Intravenous *versus* oral cyclophosphamide for lung and/or skin fibrosis in systemic sclerosis: an indirect comparison from EUSTAR and randomised controlled trials

C. Bruni[1], D.P. Tashkin[2], V. Steen[3], Y. Allanore[4], O. Distler[5], J. Grotts[6], M. Matucci-Cerinic[1], D.E. Furst[1,7], on behalf of EUSTAR, SLS I and SLS II centres collaborators

[1]*Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Firenze, Italy;*
[2]*Division of Pulmonary Medicine and Critical Care, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA;*
[3]*Rheumatology Division, Department of Medicine, Georgetown University, Washington, DC, USA;*
[4]*Université Paris Descartes, Sorbonne Paris Cité, Service de Rhumatologie A, Hôpital Cochin, Paris, France;*
[5]*Department of Rheumatology, University Hospital Zurich, Switzerland;*
[6]*Department of Medicine Statistics Core, University of California at Los Angeles, CA, USA;*
[7]*Department of Medicine, Division of Rheumatology, University of California Los Angeles, CA, USA.*

Cosimo Bruni, MD
Donald P. Tashkin, MD
Virginia Steen, MD
Yannick Allanore, MD, PhD
Oliver Distler, MD
Jonathan Grotts, MA, BSc
*Marco Matucci-Cerinic, MD, PhD**
*Daniel E. Furst, MD, MBBS**

**Co-equal senior authors.*

Please address correspondence to:
Cosimo Bruni,
Dipartimento di Medicina Clinica e Sperimentale, Divisione di Reumatologia, Università di Firenze,
Via delle Oblate 4,
50141 Firenze, Italy.
E-mail: cosimobruni85@gmail.com

Received on April 11, 2020; accepted in revised form on June 22, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 125): S161-S168.

Key words: systemic sclerosis, cyclophosphamide, oral, intravenous, EUSTAR

Competing interests: see page S-167.

ABSTRACT

Objective. *Both intravenous (IV) and oral (PO) cyclophosphamide (CYC) showed beneficial effects on skin and lung involvement in systemic sclerosis (SSc) in placebo-controlled randomised clinical trials and observational studies. Our goal was to compare the relative efficacy and safety of PO- versus IV-CYC for treating interstitial lung disease and/or skin involvement in SSc.*

Methods. *Patients were derived from the EUSTAR centres and the Scleroderma Lung Studies I and II. A minimum of 6 months of CYC treatment and 12 months follow-up were required. Serious (SAEs) and non-serious adverse events and efficacy data (change in FVC%, DLCO%, mRSS) were analysed at the end of CYC treatment (EoT) and at follow-up (FU). Analysis included descriptive statistics and linear regressions.*

Results. *Differences in ethnicity, previous DMARD exposure, previous and concomitant steroid exposure/dosage were observed in the PO (n=149) and IV (n=153) CYC groups. Adjusted and unadjusted changes in FVC%, DLCO% and mRSS were similar irrespective of mode of administration. PO patients had more leukopenia (p<0.001), haemorrhagic cystitis (p=0.011) and alopecia (p<0.001) at the EoT visit, while the IV group had more SAEs (p=0.025) and need for oxygen supplementation at FU (p=0.049).*

Conclusion. *In a comparison of PO- to IV-CYC for SSc, we found no differences in lung function or cutaneous sclerosis after one year. Some differences in side effects were seen. The results need to be considered as preliminary; however, because we needed to use a combination of RCT and registry data, with some differences in demographics and concomitant medications, well-controlled studies are warranted.*

Introduction

Systemic sclerosis (SSc) is a challenging, complex disease (1-4) in which cyclophosphamide (CYC) is one of the recommended treatments (5), in particular for lung involvement (6, 7). There have been 8 clinical trials examining the use of CYC, oral (PO), intravenous (IV) or mixed, for the treatment of interstitial lung disease (ILD) in SSc (6-13). All trials showed an effect on the lung and 7/8 trials an effect on the skin (6, 8-13). In both randomised control trials (RCTs) Scleroderma Lung Study (SLS) I & II, PO CYC was associated with a significant improvement in percent predicted forced vital capacity (FVC%), a higher rate of FVC% improving patients and a reduction of ILD extent on high resolution computed tomography (HRCT), being statistically significant when compared to placebo (SLS I) (8) and similar to mycophenolate mofetil (MMF) (SLS II) in the context of RCTs (9). These results were partially reproduced in another study when IV-CYC was administered with corticosteroids for 6 months followed by azathioprine for 6 months, compared to placebo for 12 months: in this study FVC% improved in the treatment group, with a trend toward statistical significance *versus* placebo (10). In two other studies, IV-CYC was tested against two different haematopoietic stem cell transplantation (HSCT) protocols, favouring the latter in terms of mortality and event-free survival (11, 12).

Either PO- or IV-CYC were used to treat skin fibrosis in diffuse SSc in the European Observational Cohort Study (ESOS), where the reduction of the

modified Rodnan Skin score (mRSS) with either regimen was not statistically different compared to MMF, methotrexate or non-immunosuppressive treatment (13). In the double-blind, randomised, prospective studies of PO-CYC, reductions in mRSS in the PO-CYC arm were statistically significantly more when compared to placebo in the SLS I trial and not different from MMF in the SLS II trial (14).

In the prospective RCTs of 1 to 2 years duration (8-10), the main differential toxicities of CYC *versus* placebo were haematuria and leukopenia, although adverse effects of CYC in other, uncontrolled studies included infections, amenorrhea, infertility and bladder cancer (15). The efficacy and toxicities of IV- *versus* PO-CYC were not compared in these trials.

The purpose of this study was to compare the relative efficacy and safety of IV- *versus* PO-CYC in SSc patients using data from two RCTs and the European Scleroderma Trial and Research (EUSTAR) registry.

Patients and methods

Patients

Patient inclusions required (1) meeting the ACR 1980 (16) or the ACR/EULAR 2013 classification criteria (17) for SSc; (2) enrolment in the SLS I, SLS II or the EUSTAR database; (3) ≥6 consecutive months of CYC treatment; (4) 12 months of follow-up after the last administration of CYC; (5) demographic and comorbidity data, medications, physical exams, pulmonary function tests, mRSS, measures of renal, haematologic and hepatic status and adverse events, available throughout the study period. IRB approval for EUSTAR registry, SLS I and II studies was obtained from the participating centres at their respective sites and signed informed consent for all patients was obtained, when applicable. Patients were excluded: (1) if they received >15 mg/day prednisone equivalent at baseline (BL); (2) if CYC treatment was <6 months for PO or <138 days (*e.g*. minimum of 6 pulses administered every 4 weeks) for IV.

The following parameters were obtained from the SLS I & II databases and the EUSTAR database. When data were not available from the EUSTAR database, those data were obtained with specific queries to the treating EUSTAR physician:

1. Demographic and clinical history at BL: age (years), gender, disease duration (years) from first non-Raynaud's phenomenon typical for SSc, comorbidities, smoking exposure (previous/current *vs*. never).
2. SSc-related organ involvement: muscle (clinical diagnosis of inflammatory myopathy or myositis using Bohan and Peter's criteria (18)), joint (presence of inflammatory arthritis according to clinical judgment) (19), cardiomyopathy (left ventricle ejection fraction <50% and/or presence of arrhythmias requiring treatment) (20), pulmonary arterial hypertension (defined and diagnosed according to international guidelines (21, 22)), ILD on chest high resolution computed tomography, digital ulcers (as recently defined (23)), gastrointestinal tract GIT involvement (presence of gastroesophageal reflux disease, intestinal malabsorption or small intestine bacterial overgrowth) (24, 25) and skin involvement (mRSS) (26).
3. Medication history: dose, duration and method of application for corticosteroids and CYC, previous or ongoing exposure to DMARDs (MMF, azathioprine, methotrexate or other immunosuppressants) (2).
4. Laboratory tests: FVC (% predicted), diffusing capacity for carbon monoxide (DLCO, % predicted), haemoglobin, white blood cell count (WBC), platelet count (performed during treatment and up to 30 days after last dose administration).
5. Adverse events: defined as any untoward medical occurrence during the study period. Serious adverse events included the following: death, adverse event requiring hospitalisation, adverse event associated with prolongation of hospitalisation, congenital effects (not applicable here) or adverse events resulting in persistent or significant disability/incapacity. Serious infectious events were those requiring IV antibiotics or hospitalisation.

Study design

Data on patients on PO-CYC were mostly derived from two double-blind RCTs (8, 9). In one of the trials, PO-CYC was compared to placebo for 12 months with 12 months follow-up (8). The other trial compared PO-CYC for one year followed by placebo CYC to MMF for 2 years (9). In both trials, the target CYC dosage was 2 mg per kilogram per day as tolerated. PO-CYC-treated patients' data were also derived from the EUSTAR database.

All data for the IV-CYC group were available from the EUSTAR database from 16 centres following patients using standard case report forms.

BL was the date of first CYC use, with assessment at end of treatment (EoT) and after 12 months (±3 months) off the CYC (FU). We compared efficacy between the PO and IV groups based on the change in FVC%, DLCO%, mRSS, rate of ILD "progression" (defined as decreased relative FVC% ≥10% or decreased relative FVC% between 5–9% plus DLCO% ≥15% compared to BL) and rate of mRSS responders (improved ≥5 units or 20% decline from BL). Moreover, we tested the difference in rate of adverse events and serious adverse events between the two groups. All the analyses were made at CYC EoT (*versus* BL) and at FU (*versus* EoT) visits.

Analysis

Data were summarised using median with interquartile range or mean plus standard deviation for continuous variables and number in group with percent of group for discrete variables. Univariate hypothesis testing was done using Wilcoxon Rank Sum test for continuous variables and Fisher's exact test for discrete variables. Change in the biomarkers over time was modelled using univariate linear regression with clinical characteristics as predictors: the dependent variables were change in FVC%, DLCO% or mRSS and appendix 1 lists the independent variables used in the regressions as covariates. Logistic regression was used to model the risk for categorical efficacy endpoints (progression, responders) and for safety endpoints, including both total

and specific adverse events, still taking Appendix 1 variables as covariates. Regression models are summarised as the coefficients with 95% confidence intervals and *p*-values from the Z-test. All hypothesis tests were two-sided with a *p*-value below 0.05 indicating statistical significance. Analysis was performed using the R Statistical Computing Environment (R Core Team; Vienna, Austria) and SAS 9.3 (SAS Institute Inc; Cary, NC, USA).

Results

Among 346 patients evaluated, 24 were excluded because CYC use was <6 months and 20 were using >15 mg prednisone or equivalent steroid dose at BL, resulting in 302 eligible patients. There were 149 patients given PO-CYC (31 of them from EUSTAR) and 153 receiving IV-CYC (all from EUSTAR, Fig. 1).

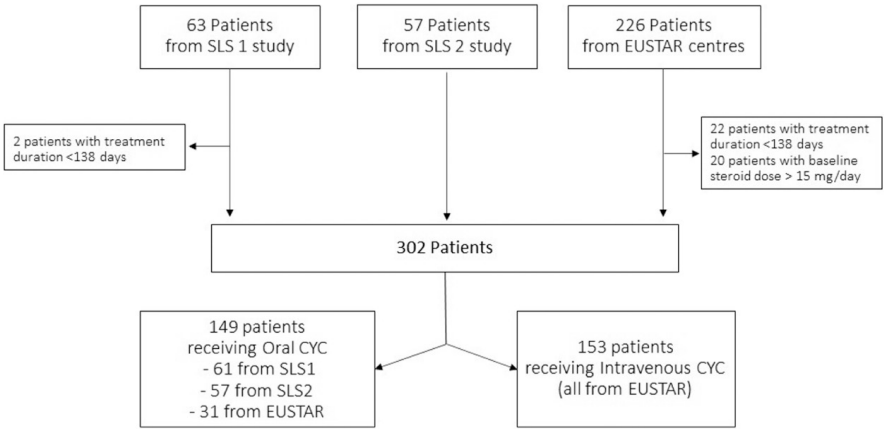

Fig. 1. Recruitment from Scleroderma Lung Study I, Scleroderma Lung Study II and EUSTAR centres.

Baseline characteristics of the patients are presented in Table I. There were some differences between the 2 groups. The PO-CYC patients were mostly derived from North America and were younger (mean age PO 48 *vs*. IV 52 years, *p*=0.003). There were more African-Americans among the PO-CYC group (15.4% *vs*. 0%, *p*<0.001), whose prognosis is thought to be worse than Caucasians (27). Likewise, there was more smoking by history (PO 14.6% vs. IV 6.6%, *p*=0.035) and concomitant hypertension in the PO-CYC than the IV-CYC groups (PO 26.3% vs. IV 16.3%, *p*=0.035). Baseline FVC% predicted was borderline worse (PO 69% *vs*. IV 83%, *p*<0.001) and DLCO% predicted was numerically worse (PO 51% predicted *vs*. IV 56% predicted, *p*=0.022). Overall, the patients given PO-CYC appeared to have slightly/borderline more severe disease and with more co-morbidities than the IV-CYC group. The IV-CYC group used more corticosteroids at the beginning of treatment (PO 34.6% *vs*. IV 72.5%, *p*<0.001). IV-CYC patients used a median of 5 (0–10) milligrams prednisone equivalent per day *versus* 0 (0–5) milligrams per day for PO patients (*p*<0.001). The IV-CYC group also used more medications: previous DMARDs exposure was significantly higher in the IV group (IV 41.3% *vs*. PO 23.5%, *p*=0.001). None of the other examined BL variables were statistically significantly different between the two groups.

The median daily dose of PO-CYC was 106 (93–135) mg, median monthly dose was 3200 (2800–4100) mg, median treatment duration was 12 (12-12) months and median total dose of PO-CYC given was 39.5 (5.7–67.1) g. In comparison, the median daily dose for IV-CYC was 33 (23–40) mg, median monthly dose 1000 (700-–200) mg and median treatment duration was 11 (6-18) months, resulting in a median total dose of 9.2 (5.6–13.6) g. The IV regimens were widely different among centres, ranging from high dose/short duration (*e.g*. 3000 mg monthly IV-CYC for 6 months) to low dose/long term (*e.g*. 500 mg monthly IV-CYC for 42 months); in a few cases, CYC was used monthly for the first 6 months, then continued as a maintenance treatment every 3 months. Broadly, IV-CYC regimens were distributed into within 6 months, 7–12 months and >12 months duration (26.2% *vs*. 39.3% *vs*. 34.5%), with median dosages still around 1000 mg monthly in the three groups (*p*=0.208). This resulted in the two routes of administration having significantly different daily (*p*=0.001), monthly (*p*=0.001) and cumulative (*p*<0.001) doses, as well as treatment duration (*p*=0.035), with more corticosteroid exposure in the IV CYC group.

The results of the efficacy and safety analyses should take into account a similar follow up duration after the end of treatment (PO 12 (12–12) *vs*. IV 12 (11–13) months, *p*=NS). At EoT visits, patients in the IV group were given more supplemental oral corticosteroids (72.5% IV *vs*. 37.2% PO, *p*<0.001), at a higher daily median dose (median 5 (2.25–10) *vs*. 0 (0–5) mg/day, *p*<0.001) than the PO-CYC group. Similarly, the IV group received more additional DMARDs as a maintenance treatment at the end of CYC administration (IV 29.4% *vs*. PO 8.1%, *p*<0.001) (28).

Efficacy

There were no efficacy differences between PO- and IV-CYC for the predefined endpoints (change in FVC%, DLCO%, mRSS%; rate of ILD progressors and mRSS responders) (Table II). Specifically, there were no differences in changes in FVC% or DLCO%, either from BL to EoT or from EoT to end of FU visits. Mean changes and differences were small and not clinically meaningful, ranging from 0 to 4% (-9 to +6% predicted) predicted for FVC% and from 0 to 3% (-5 to +1% predicted) for DLCO%. In terms of ILD progression, there was no statistically significant difference between groups at any time-point (Fig. 2, top).

Mean differences for the mRSS ranged from -2 to 0 (-7 to +7) and were neither statistically nor clinically meaningfully different (Table II); this was also true for mRSS responder rates (Fig. 2, bottom).

When adjusted for the covariates listed in Appendix 1 (among which African-American race, CYC cumulative dosage and treatment duration plus baseline: FVC%, DLCO%, mRSS, DMARDs

Table I. Description of oral and intravenous groups at baseline.

	PO CYC (149 pts)	IV CYC (153 pts)
Male gender, n (%)	28 (18,8)	29 (19.0)
Age - years, mean (SD)	48 (11)	52 (12)
Disease duration - years, mean (SD)	4 (4)	4 (4)
Caucasian race, n (%)	104 (69.8)	146 (95.4)
African-American race, n (%)	23 (15.4)	0 (0)
Diffuse skin subset, n (%)	89 (59.7)	90 (59.2)
mRSS, median (IQR)	13 (7-20)	12 (6-20)
ATA positive, n (%)	60 (50.8)	96 (59.2)
ACA positive, n (%)	4 (3.4)	9 (6,0)
ARA positive, n (%)	14 (12)	9 (8.7)
Previous steroid exposure, n (%)	42 (28.4)	70 (46.7)
Previous DMARD exposure, n (%)	35 (23.5)	62 (41.3)
Steroid treatment at baseline, n (%)	51 (34.6)	111 (72.5)
Steroid dosage at baseline (mg), median (IQR)	0 (0-5)	5 (0-10)
Smoking history, n (%)	21 (14.6)	10 (6.6)
Joint involvement, n (%)	39 (26.4)	51 (33.3)
PAH, n (%)	0 (0)	5 (3.8)
Muscle involvement, n (%)	14 (9.5)	22 (14.4)
Cardiac involvement, n (%)	8 (5.4)	15 (9.8)
Gastro-oesophageal involvement, n (%)	114 (76.5)	122 (79.7)
Intestinal malabsorption, n (%)	9 (6.0)	13 (8.6)
Bacterial overgrowth, n (%)	12 (8.1)	12 (7.9)
ILD prevalence, n (%)	125 (87.4)	143 (93.5)
FVC%, median (IQR)	69 (60-75)	83 (68-96)
Dlco%, median (IQR)	51 (40-63)	56 (42-71)
History/presence of digital ulcers, n (%)	40 (26.8)	64 (42.1)
History/presence of arterial hypertension, n (%)	40 (26.8)	25 (16.3)

CYC: cyclophosphamide; DMARD: disease modifying ant rheumatic drug; Eot: end of treatment visit; FVC: forced vital capacity; DLco: lung diffusion of carbon oxide; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; mRSS: modified Rodnan skin score; ATA: anti topoisomerase I antibodies; ACA: anti-centromere antibodies; ARA: anti RNA polymerase III antibodies; IQR: interquartile range, mg: milligrams; IV: intravenous; PO: oral.

and corticosteroids were included), no statistically significant difference was found between the two modes of administration. Similarly, no difference in the efficacy endpoints at both timepoints was detected when a 15 g cut-off was arbitrarily selected as high CYC dosage, both when considering high *versus* low dosage or testing the interaction between high/low dosage and IV/PO administration (data not shown).

Safety

Table III outlines the overall AEs, SAEs, serious infectious events or deaths. During the treatment, PO-CYC showed more general adverse events (51.0% *vs*. 26.7%, $p<0.001$), while during follow-up the IV-CYC group had more SAEs (19.3% *vs*. 9.4%, $p=0.025$) but no other differences emerged.

Table IV outlines the specific AEs, both at EoT and during FU. The differences noted during the period from BL to EoT included leukopenia (Total WBC<2500/mm^3; 22.1% PO *vs*. 1.3% IV; $p<0.001$), haemorrhagic cystitis (5.5% *vs*. 0.0%, $p=0.011$) and alopecia (19.5% *vs*. 1.3%, $p<0.001$), where PO-CYC was associated with more events. This may have been because most PO-CYC was in clinical trials, where follow-up was more frequent, more intense and probably more accurate than in the observational EUSTAR database, from which all IV-CYC patients were derived. In contrast, during follow-up, there were more SAEs in the IV group (IV 19.3% *vs*. PO 9.4%, $p=0.025$). Surprisingly, during follow-up, more IV-CYC patients required oxygen supplementation (14 *vs*. 5%, $p=0.016$), despite the fact that the PO-CYC group had numerically worse lung function at BL. When the safety analysis accounted for the covariates listed in Appendix 1 (including African-American race, DMARDs co-treatments, corticosteroids dose, CYC cumulative dosage and treatment duration among them), there was less leukopenia among the IV-CYC treated group during the treatment phase (OR 0.110, 95% CI 0.021–0.576, $p=0.009$), while no differences were seen for total AE and SAE counts or other specific AEs.

Discussion

The present study is the first to compare the efficacy of IV- *versus* PO-CYC treatment of SSc during one year plus one year of follow-up after treatment discontinuation, although done indirectly, showing no major differences in either efficacy (change in FVC%, DLCO% and mRSS) or most side effects. Leukopenia, haemorrhagic cysti-

Table II. Efficacy and safety profile of oral and intravenous CYC at end of treatment and end of follow-up evaluations.

	EoT *vs*. BL			FU *vs*. EoT		
	PO CYC (149 pts)	IV CYC (153 pts)	PO *vs*. IV *p*	PO CYC (149 pts)	IV CYC (153 pts)	PO *vs*. IV *p*
Change in mRSS	-3.0 ± 5.8	-1.9 ± 5.9	0.128	-1.4 ± 6.4	-0.8 ± 5.0	0.393
Change in %FVC	+0.1 ± 8.4	-0.6 ± 13.3	0.629	-0.5 ± 9.0	-1.1 ± 10.3	0.655
Change in %Dlco	-3.9 ± 13.5	-4.3 ± 13.0	0.794	-0.6 ± 11.0	-1.9 ± 11.3	0.369
ILD progressors rate, n (%)	17 (11.4)	28 (17.8)	0.146	22 (14.8)	18 (11.5)	0.402
mRSS responder rate, n (%)	44 (30.3)	45 (29)	0.897	29 (19.7)	21 (13.6)	0.320

BL: baseline visit; CYC: cyclophosphamide, DLco: lung diffusion of carbon oxide; EoT: end of treatment visit; FVC: forced vital capacity; FU: follow-up visit; IV: intravenous; mRSS: modified Rodnan skin score; PO: oral.

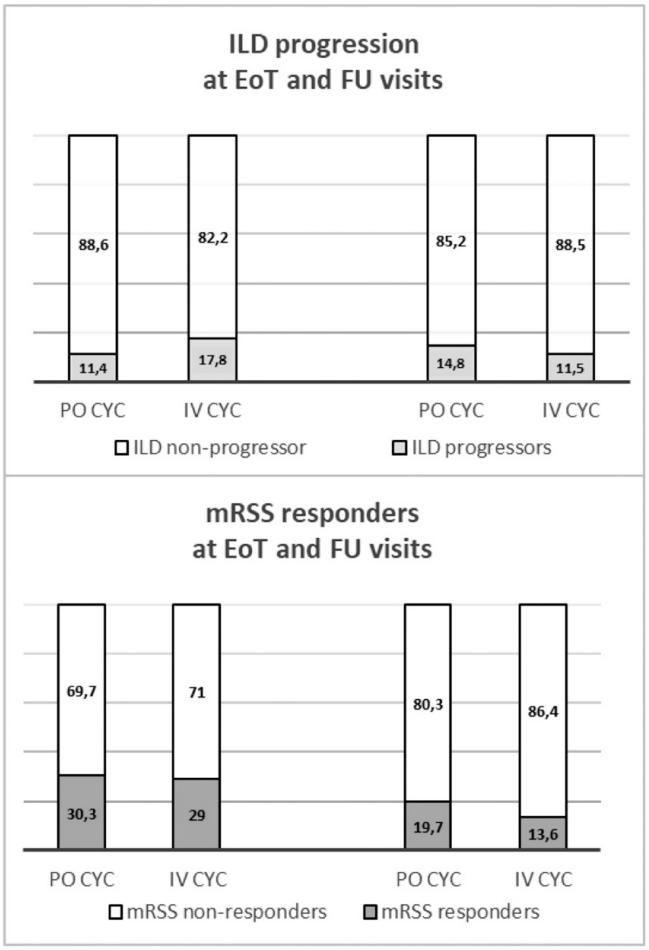

Fig. 2. Interstitial lung disease (ILD) progressors* (top) and modified Rodnan's skin score (mRSS) responders§ (bottom) at end of treatment visit (left) and end of follow-up visit (right).
IV: intravenous;
PO: oral.
*Progression defined as relative decrease in FVC% ≥10% or in FVC% between 5-9% plus DLCO% ≥15%.
§ Response defined as ≥5 units improvement or >20% improvement in mRSS.

tis and alopecia occurred significantly more frequently with PO-CYC treatment during the first year of treatment, while SAE were more frequent during the follow-up year for IV-CYC. In contrast to frequencies, the only significant difference in terms of risk was seen for leukopenia during PO treatment compared to the IV-route.

The literature reports three controlled studies of IV-CYC (10-12), one study with an analysis of a group using mixed IV- and PO-CYC (13) and three studies using PO-CYC (8, 9, 29). The three controlled studies of IV-CYC included 136 patients treated over 6-12 months and indicated favourable responses in skin, FVC%, Health Assessment Questionnaire Disability Index and with the expected toxicities (10-12), although the authors did not compare their results to PO-CYC. In the study of the mixed treatment with IV- and PO-CYC, it was not possible to separate or compare IV- *versus* PO-CYC (13). The 3 studies using PO-CYC are the two we used in our comparison (8, 9) plus a single-centre experience (29). The single-centre experience was used in this study after asking the physician for follow-up, outside the study per se.

In our analysis, we compared patients derived from significantly different populations. Although the populations were generally comparable, the patients in the controlled trials included African-American, smokers and their pulmonary function tests were numerically worse at BL than those of the patients in the EUSTAR database. Moreover, the cumulative dosage and treatment duration were significantly different among the two groups. Thus, one might have expected them to do more poorly than those in the EUSTAR database.

Nevertheless, no differences were found in response to our original question. FVC%, DLCO% and mRSS responded equally during and for one year after treatment. Similar stability was observed for both groups in the lungs (neither group changed more than the minimally important clinical cut-point of 3% predicted for FVC or >15% predicted change in DLCO) (30). Likewise, the mRSS remained stable and equal for both groups. Changes in all efficacy endpoints were still not different when also adjusted for Afro-American race, cumulative dosage, DMARD co-treatment and steroid dosages. Moreover, after dividing the patient groups into "lower dose" (IV-CYC or PO-CYC <15 g total dose) *versus* "higher dose" (IV-CYC or PO-CYC ≥15 g total dose), we still found no dose effect. These results are to be seen in the light of the small number of PO patients receiving <15 g and of IV patients receiving ≥15g of total CYC dosage (2% and 11% respectively), exemplifying some of the differences in the populations. We feel our data are

Table III. Overall safety profile of oral and intravenous CYC at end of treatment and end of follow-up evaluations.

	EoT *vs.* BL			FU *vs.* EoT		
	PO CYC (149 pts)	IV CYC (153 pts)	PO *vs.* IV *p*	PO CYC (149 pts)	IV CYC (153 pts)	PO *vs.* IV *p*
Any adverse events, n (%)	76 (51)	41 (26.7)	**<0.001**	26 (17.4)	32 (20.9)	0.536
Serious adverse events, n (%)	21 (14.5)	21 (14)	>0.999	13 (9.4)	29 (19.3)	**0.025**
Death, n (%)	0 (0)	0 (0)	N.A.	5 (3.5)	7 (4.7)	0.834
Serious infections, n (%)	5 (3.4)	7 (4.6)	0.804	3 (2)	9 (5.9)	0.154

BL: baseline visit; CYC: cyclophosphamide; EoT: end of treatment visit; FU: follow-up visit; IV: intravenous; PO: oral.

Table IV. Specific adverse events of oral and intravenous CYC at end of treatment and end of follow-up evaluations.

	EoT *vs*. BL			FU *vs*. EoT		
	PO CYC (149 pts)	IV CYC (153 pts)	PO *vs*. IV *p*	PO CYC (149 pts)	IV CYC (153 pts)	PO *vs*. IV *p*
Platelet <100000/ul, n (%)	5 (3.4)	0 (0)	0.065	1 (0.7)	0 (0)	0.966
Haemoglobin <8,0 g/dl, n (%)	2 (1.4)	1 (0.7)	0.972	1 (0.7)	1 (0.7)	>0.999
Leukocytes <2500/mm^3, n (%)	32 (22.1)	2 (1.3)	**<0.001**	0 (0)	2 (1.3)	0.515
Gastrointestinal bleeding, n (%)	4 (2.8)	2 (1.3)	0.649	2 (1.5)	1 (0.7)	0.936
Haemorrhagic cystitis, n (%)	8 (5.5)	0 (0)	**0.011**	1 (0.7)	0 (0)	0.989
Cancer new diagnosis, n (%)	2 (1.4)	2 (1.3)	>0.999	6 (4.4)	4 (2.7)	0.647
Oxygen supplementation needed, n (%)	4 (2.7)	12 (8)	0.079	3 (2)	11 (7,2)	**0.049**
Total parenteral nutrition, n (%)	2 (1.4)	0 (0)	0.469	3 (2)	1 (0.7)	0.566
Cardiomyopathy new diagnosis, n (%)	8 (5.4)	15 (9,8)	0.194	3 (2)	5 (3,3)	0.084
Amenorrhoea, n (%)	6 (4)	6 (3.9)	>0.999	0 (0)	0 (0)	N.A.
Alopecia, n (%)	29 (19.5)	2 (1.3)	**<0.001**	1 (0.7)	0 (0)	0.488

BL: baseline visit; CYC: cyclophosphamide; EoT: end of treatment visit; FU: follow-up visit; IV: intravenous; PO: oral.

not definitive and that a well-controlled trial directly comparing these two dosage forms is needed (31).

Adverse events were also generally comparable despite very different exposures to CYC in terms of both duration and cumulative dosage, in particular for the PO group. During treatment, leukopenia, alopecia and haemorrhagic cystitis were observed more frequently in patients using PO-CYC. Part of this difference may have been the result of the different nature of the studies. In the double blind RCTs, patients were more frequently and intensively followed, so more documented AEs might be expected. Incidentally, the recommended use of MESNA and IV hydration after IV-CYC might explain the lower AE rate of haemorrhagic cystitis in this group. In fact, when adjusting for covariates including concomitant DMARDs and steroids, the PO route was a risk factor only for the development of leukopenia during treatment administration, while no difference was seen regarding the development of "any adverse event" or other specific adverse event at both timepoints.

The study included 1 year of follow-up. However, 1 year of follow-up does not allow the examination of delayed side effects such as bladder cancer or other malignancies, which may not appear for years after cyclophosphamide treatment (32). Likewise, no specific attempt was made to verify infertility, although there were no differences in amenorrhoea (33).

Just as in the case of prednisone, where PO and high dose IV methylprednisolone pulse therapies are used, an examination of the use of daily PO- or monthly IV-CYC regimens leads to the consideration of high dose pulse CYC as a potential treatment regimen. High dose pulse CYC therapy (with antithymocyte globulin (ATG) ± radiation) has been used in haematopoietic stem cell transplantation (HSCT) (11, 12). In 2 HSCT studies, high dose pulsed CYC (120–200 mg per kilogram) + ATG (± radiation) was compared to the 1.0-1.4 g monthly IV-CYC control regimen for 1 year. This latter IV-CYC regimen does not differ greatly from that used in our study, where the median monthly CYC dose was 1.0 gram. The HSCT studies showed that the high dose pulsed CYC regimen (120–200 mg/kg dose once) when combined with ATG ± radiation was superior to the control IV-CYC regimen (1.0–1.4 gm monthly for 12 months) (11, 12). Assuming toxicities can be managed (34), this raises the issue of whether single high dose pulsed CYC regimens without the additional ATG ± radiation might be a logical or even preferred approach to repeated "routine" monthly pulsed CYC (35) (Supplementary Table S1).

Our study had some limitations, however. There were differences between PO- and IV-CYC in terms of patient selection, timelines, data collection and analysis, mostly based on differences in the study designs. The patients were different (although generally similar) and came from two different populations, one from prospective well-controlled clinical trials and the other from an observational cohort study. Patients from SLS studies were all treated for ILD and enrolled according to specific inclusion/exclusion criteria, while patients from the EUSTAR centres were receiving CYC on a clinical basis for either lung or skin or other organ involvements. If one were to consider propensity matching, the number of patients would have been so greatly reduced (as expected) that analysis would have been unreliable, thus making this analytic approach untenable in our study. We tried to balance this with an adjusted analysis taking different demographic, disease specific and treatment specific co-variates into account, replicating our un-adjusted results. Follow-up after treatment was for one year. As the maximum benefit of PO-CYC compared to placebo was seen at 18 months from baseline in the SLS studies, that time point could have been selected as follow-up endpoint; however, given that EUSTAR centres usually collected data annually, a follow-up duration of 18 months would have significantly reduced patient numbers. Further, given potential delayed CYC toxicities (in particular regarding cancerogenic potential), a longer duration of follow-up would be appropriate. Also, the definitions of adverse events were less well specified in the EUSTAR database, where a large number of physicians participated and where the definition of adverse events was the physicians' own estimation. This might have made the AE comparisons less exact,

although concentrating on SAEs and serious infections ameliorated this concern somewhat. Finally including patient reported outcome measures could have confirmed similar effects also from a patient's perspective (36, 37).

Despite these limitations, our study significantly improves our understanding of differences (or lack thereof) between IV- and PO-CYC in the treatment of SSc. The data also suggest that a prospective study is necessary.

Conclusion

In a comparison of PO- to IV-CYC for SSc, we found no differences in lung function or cutaneous sclerosis after one year of treatment. Some differences in side effects were seen. The results need to be considered as preliminary and well-controlled studies are both needed and warranted.

Take home messages

- Direct comparison of oral and intravenous cyclophosphamide has never been analysed in randomised clinical trials.
- In our analysis of patients receiving oral and intravenous cyclophosphamide, we observed similar efficacy outcomes for skin and lung involvement during 12 months treatment plus 12 months follow-up.
- Oral and intravenous cyclophosphamide show a slightly different safety profile during 12 months treatment plus 12 months follow-up.
- The results need to be considered as preliminary, however, because we needed to use a combination of RCT and registry data, with some attendant differences in demographics and concomitant medications.

Acknowledgement

We thank Lorenzo Tofani for his valuable support during the statistical revision of the manuscript.

Competing interests

D.P. Tashkin has received support from Genentech.

V. Steen has received consultancy and advisory board funds from Boehringer Ingelheim.

Y. Allanore has received honoraria from Boehringer, Roche, Sanofi, Bayer, Inventiva, and grants from Sanofi and Inventiva.

O. Distler has had consultancy relationship and/or has received research funding from AbbVie, Actelion, Acceleron Pharma, Amgen, AnaMar, Baecon Discovery, Blade Therapeutics, Bayer, Boehringer Ingelheim, Catenion, Competitive Corpus, Drug Development International Ltd, CSL Behring, ChemomAb, Ergonex, Galapagos NV, Glenmark Pharmaceuticals, GSK, Horizon (Curzion) Pharmaceuticals, Inventiva, Italfarmaco, iQone, iQvia, Kymera Therapeutics, Lilly, Medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Novartis, Pfizer, Roche, Sanofi, Target Bio Science and UCB in the area of potential treatments of scleroderma and its complications. Grants (2 years) from Actelion, Bayer, Boehringer Ingelheim, Kymera Therapeutics, Mitsubishi Tanabe Pharma. Patent issued: mir-29 for the treatment of systemic sclerosis (US8247389, EP2331143).

D. Furst has received grant research/support from Actelion, Amgen, BMS, Corbus, Galapagos, GSK, NIH, Novartis, Pfizer, Sanofi, Roche/Genentech, consultancy fees from Actelion, Amgen, BMS, Corbus, Galapagos, Novartis, Pfizer, and speaker's bureau for CME only.

The other co-authors have declared no competing interests.

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