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

We read with great interest the comprehensive Review article by Pope et al. on the treatment of systemic sclerosis (SSc) (Pope, J. E. et al. State-of-the-art evidence in the treatment of systemic sclerosis. *Nat. Rev. Rheumatol.* **19**, 212–226 (2023))[1]. We agree with the authors that results from cohort studies and randomized, placebo-controlled trials support the usage of several treatment strategies for SSc-interstitial lung disease (ILD), including drugs traditionally labelled as immunosuppressive, such as mycophenolate mofetil (MMF), and drugs originally approved for the treatment of fibrotic pulmonary disorders, such as nintedanib. However, we are concerned that categorizing currently available drugs as either 'immunosuppressive' or 'anti-fibrotic' is misleading[1].

Fibrosis and immune activation are broad terms that encompass a wide range of integrated physiological and pathological processes. This holds true also for ILD, in which fibrosis (that is, an imbalance of extracellular matrix (ECM) turnover) develops in conjunction with inflammation[2]. For example, inflammatory cells that infiltrate the ECM can modulate the biological properties of the tissue interstitium through the release of matrix metalloproteases that degrade structural proteins into smaller fragments that express neoepitopes. These fragments have an altered function relative to that of their original protein, such as chemotactic properties that promote the further infiltration of inflammatory cells[3].

We are unsure of the meaning of term 'anti-fibrotic'. Specifically, we wonder if this term reflects the disease for which the drug originally was approved, or its mechanism of action. We also wonder if the authors consider the classifications of immunosuppressive and anti-fibrotic to be mutually exclusive, or if an immunosuppressive drug can also be classified as an anti-fibrotic drug and vice versa. Although the clinical efficacy of modern treatments for SSc-ILD has been confirmed in well-executed clinical trials[1], knowledge of the mechanisms whereby these drugs attenuate this disease is limited. This is true for both MMF and nintedanib.

The immune-modulating effects of MMF have been well established since its successful introduction as a drug to prevent rejection after solid-organ transplantation. However, clinical and experimental studies have also shown that MMF has inflammation-independent anti-fibrotic properties. Specifically, in vitro studies have demonstrated that fibroblasts, including human lung fibroblasts and myofibroblasts, are inhibited by mycophenolate[4,5]. In vivo, MMF attenuates fibrosis in several experimental models[6]. Histological studies of recipients of solid-organ transplants show that MMF reduces fibrogenesis to an extent not seen in patients treated with other immunosuppressive agents[7]. In idiopathic pulmonary fibrosis, promising data from clinical studies have been reported for MMF[8]. On the basis of the observations noted above, we suggest that the mechanisms whereby MMF attenuates SSc-ILD extend beyond its immunosuppressive properties and affect both inflammation and homeostasis of ECM turnover.

Likewise, nintedanib probably attenuates SSc-ILD via multiple mechanisms. Nintedanib is a tyrosine kinase inhibitor that targets several intracellular proteins, including fibroblast growth factor receptors, vascular endothelial growth factor receptors and platelet-derived growth factor receptors, as well as a number of Src family enzymes, some of which are expressed by macrophages and lymphocytes[9]. Accordingly, experimental studies indicate that nintedanib inhibits experimental pulmonary inflammation[10].

In conclusion, we suggest that caution is needed when classifying available SSc-ILD treatments as either immunosuppressive or anti-fibrotic, and we welcome a discussion regarding the usage of these terms.

There is a reply to this letter by Pope, J. E. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-023-01014-3 (2023).

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Competing interests

The authors declare no competing interests.