Author's response to reviews

Title: Outcome of corticosteroid administration in autoimmune pulmonary alveolar proteinosis

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Author's response to reviews: see over
Dear Dr. Amit Gaggar:

Thank you so much for the detailed review of our manuscript (MS: 1162843494165190) entitled “Outcome of corticosteroid administration in autoimmune pulmonary alveolar proteinosis”. We have carefully revised our manuscript for some questions raised by reviewers. In preparing the revision of this manuscript, we have adequately considered the questions raised by reviewers and responded in an appropriate manner. We believe that the manuscript has been improved and hope that you will find it suitable for publication in BMC Pulmonary Medicine.

Sincerely,

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Response to Editor

Comment: Thank you for the opportunity to review your work. It has been assessed by the editorial board and two expert reviewers who found the manuscript interesting and representing an advance to the current literature. There are some revisions required before we can re-consider the manuscript for publication in BMC Pulmonary Medicine.

Response:
We appreciate favorable and the thoughtful review of our manuscript and have carefully considered and responded to each question raised in preparing a revised manuscript.

Reviewer 1
Dear Dr. Borie

C1: In the clinical course of aPAP, one would like to know, if the worsening was due to infection, to the progression of the disease or both in the entire cohort, and in the high/low dose corticosteroid group. Same question after corticosteroids withdrawal.

R1: We analyzed cumulative worsening rate based on DSS at just before and various periods during corticosteroid therapy, and 6 and 12 months after the discontinuation of corticosteroid therapy. DSS was definitely determined by arterial blood gas oxygen pressure or SpO2 except for DSS 1 and 2, corresponding to both PaO$_2$ ≥ 70 mmHg without and with symptoms, respectively. In 16 high dose group, two patients complicated pulmonary infections during the disease process, of which no patient showed increased DSS after the events of infection. In while, 15 low dose group, 4 patients complicated pulmonary infections, of which one patient accompanied increased DSS. On the other hand, in 25 patients after corticosteroids withdrawal, one patient was complicated with pulmonary infections, but none accompanied increase in DSS. As a whole, we consider that increase in DSS is not due to pulmonary infections but mainly due to exacerbation of PAP per se.

We reflect the above description by adding in Results.
Page 12, line 22.
“It is noteworthy that in 5 cases, DSS improved after the discontinuation of corticosteroid therapy and successful treatment of the infection. In 16 high dose group, two patients complicated pulmonary infections during the disease process, of which no patient showed increased DSS after the events of infection. In while, 15 low dose group, 4 patients complicated pulmonary infections, of which one patient accompanied increased DSS. On the other hand, in 25 patients after corticosteroids withdrawal, one patient was complicated with pulmonary infections, but none accompanied increase in DSS. As a whole, we consider that increase in DSS is not due to pulmonary infections but mainly due to exacerbation of PAP per se.”

**C2:** Is there any patient that improved, it does not seems so in the supplementary Table?

**R2:** Yes. There were 8 patients who improved during corticosteroid therapy. Of those, three patients improved after pulmonary infection, and five patients improved during tapering corticosteroid.

**C3:** Do the authors have evolution of GMAb levels within therapy for some patients?

**R3:**
Thank you for a nice question. In some cases, we measured GMAb levels both at the time of steroid therapy and after discontinuation of the therapy. In case 18, it was 10.7mcg/ml during the therapy, whereas 29.9mcg/ml at 5 years after discontinuation. In case 23, it was 25.2mcg/ml during the therapy, whereas 58.0mcg/ml at 1 month after discontinuation. In case 27, it was 5.9mcg/ml during the therapy, whereas it was 19.5mcg/ml at 5 years after discontinuation. Thus, it is likely that corticosteroid therapy reduces the serum GMAb level and the discontinuation reverses the level. However, as only a limited number of data sets are available at the present time, we do not mention about it.

**C4:** The number of the figure is not the number in the legends.
R4: Thank you for your careful review. In the revised manuscript, the number of figure coincided with the number in the legends.

Reviewer 2
Comments: The paper “Outcome of corticosteroid administration...” reports on a retrospective study cohort of subjects with autoimmune PAP from specialized centres in Japan. The authors generate a clear message, i.e. steroid treatment is not only harmless, but harmful in this group of subjects, who already have an immune defect.

Response:
We are very pleased and appreciated that the reviewer 2 thoroughly read our manuscript and understood precisely our message demonstrated between the lines. We respond to the reviewer’s comments appropriately and revised the manuscript.

Dear Dr. Griese
C1: A major downside of the paper is that there was no control group of PAP patients observed, which were treated similarly but with steroids. This should be more clearly discussed.

R1: Thank you for a nice comment. We agree that no control is the weak point in this study. As we have a database of large cross sectional study (Inoue, AJRCCM, 2008), we first tried to set a control group. However, the background factors were multiple and complicated such as gender, age, duration of observation periods, smoking status, history of dust exposure, history of treatment, and disease activity. Therefore, we realized that it was not so easy to set the control group without selection bias. Rather, it was reasonable to compare the worsening rate between the low- and high-dose corticosteroid groups to examine the effect of corticosteroid therapy on the DSS of patients with aPAP. Moreover, we confirmed that there was no difference in the median age, gender, DSS, smoking history, history of dust exposure, or duration of corticosteroid therapy and symptoms before the start of corticosteroid therapy between the two groups (Table 2),
In discussion, we add the following sentence, P14, line23.

To our knowledge, however, there have been no reports statistically analyzing the outcome of aPAP patients who had been treated with corticosteroid therapy.

As we have a database of large cross sectional study,\(^8\) we first tried to set a control group. However, the background factors were so multiple and complicated such as gender, age, duration of observation periods, smoking status, history of dust exposure, history of treatment, and disease activity. Therefore, we realized that it was not so easy to set the control group without selection bias. As often noted by other retrospective studies, researchers must take due care to avoid selection bias of study subjects.

**C2:** There are some anecdotal cases which already have noted more side effects with steroids in GMCSF related PAP, e.g. involving receptor GMCSF related mutations (Griese et al, BMC Pediatr. 2011), including aspergilloma or other infections, which should be mentioned in the Discussion or Introduction.

**R2:** Thank you for your kind suggestions. We add the following sentence in the second paragraph in Discussion.

Historically, corticosteroids have been used for the treatment of PAP, regardless of whether it is aPAP or secondary PAP.\(^32, 33\) besides, side effects of corticosteroid was cautioned in a case of hereditary PAP with homozygous stop mutation p. Ser25X of the GMCSF receptor alpha chain (Griese et al, BMC Pediatr. 2011). Thus, corticosteroid therapy may exacerbate the alveolar macrophage dysfunction in the above cases. For secondary PAP complicated by myelodysplastic syndrome, we recently reported that use of corticosteroid therapy significantly worsens the survival rate of patients after the diagnosis of PAP.

**C3:** The numbering of the figures is not concordant between body of manuscript and figures (3B = 4, and so on).
**R3:** We agree our mistake in numbering these numbers and corrected in the revised manuscript.

**C4:** Discussion page 15, para 3: As cause and effect are not clear these statements should be cautioned. Can it be excluded that steroids worked, i.e. induced improvement of PAP, then were reduced/stopped, followed by further resolution of infiltrates? This is not a prospective observation therefore causal conclusions are very difficult and must be done carefully.

**R4:** We agree that our statements may mislead the readers to wrong conclusions. So we revised the paragraph as follows;

Notably, 5 of 7 cases complicated by infections during corticosteroid therapy improved, not only in terms of the infection but also the aPAP itself, after the discontinuation of corticosteroid therapy and antibiotic therapy. Our representative case report in the Results section showed that GGO on HRCT mostly disappeared after corticosteroid therapy cessation, accompanied by a remarkable reduction in serum KL-6 levels. These curious phenomena are consistent with our clinical experiences and several previous case reports.\(^{38-40}\) As the number of infected cases were limited and we could not exclude that corticosteroids induced improvement of PAP, we should be careful to interpret these phenomena.

**C5:** Discussion page 15, last para: Please list the diagnoses given initially in 28 of 31 patients with PAP; what were the diseases mixed up with PAP in these tertiary care hospitals? May need more discussion to understand.

**R5:** In “Results”, page 8, in the second paragraph, we described as follows;

Of the 28 cases that were initially diagnosed as other interstitial lung diseases, the diagnoses were IIPs, drug-induced ILD, chronic hypersensitive pneumonitis, chronic eosinophilic pneumonia, and alveolar cell carcinoma in 21, 4, 1, 1, and 1 case, respectively.

We revised the forth paragraph in Discussion page 15 as follows;
In this study, 28 of 31 patients were initially assumed as other lung diseases such as IIPs, drug-induced ILD, and corticosteroid therapy was prescribed for the treatment of these diseases after clinical of radiological diagnosis based on HRCT without pathological diagnosis. As the HRCT appearance of these diseases and/or clinical features are sometimes indistinguishable from that of aPAP, the present study cautions pulmonary physicians about the casual use of corticosteroids in the absence of a definitive diagnosis by lung biopsy.