPAF-UIP should be assessed.

R2: We thank you for this insightful comment and agree that this study would benefit from inclusion of longitudinal pulmonary function and hospitalization data. Unfortunately the overwhelming majority of patients seen at our institution were referred from surrounding institutions, which do not have integrated medical records with our own. As such, a large number of patients did not have available longitudinal pulmonary function data and very few had hospitalization data which was limited to those patients hospitalized at our own institution. Given the bias this is likely to introduce, we chose to focus on transplant-free survival, as vital status and transplant data were more readily available.

Thank you again for your consideration.

Sincerely,

Justin Oldham, MD MS
Assistant Professor
Director, Interstitial Lung Disease Program
The University of California at Davis

Imre Noth, MD MS
Professor of Medicine
Director, Interstitial Lung Disease Program
The University of Chicago