May 29, 2023

Dear Editor(s),

We thank the reviewers for their constructive comments, which helped us to improve the quality of the manuscript. We have revised the manuscript according to these comments (highlighted parts in the submitted revised file). In the appendix, we have provided our response to the comments made by the reviewers.

Thank you very much.

Sincerely,

Qiaohong Wang

Deputy Chief Physician

Department of Rheumatology,

Second Affiliated Hospital, College of Medicine, Zhejiang University,

Hangzhou, China

Email: 2202015@zju.edu.cn

Appendix

Comments by Reviewer 1: In this manuscript, Wang et al reported the clinical evolution of two patients with anti-MDA5 positive DM. The interest lies mainly in the observation of Patient 2, for whom treatment with tocilizumab was introduced. Here are some concerns : - The use of TCZ in this clinical context is not classic. Why did the authors opt for this strategy and not for targeting another cytokine, such as IFN type I or TNF alpha? Authors should discuss this aspect. - Line 34, 147 : Change Pneumocystis carinii by Pneumocystis jirovecii - Line 215: Specify that in the cited case report, 6 patients were treated efficiently with TCZ.

Response to comments of Reviewer 1: We thank the reviewer for his/her constructive comments. We have revised the manuscript according to these comments, as explained in the following.

1) Pneumocystis carinii was replaced by Pneumocystis jirovecii (Line 34, 147; highlighted)
2) The number of cases (i.e., six) successfully treated by tocilizumab in the cited case report was added to the manuscript (Line 215-216; highlighted).
3) The following text was added to the manuscript (Line 214-233; highlighted):
    a. "To our knowledge, there is only one prior report of using tocilizumab for treatment of dermatomyositis, where tocilizumab was found to be effective for the treatment of six patients (14). With respect to targeting other cytokines, such as tumor necrosis factor-alpha (TNF-α) and type 1 interferon (T1-IFN), we should point out the following. First, examining data of 122 cases of new-onset or exacerbation of ILD secondary to administration of biologic therapies revealed that in 97% of cases the biologic agent used was blocking TNF-α (15), which discouraged us from considering targeting TNF-α in our patients. With respect to the significance of type 1 interferon (T1-IFN) in the pathogenesis and treatment of MDA5^{+}-DM-RP-ILD we should say that high T1-IFN signatures in serum and affected skin of MDA5^{+}-DM-RP-ILD patients have been reported highlighting the potential of targeting T1-IFN as a treatment strategy in such patients (16). Nevertheless, we are unaware of a report in the literature that has tested this

treatment strategy in patients with MDA5^{+}-DM-RP-ILD. In this context, we should point out that a Phase I b randomized, double-blind, controlled clinical study of Sifalimumab found elevated T1-IFN gene signaling in 77% of patients with inflammatory myopathy (17). Sifalimumab is currently not marketed in China and its efficacy in treating polymyositis/dermatomyositis-related pulmonary interstitial lesions remains to be observed. Thus, due to the very high mortality of MDA5^{+}-DM-RP-ILD and the circumstances around targeting TNF-α and T1-IFN, our decision to use tocilizumab was based on the above-mentioned prior report (14) and also the fact that IL-6 is closely related to the pathogenesis of MDA5^{+}-DM-RP-ILD (18)."

Comments by Reviewer 2: Authors to please detail about Consent form in English Anti MDA5 dermatomyositis incidence and prevalence in general population Role of Lung Transplantation for IPF associated with this disease Details about Hormonal therapy Pulmonary function test both pre and post therapy Share the images of x - ray HRCT Chest done. I must congratulate authors for their sincere effort in writing up of this manuscript.

Response to comments by Reviewer 1: We thank the reviewer for his/her favorable view about our manuscript. We should say that the incidence rate of inflammatory myopathy outside China has been reported to be (0.5-8.4) per 100,000, but there is no exact epidemiological data in China. The prevalence of MDA5-DM-ILD in the general population and the incidence and prevalence of MDA5-DM-ILD have not been reported. With respect to lung transplantation, we should say that since MDA5-DM-ILD is an immune-related interstitial lung disease, active treatment of the primary disease is generally advocated, lung transplantation is not advocated, and there are no relevant reports for the use of lung transplantation for treating this disease. Due to the acute inflammatory stage of the disease and the severe illness and unsatisfactory coordination, neither of the two cases underwent lung function examination.