

Lancet Respiratory Medicine – invited commentary

Scleroderma Lung Study-II - clarity or obfuscation?

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Systemic sclerosis (scleroderma; SSc) is one of the most recalcitrant of immune-mediated rheumatic diseases due to its clinical impact and the high mortality associated with internal organ complications [1]. Lung fibrosis has emerged as the major causes of scleroderma-related death and with better treatments for pulmonary arterial hypertension, the other main lethal lung manifestation, this looks set to continue [2].

Trials of therapies for lung fibrosis in SSc have been challenging. Publication of the primary clinical results from the Scleroderma Lung Study-II (SLS-II) should represent an important landmark in modern evidence-based practice [3]. Building upon the platform of the preceding SLS-I trial enabled a highly original study design with 12 months of oral cyclophosphamide (CYC) compared with 24 months of oral MMF with a target daily dose of 3g. In SLS-I statistically significant superiority of CYC over placebo was observed at 12 months, although treatment effect was modest, and some have said of dubious clinical relevance [4]. Moreover, in SLS-I the primary end point (% predicted FVC) continued to improve after stopping CYC and reached its maximum at 18 months, but had disappeared at 24 months although other clinical endpoints were more durable [5]. These included improved skin thickening (modified Rodnan skin score, MRSS) and dyspnea scores, adding to the weight of opinion that SLS-I was positive. This is critical to interpretation of SLS-II since it was predicated upon the assumption that CYC for 12 months is efficacious for lung function but that lung function benefit would be lost by 24 months. In the event, this late deterioration did not occur, which raises a dilemma that both treatment arms look similarly effective, although MMF was certainly better tolerated.

The rationale for testing MMF in a large prospective trial is strong. Accepting from SLS-I the evidence that CYC improved FVC and a host of other clinically meaningful end points and that this effect was at a level of clinical significance in long term follow up, with defined subsets (essentially those with more severe disease) showing the greatest benefit, then the next important clinical question was whether MMF could achieve as much and with better tolerability or safety. Observational cohorts and small trials had given a taste of what might be seen and were generally supportive but not sufficiently robust to recommend this approach [6,7]. SLS-II represents a triumph of intelligent recruitable study design. It shows clear evidence for improvement in both treatment arms and unequivocal data that show that MMF is better tolerated. There is a hint of superiority for DLco, which may be the best measure of global alveolar capillary function in SSc and has been shown on many occasions to predict higher mortality when diminished [8]. There were fewer deaths in the MMF arm and long term follow up may eventually provide unequivocal evidence of superiority, analogous to the trials of ASCT that showed long term survival advantage [9], but these data will not be available for several years.

In the meantime, practicing physicians need to choose the best treatment for their patients and the SLS-II underpins this. It supports the recommendations emerging from experts about possible treatment for SSc lung fibrosis with MMF and is in line with earlier retrospective datasets. It should be welcomed with

cautious enthusiasm. More studies will emerge and additional trials are planned. It is clear that even better therapies are needed, and so MMF may emerge as a background immunotherapy to which other drugs are added. Additional targeting of vasculopathy, the immuno-inflammatory compartment and epithelial-mesenchymal dysregulation may eventually become a reality.

At present, we should learn from SLS-II in terms of clinical trials design to refine our endpoints and improve cohort selection for future studies. SLS-II may not have demonstrated superior efficacy but the take home message is clear – on the balance of probabilities, oral MMF treatment at 3g per day is likely to stabilize or improve scleroderma lung fibrosis and has acceptable tolerability. Whether CYC infusional treatment followed by MMF is better than oral treatment alone cannot be answered. This is a pity since this is the most frequent approach to CYC use in many specialist scleroderma centres, and an earlier controlled trial suggested comparable benefit from 6 months of intravenous CYC to that seen in SLS-I, but with lower toxicity [10]. Likewise, newer approaches such as rituximab are under evaluation and the precise place of these approaches is unclear. Ironically, as the authors speculate, available but unproven rescue treatments may have sabotaged the elegant design in SLS-II by attenuating the decline observed in SLS-I when used in patients progressing after CYC therapy.

The key message from the paper is that MMF is tolerable and may be valuable in treating lung fibrosis in SSc. It may now be time to accept this and move on with testing more innovative therapies to achieve greater clinical improvements and to better define patients that are most likely to respond.

References

1. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, Bancel DF, Allanore Y, Müller-Ladner U, Distler O, Iannone F, Pellerito R, Pileckyte M, Miniati I, Ananieva L, Gurman AB, Damjanov N, Mueller A, Valentini G, Riemekasten G, Tikly M, Hummers L, Henriques MJ, Caramaschi P, Scheja A, Rozman B, Ton E, Kumánovics G, Coleiro B, Feierl E, Szucs G, Von Mühlen CA, Ricciari V, Novak S, Chizzolini C, Kotulska A, Denton C, Coelho PC, Kötter I, Simsek I, de la Pena Lefebvre PG, Hachulla E, Seibold JR, Rednic S, Stork J, Morovic-Vergles J, Walker UA. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis.* 2010 Oct;69(10):1809-15.
2. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoepfer MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grünig E, Oudiz RJ, Vonk-Noordegraaf A, White RJ, Blair C, Gillies H, Miller KL, Harris JH, Langley J, Rubin LJ. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *N Engl J Med.* 2015 Aug 27;373(9):834-44.
3. Tashkin et al – Mycophenolate Mofetil versus Oral Cyclophosphamide in Scleroderma related Interstitial Lung Disease: Scleroderma Lung Study II (SLS-II), a double-blind, parallel group, randomised controlled trial– *Lancet Respiratory Medicine* 2016
4. Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver RM, Goldin J, Arriola E, Strange C, Bolster MB, Seibold JR, Riley DJ, Hsu VM, Varga J, Schraufnagel D, Theodore A, Simms R, Wise R, Wigley F, White B, Steen V, Read C, Mayes M, Parsley E, Mubarak K, Connolly MK, Golden J, Olman M, Fessler B, Rothfield N, Metersky M, Khanna D, Li N, Li G; Scleroderma Lung Study Research Group. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *Am J Respir Crit Care Med.* 2007 Nov;176(10):1026-34.

5. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, Arriola E, Silver R, Strange C, Bolster M, Seibold JR, Riley DJ, Hsu VM, Varga J, Schraufnagel DE, Theodore A, Simms R, Wise R, Wigley F, White B, Steen V, Read C, Mayes M, Parsley E, Mubarak K, Connolly MK, Golden J, Olman M, Fessler B, Rothfield N, Metersky M; Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med*. 2006 Jun 22;354(25):2655-66. PubMed PMID: 16790698.
6. Nihtyanova SI, Brough GM, Black CM, Denton CP. Mycophenolate mofetil in diffuse cutaneous systemic sclerosis--a retrospective analysis. *Rheumatology (Oxford)*. 2007 Mar;46(3):442-5.
7. Mendoza FA, Nagle SJ, Lee JB, Jimenez SA. A prospective observational study of mycophenolate mofetil treatment in progressive diffuse cutaneous systemic sclerosis of recent onset. *J Rheumatol*. 2012 Jun;39(6):1241-7. doi: 10.3899/jrheum.111229. Epub 2012 Apr 1. PubMed PMID: 22467932.
8. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, Wells AU, Denton CP. Prediction of pulmonary complications and long-term survival in systemic sclerosis. *Arthritis Rheumatol*. 2014 Jun;66(6):1625-35.
9. van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, Schuerwegh AJ, Marijt EW, Vonk MC, Schattenberg AV, Matucci-Cerinic M, Voskuyl AE, van de Loosdrecht AA, Daikeler T, Kötter I, Schmalzing M, Martin T, Lioure B, Weiner SM, Kreuter A, Deligny C, Durand JM, Emery P, Machold KP, Sarrot-Reynauld F, Warnatz K, Adoue DF, Constans J, Tony HP, Del Papa N, Fassas A, Himsel A, Launay D, Lo Monaco A, Philippe P, Quéré I, Rich É, Westhovens R, Griffiths B, Saccardi R, van den Hoogen FH, Fibbe WE, Socié G, Gratwohl A, Tyndall A; Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA*. 2014 Jun 25;311(24):2490-8.
10. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, Roberts C, Desai S, Herrick AL, McHugh NJ, Foley NM, Pearson SB, Emery P, Veale DJ, Denton CP, Wells AU, Black CM, du Bois RM. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum*. 2006 Dec;54(12):3962-70.