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Reply to: Is classifying SSc-ILD drugs as either immunosuppressive or anti-fibrotic misleading?

We thank the authors for their thoughtful letter regarding our Review article (Pope, J. E. et al. State-of-the-art evidence in the treatment of systemic sclerosis. *Nat. Rev. Rheumatol.* **19**, 212–226 (2023))[1], as they raise some interesting points (Andréasson, K. et al. Is classifying SSc-ILD drugs as either immunosuppressive or anti-fibrotic misleading? *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-023-01013-4 (2023))[2]. We agree that it is simplistic to categorize drugs as either immunosuppressant (anti-inflammatory) or anti-fibrotic when considering the treatment of interstitial lung disease (ILD) and pulmonary fibrosis in systemic sclerosis (SSc) and also when considering the complex nature of SSc in other organs, such as pulmonary arterial hypertension (PAH) and skin disease. For instance, mycophenolate mofetil (MMF) is described as a strong immunosuppressive, but it also has anti-proliferative and anti-fibrotic effects[3]. Other important work demonstrates that fibrosis and inflammation co-occur in fibrotic lungs and can alter and/or upregulate each other's processes[4].

Janus kinase (JAK) inhibitors might have beneficial effects in SSc and ILD, although randomized controlled trials need to be performed. In vitro, JAK inhibitors affect M1 macrophages, which are mainly pro-inflammatory, and profibrotic M2 macrophages. Inhibition of JAK signalling has important anti-inflammatory effects, with reduced expression of certain markers (CD86, MHCII and TLR4) in M1 macrophages and reduced secretion of markers of M2a activation (CD206 and CCL18), which suggests that immunosuppressive effects can occur in conjunction with less-studied anti-fibrotic actions[5].

Cyclophosphamide, which is thought categorically to be a strong immunosuppressive, could have effects on fibrosis in SSc-associated ILD (SSc-ILD). In the Scleroderma Lung Study I, cyclophosphamide seemed to provide more benefit when fibrosis and honeycombing were present, although whether that response is attributable to the drug's anti-inflammatory effects or to the fact that patients with the most progressive disease (those with fibrosis) were the most likely to worsen if not treated is unclear[6].

The terminology for anti-fibrotics in pulmonary fibrosis can also be somewhat misleading. Nintedanib is not considered an immunosuppressant[7]. By targeting the receptors of pro-fibrotic mediators such as platelet-derived growth factor, fibroblast growth factor, vascular endothelial growth factor and colony-stimulating factor 1, nintedanib reduces fibrosis and can also alter macrophage activation. This drug also affects T cell activation through the lymphocyte-specific tyrosine protein kinase Lck, causing reduced production of extracellular matrix and activation of fibroblasts[7]. In animal models of pulmonary fibrosis, however, nintedanib has anti-inflammatory effects and reduces the expression of IL-1β and tissue inhibitor of metalloproteinase-1; lung tissue from mice with experimental pulmonary fibrosis showed diminished inflammation and granuloma formation in addition to a reduction in fibrosis[7]. Similarly, pirfenidone is considered anti-fibrotic and has anti-inflammatory and antioxidant effects[8].

Finally, it is difficult to know by which mechanism the new biologic drug sotatercept improves PAH. Sotatercept is an activin receptor type IIA–Fc fusion protein that selectively traps activins and growth differentiation factors in PAH. It can also reverse or reduce the expression of pro-inflammatory and proliferative genes in rodent models of PAH, which suggests that it also has anti-inflammatory activity[9].

So, now that we are in an era of increasing knowledge of the signalling effects of drugs and their implications within tissues and/or organ systems, categorizing treatments as 'immunosuppressive' and 'anti-fibrotic' is simplistic, and it is probably time to re-classify them with the understanding that their mechanisms can be complex.

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References

1. Pope, J. E. et al. State-of-the-art evidence in the treatment of systemic sclerosis. *Nat. Rev. Rheumatol.* **19**, 212–226 (2023).
2. Andréasson, K. et al. Is classifying SSc-ILD drugs as either immunosuppressive or anti-fibrotic misleading? *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-023-01013-4 (2023).
3. Nambiar, A. M., Anzueto, A. R. & Peters, J. I. Effectiveness and safety of mycophenolate mofetil in idiopathic pulmonary fibrosis. *PLoS ONE* **12**, e0176312 (2017).
4. Wigén, J., Elowsson-Rendin, L., Karlsson, L., Tykesson, E. & Westergren-Thorsson, G. Glycosaminoglycans: a link between development and regeneration in the lung. *Stem Cells Dev.* **28**, 823–832 (2019).
5. Lescoat, A. et al. Combined anti-fibrotic and anti-inflammatory properties of JAK-inhibitors on macrophages in vitro and in vivo: perspectives for scleroderma-associated interstitial lung disease. *Biochem. Pharmacol.* **178**, 114103 (2020).
6. Barnes, H. et al. Cyclophosphamide for connective tissue disease-associated interstitial lung disease. *Cochrane Database Syst. Rev.* **1**, CD010908 (2018).
7. Wollin, L. et al. Antifibrotis and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. *J. Pharmacol. Exp. Ther.* **349**, 209–220 (2014).
8. Shah, P. V. et al. A review of pirfenidone as an anti-fibrotic in idiopathic pulmonary fibrosis and its probable role in other diseases. *Cureus* **13**, e12482 (2021).
9. Joshi, S. R. et al. Sotatercept analog suppresses inflammation to reverse experimental pulmonary arterial hypertension. *Sci. Rep.* **12**, 7803 (2022).

Competing interests

J.E.P. declares that she has research grants from AbbVie, Bayer, BI, BMS, Frensenius Kabi, Lilly, Mallinckrodt Pharmaceuticals, Merck, Roche and Seattle Genetics; that she has consulted for AbbVie, Amgen, BI, BMS, Celltrion, EMERALD, Frensenius Kabi, Galapagos, Gilead, Janssen, Lilly, Mallinckrodt Pharmaceuticals, Medexus, Merck, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Roche, Sandoz, Samsung, Sanofi, Sobi, Teva and Viatris; and that she has been a speaker or attended an advisory board for AbbVie, Amgen, BI, BMS, Frensenius Kabi, Galapagos, Gilead, Janssen, Lilly, Merck, Novartis, Pfizer, Sandoz, Sanofi and UCB.