Author’s response to reviews

Title: Antifibrotic treatment response and prognostic predictors in patients with idiopathic pulmonary fibrosis and exposed to occupational dust.

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Author’s response to reviews:

Dear Editor,

We are pleased to submit to your attention the revision of the manuscript PULM-D-19-00290 'Antifibrotic treatment response and prognostic predictors in patients with idiopathic pulmonary fibrosis and exposed to occupational dust' to be considered suitable for publication in BMC Pulmonary Medicine.

We have addressed point by point all the comments raised by the reviewers. We have prepared a marked-up copy of the manuscript that highlights changes made to the original version and, below, replies to the reviewers.
We hope that now the manuscript meets BMC Pulmonary Medicine’s publication criteria and could be suitable for publication in your journal.

All authors have read and approved the present version for submission to BMC Pulmonary Medicine and also confirm no conflicts of interest related to the study content.

We look forward to hearing from you in due course.

Best regards,

Piera Boschetto

Pulmonary Medicine revision.

Reviewers’ comments:

We thank Reviewer 1 for his constructive comments. We have rewritten the manuscript following his suggestions. We hope that we have adequately addressed his comments.

Reviewer 1

Major concerns:

R1C1. Some data in Table 2 don't seem to be accurate like mean FEV in not exposed in baseline and at 12 month in L and in %.

RR1C1. We agree and we accordingly repeated all analyses reported in Table 2, and double-checked all data. Unfortunately, for some of the variables listed in the Table, we incorrectly reported the value recorded in the pre-therapy assessment, and not the one recorded at the baseline assessment. We sincerely apologize for the error, and we have now re-checked and corrected all data. Please acknowledge that there were no substantial differences.

R1C2. GAP score has been validated at diagnosis and not at 1 year.

RR1C2. We thank the Reviewer for this point; indeed GAP has not been validated at 1 year. Nevertheless, we thought we could calculate and report it since, in the article “A multidimensional index and staging system for idiopathic pulmonary fibrosis”, Ley et al. found that “The GAP models performed similarly (read to the diagnostic visit) in pooled follow-up visits”( Ann Intern Med 2012;156:684-691). However, we acknowledge that GAP has not been
circumstantially validated at 1 year and this issue is now declared in the Methods and Discussion sections (page 5 and page 11).

R1C3. The table 3 should be redone. The interesting value is the decline of FVC and the decline of DLCO. Hopefully higher baseline FVC is associated with higher FVC at 1 year.

RR1C3. We totally agree that baseline FVC and DLCO should have been added to the final models predicting the variation of FVC and DLCO after therapy, respectively. In the previous version of the manuscript, we chose to report only pre-therapy FVC values in both predictive models (predicting FVC or DLCO) because baseline and pre-therapy values of FVC were highly collinear (spearman rho 0.96). We now re-added baseline FVC as covariate in the models (in Table 3) in order to allow the reader to take note of such an important finding.

R1C4. LTOT is not a good endpoint and should be tempered as the initiation of LTOT is highly variable from one physician to another.

RR1C4. According to the Reviewer’s suggestion, LTOT endpoint has been tempered. See: 1. last lines of the Background (page 3); 2. “Initiation of LTOT” paragraph of the Methods (page 5); and 3. Discussion, where the sentence “To our knowledge, this is the first study in which dust exposure at work has been assessed in relation to LTOT in IPF patients” has been deleted (page 10).

Minor issues:

R1C1. Table 1 the p value could be given for the gender.

RR1C1: Done. Thank you.

Reviewer 2:

We thank Reviewer 2 for her constructive comments. We have rewritten the manuscript following her suggestions. We hope that we have adequately addressed her comments.
Major concerns:

R2C1. Of note, having an occupational dust exposure was defined as having been exposed to dusts 10 or more years prior to a diagnosis of IPF. One of the major limitations of such a study is the lack of established methodology to quantify the dust exposure. It is unknown if the intensity of the dust exposure differed between different occupations. For instance, previous studies have shown that carpenters have one of the highest occupational exposure to asbestos. As the authors collected data about the job title, can they review if those patients whose occupation is associated with the highest/heaviest dust exposure had different outcomes in terms of change in FVC, mortality, use of LTOT etc.

RR2C1. Thank you for the comment. As hypothesized by the Reviewer, the intensity of dust exposure changes between different occupations. We verified every patient job title and working history in our dust exposed sample and we divided it in two categories: highest/heaviest dust exposure and moderate dust exposure. In our study, 46 exposed subjects had complete data at 12 month follow-up visit: 50% of whom had probable intense exposure (for example: turners, construction workers, carpenters, textile workers) and the remaining 50% moderate exposure (example: cleaners, farmers, breeders). The statistical analysis (Table) of these two categories showed no significant differences for the spirometric parameters at diagnosis and at 12 months. With regard to mortality data, even the 6 deaths recorded in the exposed group are equally divided: 3 with intense exposure and 3 with moderate exposure. Among the exposed, 16 are in oxygen therapy, 9 of them with intense occupational exposure and 7 with moderate exposure; again no one significant difference between the two groups. Finally, we checked possible differences in outcomes between the group of highest/heaviest exposed and the non-exposed, but, as expected, none were found. This point is now mentioned in the Discussion section (limitations of the study; pages 10 and 11).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Exposed(n=46)</th>
<th>Moderate exposure</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highest/heaviest exposure</strong></td>
<td>(23)</td>
<td>(23)</td>
<td></td>
</tr>
<tr>
<td>Mean FVC, L (SD), at diagnosis</td>
<td>2.6 (0.6)</td>
<td>2.5 (0.6)</td>
<td>0.84</td>
</tr>
<tr>
<td>Mean FVC, % predicted (SD), at diagnosis</td>
<td>82.2 (17.4)</td>
<td>86.0 (21.2)</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean FVC, L (SD), 12 months</td>
<td>2.5 (0.5)</td>
<td>2.5 (0.6)</td>
<td>0.96</td>
</tr>
<tr>
<td>Mean FVC, % predicted (SD), 12 months</td>
<td>80.1 (17.9)</td>
<td>80.9 (18.1)</td>
<td>0.87</td>
</tr>
<tr>
<td>Mean DLCO, % predicted (SD), at diagnosis</td>
<td>50.3 (16.5)</td>
<td>49.1 (12.7)</td>
<td>0.77</td>
</tr>
<tr>
<td>Mean DLCO, % predicted (SD), 12 months</td>
<td>47 (21.3)</td>
<td>42.7 (14.5)</td>
<td>0.43</td>
</tr>
<tr>
<td>*Difference in Mean FVC, L (SD)</td>
<td>-0.17(0.36)</td>
<td>-0.08(0.31)</td>
<td>0.39</td>
</tr>
<tr>
<td>* Difference in Mean FVC, %</td>
<td>-2.19(10.64)</td>
<td>-5.12(8.22)</td>
<td>0.30</td>
</tr>
</tbody>
</table>
FVC: Force Vital Capacity; DLCO: diffusing capacity of the lungs for carbon monoxide; LTOT: long-term oxygen therapy;

* Difference between the value at 12 months and at diagnosis.

R2C2. Both groups had exposures to asbestos - almost 50% in the exposed group and almost 20% in the non-exposed group. The mean duration of exposure is similar between both groups. What constituted exposure to asbestos? Did any of these patients have asbestos exposures that would support a diagnosis of asbestosis? For instance a heavy exposure for few years may be equivalent to a small exposure for many years. This needs to be clarified. Including a group of patients with asbestosis may influence the results of this study.

RR2C2. We agree that asbestos exposure needs to be researched and extensively investigated in the diagnostic workup of IPF. Of almost 50% of patients in the exposed group who had exposure to asbestos, 17 had an occupational exposure, while the others were exposed non-occupationally (household and neighbourhood); of the non-exposed group only 3 had been exposed in occupational settings. The estimated non-occupational exposure is not sufficient to support a diagnosis of asbestosis. We paid particular attention in investigating not only the timing but also the intensity of asbestos exposure aware that a heavy exposure for few years may be equivalent to a small exposure for many years. Considering time and intensity of exposure, the latter estimated by job title and working history, only a few patients in the exposed group had an asbestos exposure that could support a diagnosis of asbestosis. Just because, as you state in R2C4, patients suffering from asbestosis experience a better survival rate than the general IPF population, we took specific care to ascertain a correct differential diagnosis. In subjects with a significant asbestos exposure, IPF were diagnosed during a multidisciplinary dynamic discussion after formal work-up, including extensive patient history, chest radiograph and CT scan (also looking for benign asbestos-associated pleural disease such as pleural plaques, diffuse pleural fibrosis and benign asbestos pleural effusion), but rarely searching for asbestos bodies in BAL and lung tissue. This issue has been clarified in the Discussion section (pages 8 and 9).

R2C3. Please can the authors comment on the following statement: in the text - in the non-exposed group the mean duration of dust exposure was 1.2 ± 2.8 years (page 7), but in table 1 the mean duration of asbestos exposure in the non-exposed group is 5.8 ±(13.6) years. The SD
seems large as this suggests asbestos exposure may be > 10 years prior to diagnosis of IPF. Please review these data.

RR2C3. We apologize for this confusing point. We used “dust exposure” to indicate occupational exposure to dusts that are known to be implicated in the pathogenesis of IPF, thus excluding specific asbestos exposure. We have now explicated this point in the revised manuscript (page 6), hoping to have clarified the misunderstanding.

R2C4. Baseline lung function is similar across the exposed and non-exposed groups and does not change after 1 year of treatment. These data suggest this cohort has milder/limited disease and slow progression. It may reflect inclusion of a group of patients with asbestosis. Can this be addressed along with point 2 above.

RR2C4. See RR2C2.

R2C5. One of the limitations with this study is the absence of a placebo-controlled group. Hence it is not possible to comment on whether anti-fibrotic treatment is effective in slowing disease progression/reduce the number of patients experiencing decline in FVC>10% regardless of dust exposure. Similarly there are no data to demonstrate that dust exposure does not impact the beneficial effect of anti-fibrotic therapy at 1 year. The data presented suggest that for patients on anti-fibrotic therapy, dust exposure > 10 years from diagnosis does not affect the rate of progression as the number of patients with decline in FVC>10% is similar in the dust exposed and the non-exposed groups (as shown in additional file 1). Potential control group would be those patients who did not have anti-fibrotic treatment. Although a small number, did these patients have lung function at 12 months which could be used as a small untreated control group? The authors need to amend the statement they have provided in the conclusion on page 10 and abstract page 3 to reflect this.

RR2C5. We totally agree that the results presented in the supplemental Table 1 would largely benefit from the addition of data on patients without pharmacological treatment. However, please acknowledge that, as reported in the Results (section “Pulmonary function tests and prognostic indices”, line 4), complete information on the 12-month lung function was available for only 89 patients, all under anti-fibrotic treatment. Therefore, the analyses could be restricted only to this sub-sample of patients. Please also acknowledge, however, that we recognized this (serious) drawback in the limitation section of the manuscript, and we added the following paragraph: “Second, complete data on lung function at diagnosis and after 12 months was available for only 89 patients, all under pharmacological treatment. Thus, given the absence of follow-up data for the group of untreated patients, it was not possible to comment on whether anti-fibrotic treatment is effective in slowing disease progression/reduce the number of patients experiencing decline in
FVC>10% regardless of dust exposure. Similarly, there are no data to demonstrate that dust exposure does not impact on the beneficial effect of anti-fibrotic therapy at 1 year”.

Finally, please acknowledge that we amended the previous second paragraph of the Discussion (page 10, lines 1-6): “Both pirfenidone and nintendanib have been shown to lessen the decline in pulmonary function in patients with IPF [19]. In particular, they reduce the number of patients experiencing a decline in FVC of 10% or greater with the result of slowing the disease progression. Our data confirm these findings as lung function measurements were not decreased at 12 month treatment assessment of patients given either one drug or the other. In addition, we have shown that exposure to dust at work does not seem to impact on the beneficial effect of 1 year pirfenidone and nintendanib” as follows:

“Both pirfenidone and nintendanib have been shown to lessen the decline in pulmonary function in patients with IPF [19]. In particular, they reduce the number of patients experiencing a decline in FVC of 10% or greater with the result of slowing the disease progression, as compared with no therapy [19]. Although we could not compare the rate of disease progression between patients with and without pharmacological treatment, we found that exposure to dust at work does not seem to impact on the beneficial effect of 1 year pirfenidone and nintendanib”(pages 9 and 10).

Minor comments:

R2C1. Page 8 and in table 1: familiarity for IPF - better to say "family history of IPF of familial IPF.

RR2C1. Thanks. We have amended the manuscript accordingly.