Author’s response to reviews

Title: Successful resumption of tocilizumab for rheumatoid arthritis after resection of a pulmonary Mycobacterium avium complex lesion: A case report

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Martina Sterclova, M.D.
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RE: PULM-D-15-00031

To the Editors
We appreciate the important comments and thoughtful suggestions by the reviewers, which have enriched the manuscript and produced a more balanced and better account of the research. The manuscript has been carefully rechecked and appropriate changes have been made according to the reviewers’ suggestions. Here, we are submitting the revised manuscript originally entitled "Successful resumption of biological treatment for rheumatoid arthritis after resection of a pulmonary Mycobacterium avium complex lesion: A case report" (PULM-D-15-00031). The point-by-point responses are following. We hope that the revised manuscript is now suitable for publication in BMC Pulmonary Medicine.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,
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Response to Reviewers

We thank the reviewers for their insightful and valuable comments, which have helped us to improve the manuscript. Our specific responses to the points you have raised are listed below, and the relevant changes are highlighted in the revised manuscript.

Reviewer #1

GENERAL COMMENTS

This is a well written and interesting case-report focusing on one of the most frequent pulmonary complications during treatment with biologics.

I have only a couple of minor suggestions to the current version of the manuscript.
MINOR COMMENTS

C1: The conclusion of the discussion does not match the conclusion of the abstract, appearing too strong or too optimistic (especially the use of "enable"). I suggest changing the conclusion of the abstract according to the last two sentences of the discussion.

R1: We appreciate the suggestion and have changed the conclusion of the abstract as below (line 45-48).

This case suggested that TCZ could be safely reintroduced after the resection of a pulmonary MAC lesion. Although the use of biological agents is generally contraindicated in patients with pulmonary MAC disease, especially in those with a fibrocavitary lesion, a multimodality intervention for MAC including both medical and surgical approaches may enable introduction or resumption of biological agents.

C2: Is the DAS 28-CRP index available in this patient at treatment start with TCZ? Please add in the "case presentation".

R2: The DAS 28-CRP index was 3.81 at treatment start with TCZ. We have inserted this index in the "case presentation" (line 83-84). We have also added VAS index (37 mm) as following.

At this time, the visual analogue scale (VAS) was 37 mm and the disease activity score (DAS) 28-C-reactive protein (CRP) was 3.81.

C3: It would be interesting to add a picture of the histological confirmation after lobectomy, if available.

R3: We appreciate the important comment. The picture of the lung pathology has been added as Figure 3.

Figure 3. Photograph and photomicrographs of the lung. (A) Photograph of a cross-sectional specimen from the resected right upper lung. (B, C) Photomicrographs showing an epithelioid granuloma with necrosis (B: bar, 5 mm; C: bar, 500 µm). (D) Photomicrograph showing Langhans giant cells (arrowheads) and epithelioid cells (arrow) (bar, 100 µm).

Reviewer #2

GENERAL COMMENTS

Namkoong et al present a case report of patient with Crohn’s and RA receiving tocilizumab for control of disease who developed MAC Lung infection. It is a reasonably straightforward case report, although confounded by very odd management choices prior to presenting to the MAC team (ie persistent low dose single agent macrolide for small pulmonary nodule?). Lots can be done to improve the description of the case and discussion.
Major points

C1: The monotherapy clarithromycin treatment must better be presented – and it must be made clear that this was neither standard of care nor appropriate. Please clarify here as well that MAC cultures were negative (merely reporting bacterial cultures implies just routine sputum culture and not NTM).

R1: We appreciate the important comment. As the reviewer pointed out, clarithromycin monotherapy was neither the standard of care nor an appropriate treatment, although the monotherapy was introduced before the referral of the patient to our department. We have added the following sentence to emphasize that clarithromycin was prescribed as a monotherapy before the exacerbation, in the “Case presentation” section (line 85-87).

Although the patient had no respiratory symptoms with no pathogenic bacteria isolated from the sputum, she was prescribed 400 mg/day clarithromycin (CAM) as a monotherapy before her referral to our department.

We also added three sentences in “Conclusion,” as follows (line 127-131).

In this case, HRCT taken before the initiation of TCZ treatment showed small nodular opacity in the right upper lobe, suggesting pre-existing MAC disease. Since monotherapy with macrolides can induce macrolide-resistance, it is not an appropriate treatment in the presence of MAC disease. Therefore, bronchoscopy should have been performed to make a diagnosis of pulmonary MAC disease so that combination chemotherapy could be introduced at an earlier time point.

C2: What was the treatment response clinically and microbiologically after the three months of medical therapy prior to lung resection (monthly sputum samples showed what)? What was the justification for lobectomy after three months if she was improving or was this refractory to medical therapy with repeated sputum samples? (They only report surgically excised tissue being culture positive at three months). Why not right at diagnosis? Very odd and should be justified.

R2: As the reviewer pointed out, three months of medical therapy responded clinically in this case. In fact, her hemoptysis disappeared. Regarding microbiological response, we could not perform microbiological evaluation because the sputum also disappeared. Even with sputum induction, we could not obtain a sputum sample. In terms of radiological findings, we confirmed that the chemotherapy also reduced the infiltrates around the cavity. However, the cavitary lesion did not show improvement even after three months of medical therapy. In general, a cavitary lesion of MAC pulmonary disease is difficult to be resolved only by chemotherapy. Especially for this patient with high disease activity of RA, we think it reasonable to resect the cavitary lesion in order to resume biological agents safely by surgery. To address this point, we added the following sentences in the “Discussion” section (line 147-152).
One of the discussion points is the validity of surgical resection against MAC disease. In this case, her hemoptysis disappeared after three months of chemotherapy and the infiltrates around the cavity were also resolved. However, the cavitary lesion, which could discharge mycobacteria and might predispose the patient to later recurrence, was not changed. In general, the cavitary lesion of MAC patients is difficult to be resolved by chemotherapy alone and is good indication for surgical resection. Especially for this patient with high disease activity of RA, we thought it reasonable to remove the cavitary lesion surgically in order to resume biological agents.

C3: How long was medical therapy continued after surgical excision?

R3: Thus far, we have been continuing the antimicrobial chemotherapy for 1.5 years after the surgery. As the patients are still receiving TCZ and other immunosuppressive therapies, we are planning to stop the antimicrobial chemotherapy with full caution.

C4: The discussion reads; “Because of the negative sputum culture, it was not possible to make a diagnosis of MAC pulmonary disease.” They report two positive cultures before hand… MAC disease was dx by ATS criteria.

R4: We meant that the sputum culture was negative before the initiation of TCZ treatment. The two positive cultures were confirmed 2 years after TCZ treatment for the first time in this case, as described in the “Case presentation” section.

C5: Biological agents is a very non-descript term for many monoclonal antibodies increasingly being developed for control of chronic inflammatory diseases. The authors should be more specific with their terminology through the text as the mechanism of action and resultant degree of susceptibility to infections quite variable.

R5: We agree to the comment and have changed the terminology from “biological agents” to “tocilizumab” or “anti-interleukin-6 receptor antibody.” We also changed the title in accordance with the comment. In addition, some descriptions have been added to clarify the degree of susceptibility to infections among various types of biological agents as follows:

Title: Successful resumption of tocilizumab for rheumatoid arthritis after resection of a pulmonary Mycobacterium avium complex lesion: A case report

Abstract (line 36-37)

Case presentation: A 63-year-old woman who had been treated with tocilizumab (TCZ), anti-interleukin-6 receptor antibody, for RA presented to our outpatient clinic due to hemoptysis.

Background (line 53-70)

According to the recent systematic review, both standard-dose and high-dose biological agents are associated with the increased risk of serious infections, compared with traditional disease-modifying anti-rheumatic drugs (DMARDs). With respect to the difference in susceptibility
between the classes of biologics, no difference in the risk of infection has been reported between TCZ and others, although the Cochrane review in 2011 reported that abatacept, cytotoxic T lymphocyte antigen 4-immunoglobulin, was significantly less likely to cause infection than infliximab and TCZ. Moreover, it has been shown that biological agents are associated with a significant increase in mycobacterial diseases. Concerning the types of mycobacterial diseases, Winthrop and coworkers reported that NTM infections were more common than tuberculosis among patients receiving biologics. Especially in Japan, the most recent nationwide survey revealed that the incidence rate of pulmonary NTM disease (14.7 persons per 100,000 person-years) may exceed that of tuberculosis in general population, and that Japan may have one of the highest incidence rates of pulmonary NTM disease worldwide. Whereas tuberculosis can usually be controlled by the standard chemotherapy, no effective chemotherapy has been established against Mycobacterium avium complex (MAC), leading to aggravation of MAC infection during immunosuppressive therapy. According to Japanese postmarketing surveillance of TCZ in RA patients, the incidence of NTM infections (0.22%) is higher than that of tuberculosis (0.05%). Although many of RA patients have underlying pulmonary lesions and other risk factors for potential NTM infection, it is still controversial whether biological agents can be a risk of exacerbation of pre-existing pulmonary NTM disease. Consequently, a strategy for the management of NTM in RA patients subjected to treatment with biologics remains to be established.

Minor points;

C6: The line numbering of the manuscripts are blurred (I presume one numbering system in their manuscript and another in the journals PDF formation section).

R6: We are sorry for the careless mistake and have corrected the line numbering of the manuscripts both in the ‘Word’ formation and the ‘PDF’ formation.

C7: Error in the abstract “TCZ was resumed for the exacerbation”

R7: The error has been corrected.

C8: Not sure how “multidisciplinary” is relevant here. Multi-modality perhaps (surgical and medial therapy)…

R8: According to the comment, we have changed the terminology from “multidisciplinary” to “multimodality” in the revised manuscript.

C9: Some medications are listed as mg/kg/day whereas others are total dose (without mention of what her weight actually was). Must better clarify especially as atypical doses appear to have been commonly employed.

R9: We unified the indication method to the total dose; namely, we deleted “mg/kg/day.”
We also added her weight in the manuscript, as follows: (line 78-79)

Her height was 165.0 cm and body weight was 46.0 kg.

C10: Line 73 – it must be clarified in the text that TCZ was added to the MTX/Pred and not substituted.

R10: TCZ was added after the cessation of MTX. In this regard, we have changed the text as follows: (line 81-83)

Because the disease activity was not properly controlled with these medications, methotrexate was stopped and 360 mg of TCZ was administered intravenously once every 4 weeks from October 2011.

Reviewer #3

GENERAL COMMENTS

The case-report is aimed at describing an NTM disease in a Japanese woman with RA and treated with TCZ. After a surgical intervention she resumed the biological therapy together with the anti-bacterials. The topic is potentially interesting; however, the new findings do not emerge from the critical discussion.

SPECIFIC COMMENTS

Background

C1: Several lines are not supported by sound references. The Authors should include one or more references for every line.

R1: According to the comment, we have added appropriate references for every line in the ‘Background’ section.

C2: More details on the TB and NTM incidence are needed. Furthermore, there should be a geographical variability in terms of transmission of infectious agents.

R2: We appreciate the important comment. The details in the incidence of pulmonary NTM disease and tuberculosis have been added as below (line 61-67).

Especially in Japan, the most recent nationwide survey revealed that the incidence rate of pulmonary NTM disease (14.7 persons per 100,000 person-years) may exceed that of tuberculosis in general population, and that Japan may have one of the highest incidence rates of pulmonary NTM disease worldwide. Whereas tuberculosis can usually be controlled by the standard chemotherapy, no effective chemotherapy has been established against Mycobacterium
avium complex (MAC), leading to aggravation of MAC infection during immunosuppressive therapy. According to Japanese postmarketing surveillance of TCZ in RA patients, the incidence of NTM infections (0.22%) is higher than that of tuberculosis (0.05%).

C3: The last line of this section is meaningless. The Authors should better explain what they mean.

R3: Thank you for the comment. The sentence has been changed as below (line 72-74).

Although the use of biological agents is generally contraindicated in patients with pulmonary MAC disease, especially in those with a fibrocavitary lesion, a multimodality approach for MAC may enable introduction or resumption of biological agents.

C4: More rationale is needed to better introduce the topic, including the infectious disease risk in RA patients.

R4: As you pointed out, we added more contents including the risk of infectious disease among RA patients in the Background. The difference in the risk of infectious disease between the classes of the biological agents is also mentioned in the revision.

Background (line 53-70)

According to the recent systematic review, both standard-dose and high-dose biological agents are associated with the increased risk of serious infections, compared with traditional disease-modifying anti-rheumatic drugs (DMARDs). With respect to the difference in susceptibility between the classes of biologics, no difference in the risk of infection has been reported between TCZ and others, although the Cochrane review in 2011 reported that abatacept, cytotoxic T lymphocyte antigen 4-immunoglobulin, was significantly less likely to cause infection than infliximab and TCZ. Moreover, it has been shown that biological agents are associated with a significant increase in mycobacterial diseases. Concerning the types of mycobacterial diseases, Winthrop and coworkers reported that NTM infections were more common than tuberculosis among patients receiving biologics. Especially in Japan, the most recent nationwide survey revealed that the incidence rate of pulmonary NTM disease (14.7 persons per 100,000 person-years) may exceed that of tuberculosis in general population, and that Japan may have one of the highest incidence rates of pulmonary NTM disease worldwide. Whereas tuberculosis can usually be controlled by the standard chemotherapy, no effective chemotherapy has been established against Mycobacterium avium complex (MAC), leading to aggravation of MAC infection during immunosuppressive therapy. According to Japanese postmarketing surveillance of TCZ in RA patients, the incidence of NTM infections (0.22%) is higher than that of tuberculosis (0.05%). Although many of RA patients have underlying pulmonary lesions and other risk factors for potential NTM infection, it is still controversial whether biological agents can be a risk of exacerbation of pre-existing pulmonary NTM disease. Consequently, a strategy for the
management of NTM in RA patients subjected to treatment with biologics remains to be established.

Case-presentation

C5: What do they mean with "almost normal findings"?

R5: As the description was confusing, we have changed it to “normal” in the revised manuscript (line 84).

C6: From the pictures it is unclear where the upper lobe was resected.

R6: We agree to the comment. To clarify that the right upper lobe was resected, a photograph of a cross-sectional specimen from the right upper lung has been added as Figure 3A.

Figure 3 Photograph and photomicrographs of the lung. (A) Photograph of a cross-sectional specimen from the resected right upper lung. (B, C) Photomicrographs showing an epithelioid granuloma with necrosis (B: bar, 5 mm; C: bar, 500 µm). (D) Photomicrograph showing Langhans giant cells (arrowheads) and epithelioid cells (arrow) (bar, 100 µm).

Conclusions

C7: The comparison with previous similar cases was not performed. On this basis, it is important to better underline the new findings of the report.

R7: We appreciate the important comment. As you suggested, we have strengthened the contents concerning comparisons with preceding studies, as shown below. Accordingly, we also emphasized the new finding showing the safe resection for the first time (line 122-126).

In the case series by Mori and colleagues, anti-TNF agents could be safely reintroduced in 7 patients without exacerbation of the MAC infection. Nakahara and coworkers also described a case of successful reintroduction of TCZ without aggravation of MAC infection under the standard chemotherapy. However, there has been no report of surgical resection of MAC lesion followed by successful reintroduction of biologics. In this regard, this is the first case report which indicates that biological agents might be safely resumed after surgery.