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Letter to the Editor (Matters arising from published papers)

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Comment on: Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study: reply

Dear Editor, Thank you for the comments [1] on our article [2]. Dr Watanabe has raised some interesting points [1], and we appreciate the opportunity to discuss our TAKT study. First, regarding the steroid-sparing effect of tocilizumab (TCZ), we recommended that glucocortioids should be tapered slowly in patients with refractory Takayasu arteritis receiving TCZ to avoid further relapses [2]. Furthermore, according to a report by Ohigashi *et al.*, prednisone dose reduction rate was the significant predictor of relapse identified during glucocorticoid treatment of patients with Takayasu arteritis [3]. European League Against Rheumatism recommendations for the management of Takayasu arteritis state that the treatment target is sustained remission plus glucocorticoid tapering without relapse [4]. Although aiming for treatment targets to discontinue glucocorticoids entirely is ideal, we believe that it is important to consider disease activity and comorbidities, such as ulcerative colitis, when adjusting the glucocorticoid dose. Regarding the comment about discontinuing tocilizumab in patients with Takayasu arteritis, this would have to be investigated in future studies because it was not investigated in our TAKT study. Severe disease flares after withdrawal of tocilizumab have been reported [5], and the option to switch to another immunosuppressant is an important consideration for patients who need to withdraw from tocilizumab treatment.

Second, regarding the comment that improvement shown on imaging was not as high as expected considering the steroid-sparing effect of tocilizumab, we believe that 85.7% of patients in our study [2] demonstrating stable or improved disease via imaging evaluation is clinically relevant because 75% of patients treated with methotrexate and glucocorticoids developed new vascular lesions in a retrospective longitudinal cohort study [6]. It is unlikely that increased interleukin-6 (IL-6) levels after tocilizumab treatment contributed to fibrosis in our study because, although serum IL-6 levels do increase after tocilizumab treatment, this results from occupancy of soluble and membrane-bound IL-6 receptors by tocilizumab and, therefore, IL-6 signalling is blocked [7].

Third, regarding the four patients who showed deterioration on imaging in our study [2], we agree that a proportion of patients are likely not responsive to tocilizumab therapy. There was no clear relationship between baseline HLA-B52 status or elevated CRP levels and efficacy outcomes at week 96 in patients who had their glucocorticoid dose reduced to <0.1 mg/kg/day. Initiation of immunosuppressive treatments, other than glucocorticoids, was not permitted in our study but it is possible that there might have been fewer patients showing worsening disease on imaging if this had been allowed. In a real-world setting, an increase in glucocorticoid dose or additional immunosuppressive therapy should be considered in patients with radiographic evidence of worsening disease to prevent further vascular damage. We agree that identifying biomarkers that can be used to target patients for whom tocilizumab is likely to be effective is an important issue that warrants further research.

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References

1 Watanabe R. Comment on: Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study. Rheumatology 2020;59:e46–7.

2 Nakaoka Y, Isobe M, Tanaka Y *et al*. Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study. Rheumatology 2020;59:2427–34.

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3 Ohigashi H, Haraguchi G, Konishi M *et al*. Improved prognosis of Takayasu arteritis over the past decade—comprehensive analysis of 106 patients. Circ J 2012;76: 1004–11.

4 Hellmich B, Agueda A, Monti S *et al*. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19–30.

5 Arita Y, Nakaoka Y, Otsuki M *et al*. Cytokine storm after cessation of tocilizumab in a patient with refractory Takayasu arteritis. Int J Cardiol 2015;187:319–21.

6 Freitas DS, Camargo CZ, Mariz HA, Arraes AE, de Souza AW. Takayasu arteritis: assessment of response to medical therapy based on clinical activity criteria and imaging techniques. Rheumatol Int 2012;32:703–9.

7 Nishimoto N, Terao K, Mima T *et al*. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood 2008; 112:3959–64.