Rational repurposing of tocilizumab for treatment of lung fibrosis in systemic sclerosis

Christopher P. Denton FRCP[1] and Dinesh Khanna MD[2]

[1]University College London, London, United Kingdom

[2]University of Michigan Scleroderma Program, Ann Arbor, MI, USA, and [2]University College of London, London, UK

Corresponding author:
Professor Christopher Denton
Centre for Rheumatology and Connective Tissue Diseases
Division of Medicine
University College London
Royal Free Campus
Rowland Hill Street
London
NW3 2PF

c.denton@ucl.ac.uk

Recent approval of tocilizumab by the USA Food and Drug Administration (FDA) for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) is a welcome step towards better treatment and outcomes for systemic sclerosis (SSc). SSc-ILD has emerged as one of the major causes of death in a disease with very high burden and unmet need. This is the second drug approved by FDA for this indication and the first biological agent approved for any aspect of SSc [1], underpinned by a substantial body of translational medical research.

That approval was based on two well conducted clinical trials which failed to meet their primary efficacy endpoint of significant benefit for modified Rodnan skin score (MRSS) is perhaps more of a surprise. This is a reflection of the robustness of the data for the lung fibrosis subgroup in the Phase 3 focuSSced trial [2] and the limitations of using MRSS as a clinical trial endpoint. Skin and lung are not the same in early SSc and the tendency for MRSS to improve at a group level even in patients on placebo makes it a challenging outcome measure. Conversely, lung function decline appears to be a consistent feature of SSc and reduction in the rate of decline has been shown for nintedanib [3] and tocilizumab. These results may have broader implications for future clinical trial design in SSc. It is notable that there was benefit in a range of other endpoints including the American College of Rheumatology composite combined response index in SSc (ACR-CRISS) suggesting further potential impact on SSc.

It is not a surprise that blocking IL6 is beneficial in SSc-ILD based upon compelling data showing that patients with high levels of circulating IL6 have a worse outcome [4], and in two independent cohorts serum level of IL-6 predicted decline in lung function in those with more preserved FVC, suggesting particular role in pathogenesis of early stage SSc-ILD [5]. Robust mechanistic data from skin biopsies in the Phase 2 faSScinate trial of tocilizumab showed that, in the skin, activated fibroblasts can be almost completely attenuated after 6 months of therapy [6]. If analogous changes occur in lung fibroblasts, this explains the remarkable slowing of progression observed in both tocilizumab trials. The anti-fibrotic effect of blocking IL6 signalling was confirmed by quantitative analysis of HRCT fibrosis in the focuSSced trial [2]. This finding also raises the possibility that efficacy of tocilizumab in other indications such as giant cell arteritis or rheumatoid arthritis may also be at least partially mediated by impact on vascular or connective tissue scarring or fibrosis, rather than just inflammation.

In addition to increasing potential treatment options for SSc-ILD, this approval also highlights the importance of systematic thorough investigation of all SSc patients to detect the presence of lung fibrosis and assess the likelihood of progression. That both approved therapies slow progression rather than improve lung function puts the emphasis on earlier intervention to preserve functional lung tissue. To this end, all patients with SSc are recommended to undergo HRCT for early identification of lung fibrosis, although this is not yet standard practice in all centres [7]. In addition, previous approaches of careful observation of disease that less extensive, and involves less than 20% of lung volume, may not be appropriate in cases likely to progress rapidly. This will require a shift in practice and also makes the need for validated prognostic biomarkers of SSc-ILD more pressing.

Having two drugs approved for SSc-ILD is a undoubtedly major step forward for patients. It also builds upon the robust clinical trial data supporting use of immunosuppression for SSc-ILD. The best outcomes in terms of improvement in fibrosis have been seen after myeloablative autologous stem cell transplant but this is a major undertaking not suitable for the majority of cases [8]. The Scleroderma Lung Study (SLS) I and SLS II trials support use of immunosuppression with cyclophosphamide or mycophenolate mofetil (MMF) [7]. There are limited trial data for rituximab as

an alternative to cyclophosphamide and other trials results are waited [9]. In SENSCIS nintedanib was shown to have numerically greater benefit in combination with MMF [10].

This is an exciting time for treatment of lung fibrosis in SSc and may herald use of combinations of drugs. But as options for treatment increase, the availability of high quality up to date expert guidance becomes more important [7]. In addition, it is likely that other drugs will now be tested in SSc-ILD and so more progress may be made for patients. In the end the drug development paradigm for SSc may change with focus moving away from the skin measures towards lung function. Since the major patient burden of SSc involves many organs beyond lung, it is important to also explore broader impact of approved therapies on the disease. One note of caution is that in the pivotal trials that led to approval, neither nintedanib nor tocilizumab showed significant benefit in patient reported outcome or breathlessness. More work needs to be done both in clinical trial design, developing outcome measures that are relevant to those with SSc-ILD, and also to ensure that statistical benefit in trials translates to much needed improvement in how patients feel and function.

References

1. Press release - https://www.roche.com/media/releases/med-cor-2021-03-05b.htm
2. Khanna D, Lin CJF, Furst DE, Goldin J, Kim G, Kuwana M, Allanore Y, Matucci-Cerinic M, Distler O, Shima Y, van Laar JM, Spotswood H, Wagner B, Siegel J, Jahreis A, Denton CP; focuSSced investigators. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2020 Oct;8(10):963-974. doi: 10.1016/S2213-2600(20)30318-0. Epub 2020 Aug 28.
3. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, Raghu G, Sauter W, Girard M, Alves M, Clerisme-Beaty E, Stowasser S, Tetzlaff K, Kuwana M, Maher TM; SENSCIS Trial Investigators. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. N Engl J Med. 2019 Jun 27;380(26):2518-2528. doi: 10.1056/NEJMoa1903076. Epub 2019 May 20. PMID: 31112379.
4. Khan K, Xu S, Nihtyanova S, Derrett-Smith E, Abraham D, Denton CP, Ong VH. Clinical and pathological significance of interleukin 6 overexpression in systemic sclerosis. Ann Rheum Dis. 2012 Jul;71(7):1235-42. doi: 10.1136/annrheumdis-2011-200955. Epub 2012 May 14. PMID: 22586157.
5. De Lauretis A, Sestini P, Pantelidis P, Hoyles R, Hansell DM, Goh NS, Zappala CJ, Visca D, Maher TM, Denton CP, Ong VH, Abraham DJ, Kelleher P, Hector L, Wells AU, Renzoni EA. Serum interleukin 6 is predictive of early functional decline and mortality in interstitial lung disease associated with systemic sclerosis. J Rheumatol. 2013 Apr;40(4):435-46. doi: 10.3899/jrheum.120725. Epub 2013 Feb 1. PMID: 23378460.
6. Denton CP, Ong VH, Xu S, Chen-Harris H, Modrusan Z, Lafyatis R, Khanna D, Jahreis A, Siegel J, Sornasse T. Therapeutic interleukin-6 blockade reverses transforming growth factor-beta pathway activation in dermal fibroblasts: insights from the faSScinate clinical trial in systemic sclerosis. Ann Rheum Dis. 2018 Sep;77(9):1362-1371. doi: 10.1136/annrheumdis-2018-213031. Epub 2018 May 31. PMID: 29853453; PMCID: PMC6104680.CT recommendation – L rheum recommendations
7. Anna-Maria Hoffmann-Vold, Toby M Maher, Edward E Philpot, Ali Ashrafzadeh, Rafic Barake, Simone Barsotti, Cosimo Bruni, Paolo Carducci, Patricia E Carreira, Ivan Castellví, Francesco Del Galdo, Jörg H W Distler, Ivan Foeldvari, Paolo Fraticelli, Peter M George, Bridget Griffiths, Alfredo Guillén-Del-Castillo, Abdul Monem Hamid, Rudolf Horváth, Michael Hughes, Michael Kreuter, Florentine Moazedi-Fuerst, Jacek Olas, Suman Paul, Cinzia Rotondo, Manuel Rubio-

Rivas, Andrei Seferian, Michal Tomčík, Yurdagül Uzunhan, Ulrich A Walker, Ewa Więsik-Szewczyk, Oliver Distler. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements, The Lancet Rheumatology, Volume 2, Issue 2, 2020, Pages e71-e83, ISSN 2665-9913,

8. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, Pinckney A, Welch B, Mayes MD, Nash RA, Crofford LJ, Eggleston B, Castina S, Griffith LM, Goldstein JS, Wallace D, Craciunescu O, Khanna D, Folz RJ, Goldin J, St Clair EW, Seibold JR, Phillips K, Mineishi S, Simms RW, Ballen K, Wener MH, Georges GE, Heimfeld S, Hosing C, Forman S, Kafaja S, Silver RM, Griffing L, Storek J, LeClercq S, Brasington R, Csuka ME, Bredeson C, Keever-Taylor C, Domsic RT, Kahaleh MB, Medsger T, Furst DE; SCOT Study Investigators. Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma. N Engl J Med. 2018 Jan 4;378(1):35-47. doi: 10.1056/nejmoa1703327. PMID: 29298160; PMCID: PMC5846574.
9. Saunders P, Tsipouri V, Keir GJ, Ashby D, Flather MD, Parfrey H, Babalis D, Renzoni EA, Denton CP, Wells AU, Maher TM. Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial. Trials. 2017 Jun 15;18(1):275. doi: 10.1186/s13063-017-2016-2. PMID: 28619061; PMCID: PMC5471887.
10. Highland KB, Distler O, Kuwana M, Allanore Y, Assassi S, Azuma A, Bourdin A, Denton CP, Distler JHW, Hoffmann-Vold AM, Khanna D, Mayes MD, Raghu G, Vonk MC, Gahlemann M, Clerisme-Beaty E, Girard M, Stowasser S, Zoz D, Maher TM; SENSCIS trial investigators. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. Lancet Respir Med. 2021 Jan;9(1):96-106. doi: 10.1016/S2213-2600(20)30330-1. PMID: 33412120.