**Does high dose extended course cyclophosphamide and methylprednisolone pulse therapy have a role in the management of systemic sclerosis related interstitial lung disease?**

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**Key message:** SSc-interstitial lung disease that deteriorates despite initial CYC does not stabilise with dose escalation; consider alternative therapies.

Sir, cyclophosphamide (CYC) is currently recommended for the treatment of Systemic Sclerosis-Interstitial Lung Disease (SSc-ILD) (1). The relatively marginal benefit observed in two key randomised controlled trials (2,3), and a meta-analysis (4) however, have questioned the true long-term efficacy. The paucity of data in patients selected on the basis of ILD progression could partly explain the challenges in demonstrating a clinically relevant benefit (5).

At our tertiary centre, we undertook a retrospective and pragmatic evaluation of the effectiveness of our historical pulse CYC and methylprednisolone (MP) therapy regimen in patients with SSc and recently deteriorated ILD, defined as: decrease (>10% decline in predicted value to previous recording) of DLCO±FVC in ≤6 months and/or worsening of ILD on high resolution computed tomography (HRCT) chest; and/or a new diagnosis of ILD defined by ≤6 months onset of shortness of breath and ground glass changes on HRCT scan and/or DLCO±FVC<80% of predicted value. Presence of new±deterioration of ILD was based on standard clinical evaluation (with no routine formal scoring) by the multidisciplinary team (comprising chest physician and radiologist). Here, we provide a descriptive report to evaluate whether there is a role for higher dose ± extended pulse CYC in SSc patients based on the above criteria.

All patients fulfilled 2013 ACR/EULAR SSc classification criteria (6). Of 55 patients identified, complete data were available on 45 patients. Ethical approval was not required as this report was an audit of standard practice, which the Leeds Teaching Hospitals NHS Trust approved. The treatment strategy at the time comprised 6 pulses intravenous CYC 15mg/kg plus MP 10mg/kg (x3 3-weekly and x3 4-weekly). This was

followed by one of three strategies based on physician judgment (incorporating lung physiology/radiology): no maintenance immunosuppression, 7/45; maintenance immunosuppression [azathioprine target dose of 2.5 mg/kg/day or mycophenolate mofetil (MMF) 2g/day or pulse CYC 15mg/kg plus MP 10mg/kg 4-10 weekly (low dose extended)], 22/45; escalation protocol with pulse CYC 22.5mg/kg plus MP 10mg/kg (high dose extended), 16/45. Three/45 patients were on stable 5mg/day oral prednisolone during standard and/or extended protocols.

FVC% and DLCO% were classified as improved, stable, worsened if >10% increase, 0-10% change and >10% decrease respectively. Patients were defined responders when both FVC% and DLCO% showed at least stable results (and/or improved) and termed non-responders if FVC% and/or DLCO% worsened.

Statistical analysis was performed using GraphPad Prism software V.6.0. Binomial variables were expressed as numbers and percentages, continuous variables as mean ± standard deviation (SD). Significant differences between responders and non-responders to the standard protocol were defined as those at a level of $p<0.05$, by unpaired t-test or Fisher's/chi-square test.

Of the 45 subjects, 6 (13.3 %) were male, 41 (91.1%) ANA positive, 9 (20%) antiScl-70 positive and 2 (4.4%) anti-centromere (ACA) positive. Mean (SD) disease duration was 9.33 (±11.45) years from Raynaud's Phenomenon (RP), 5.98 (±7.59) from the 1$^{st}$ non-RP symptom. Twenty-seven (60%) were never-smokers, 12 (26.7%) ex-smokers, 6 (13.3%) current smokers. Mean (SD) baseline predicted FVC% was 76.16% (±19.26) and DLCO%

was 49.17% (±14.1). Thirty-seven of the 45 patients had a chest HRCT scan at baseline and, of these patients, 22 (59.5%) had ground glass and 31 (83.8%) had basal fibrosis.

Figure 1 summarises the treatment strategy, patient flow and response to therapy. Following the standard protocol, 7/45 (15.6%) improved, 20/45 (44.4%) remained stable, 18/45 (40%) worsened. Of FVC changes, 10/24 patients (41.7%) with baseline FVC<80%, showed an improvement; 11/24 (45.8%) remained stable, 3/24 (12.5%) worsened; of DLCO changes, 11/45 (24.4%) showed an improvement, 16/45 (35.6%) remained stable, 18/45 (40%) worsened. Compared to non-responders, responders were younger (p=0.005), with lower mean FVC% (p=0.009) and higher proportion with baseline FVC<80% (p=0.037). Other baseline clinical characteristics were not significantly different (p>0.05). Twenty-nine (64.4%) subjects underwent maintenance protocol or had no immunosuppression, 16 (35.6%) underwent escalation protocol. No patients developed scleroderma renal crisis or other severe side effects requiring hospitalization or died during this period. Side effects during standard/extended CYC protocol included: nausea (6/45,13.3%), tiredness and general malaise (5/45,11.1%), diarrhea (4/45,8.9%), urinary tract infections (4/45,8.9%), vomiting (3/45,6.7%), upper respiratory tract infections (2/45,4.4%), leucopenia (2/45,4.4%), hair loss (2/45,4.4%). No patients required CYC/MP pulses therapy withdrawal because of side effects.

Whilst we channeled the treatment strategy following standard CYC, the extended pulses were administered to those with continued deterioration and/or persistent ground glass changes on HRCT chest; whether in the context of an overall improved, stable or worsened response definition. Despite escalating immunosuppression in those

showing a downward trend (n=8), only 1 (12.5%) stabilised with the rest continuing to decline. Both the two patients that worsened following the standard protocol and then received MMF maintenance therapy, stabilized in lung function.

Whilst this retrospective report holds imperfections and caution is needed with interpretation, the take home message from our real-life practice is that patients that deteriorate despite initial pulse CYC (40% in our cohort) are unlikely to benefit from further escalated CYC dose. Alternative targeted agents that have a biological rationale for use in SSc or haematopoietic stem cell transplantation should be increasingly applied in this patient group (7, 8).

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**Figure 1. Treatment strategy in 45 Systemic Sclerosis-interstitial lung disease patients**

Diagram showing treatment strategy, flow of patients, forced vital capacity and diffusion lung capacity of carbon monoxide response to cyclophosphamide and methylprednisolone pulse therapy in 45 SSc-ILD patients at our tertiary centre. SSc: systemic sclerosis; ILD: interstitial lung disease.