RHEUMATOLOGY ADVANCES IN PRACTICE

Letter to the Editor (Matters arising from published papers)

Rheumatology Advances in Practice 2022;00:1–2
http://doi.org/10.1093/rap/rkac025
Advance Access Publication 11 April 2022

Comment on: Combination of immunosuppressive therapy and nintedanib improves capillaroscopic changes in systemic sclerosis-interstitial lung disease: a case report. Reply

Dear Editor, We are pleased that Sugimoto *et al.* [1] read our case report and provided their valuable opinion. We understand that they are concerned about the effectiveness of immunosuppressive therapy on nailfold capillary damage in SSc complicated with interstitial lung disease (ILD), the effectiveness of early treatment on nailfold capillary abnormalities in SSc-ILD and the therapeutic effect of nintedanib on nailfold capillary abnormalities in SSc-ILD.

First, previous reports have demonstrated the effectiveness of immunosuppressive treatments, such as cyclophosphamide and haematopoietic stem cell transplantation, against nailfold capillary damage in SSc [2]. Sugimoto *et al.* [1] pointed out that tacrolimus (TAC) may improve microvascular damage in SSc-ILD. Lemmers *et al.* [2] also reported that low-dose prednisolone (PSL) and TAC improved nailfold capillary abnormalities in SSc-ILD from a late pattern to an early pattern. In the present report, the patient was treated with immunosuppressive therapy, including PSL and TAC [3]. Th2 activation is related to the pathomechanism of SSc [4]. Th2-producing IL-4 and IL-13 are related to fibrosis in SSc. We have previously reported that combination therapy with PSL and TAC is effective against SSc-ILD, suggesting that TAC suppresses Th2 cell activation in SSc-ILD [4]. In SSc-ILD, the presence of ILD was associated with a late pattern of nailfold capillary abnormalities [2]. Therefore, inhibiting fibrosis progression with TAC therapy may ameliorate nailfold capillary abnormalities in SSc-ILD. However, further studies are required to determine whether TAC inhibits microvascular damage in SSc-ILD.

Second, in the present study, SSc-ILD was treated in the early phase, therefore the microvascular damage was less severe. Immunosuppressive therapy in the early phase improves the prognosis of SSc-ILD because inflammation before fibrosis can be reversed during early treatment [5]. Sugimoto *et al.* [1] pointed out that nailfold capillary abnormalities in SSc in the early and active patterns can be reversible. Kubo *et al.* [6] previously reported that nearly 30% of patients with early and active patterns have ILD in SSc, therefore immunosuppressive therapy may affect nailfold capillary abnormalities in these patients. Further studies are needed to determine whether changes in nailfold capillary abnormalities after immunosuppressive treatment differ between early, active and late patterns in patients with SSc.

Third, nintedanib treatment in the early phases may improve microvascular damage in patients with SSc-ILD. In the SENSCIS trials (NCT02597933), nintedanib slowed the annual rate of decline in forced vital capacity (FVC) compared with the placebo group in SSc-ILD [7]. Additionally, treatment response of nintedanib was similar in patients with well-preserved lung volume (FVC $>$90% predicted) compared with less well-preserved lung volume in patients with idiopathic pulmonary fibrosis, highlighting the importance of early nintedanib treatment [8]. Overall, these findings suggest that early nintedanib treatment may have ameliorated nailfold capillary abnormalities of SSc-ILD in the present study. Further studies are needed to determine whether the effectiveness of nintedanib on nailfold capillary abnormalities in SSc-ILD differs between early and late treatments.

Our patient was treated with immunosuppressants (PSL and TAC) and antifibrotic therapy (nintedanib). Therefore we did not elucidate whether immunosuppressive or antifibrotic therapy mainly improved microvascular damage in SSc-ILD. As Sugimoto *et al.* [1] pointed out, further verification is needed to determine the effect of immunosuppressive and antifibrotic therapies on microvascular damage in SSc-ILD.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

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Accepted 22 March 2022
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