David against Goliath: may we target and defeat interstitial lung disease in systemic sclerosis?

I. Miniati, M.L. Conforti, S. Guiducci, M. Matucci Cerinic

Dept of Medicine, Division of Rheumatology, DenoThe center, University of Florence, Italy.

Irene Miniati, MD, Rheumatologist; Maria Letizia Conforti, MD, Rheumatologist; Serena Guiducci, MD, Fellow in Rheumatology; Marco Matucci Cerinic, MD, Professor of Rheumatology.

Please address correspondence to: Irene Miniati, Div. Rheumatology, Villa Monna Tessa, Viale Pieraccini 18 50139 Firenze, Italy.
E-mail: irene_miniati@hotmail.com

Received on May 2, 2007; accepted in revised form on May 4, 2007.

Key words: Cyclophosphamide, mycophenolate mofetil, interstitial lung disease, systemic sclerosis, scleroderma.

In systemic sclerosis (SSc), alveolitis is an early event that may lead to interstitial lung disease (ILD), which is the main cause of morbidity and mortality (1). It has been demonstrated that a higher percentage of lymphocytes and neutrophils at broncho-alveolar lavage (BAL) predict those patients more likely to respond to immunesuppressive treatment (2). For this reason, alveolitis should be detected early and treated promptly to block the evolution to ILD. However, the beneficial effect of immunesuppressive drugs for the treatment of ILD in SSc is still under scrutiny.

Following the encouraging results obtained in idiopathic pulmonary fibrosis, cyclophosphamide (CYC) has been proposed, in non-randomised trials, as a novel treatment for lung involvement in SSc (3, 4). CYC favoured stabilization or an improvement of lung function tests, HRCT score and functional status suggesting a beneficial effect in early diffuse SSc.

CYC is a DNA-alkylating agent working through the covalent binding of highly reactive alkyl groups with nucleophilic groups of nucleic acids. Metabolic activation generates bifunctional alkylating nitrogen mustards of CYC reacting with nitrogen-7 atom of purine bases in DNA (5). CYC is first hydroxylated by hepatic microsomal mixed-function oxidases (CYP enzymes) to tautomeric intermediates (4-hydroxycyclophosphamide and aldophosphamide), which may be the efficient circulating metabolites. CYC pharmacokinetics may vary significantly among patients, both in adults and children: this likely reflects differences in the expression of individual CYP enzymes. Variation may also result from concomitant drug therapy with inducing (phenobarbital, phenytoin, dexamethasone), or inhibiting (morphine, progesterone, systemic antifungals) CYP enzymes (6).

The optimal CYC dosage and length of treatment for ILD in SSc have not yet been determined. In non-randomised trials, deterioration after treatment withdrawal occurs in most patients treated for 6 months with i.v. CYC (7) while a further improvement may, instead, be observed in those patients treated for 12 months (8, 9). A recent prospective observational study by Airò has evaluated the effect of i.v. CYC for 18 months, using a cumulative dose of 12.75 g. Out of fifteen patients enrolled, 2 withdrew because of disease progression. The results indicate a significant improvement of mean FVC ($p = 0.05$), a decline of DLCO and an outcome independent of SSc subset and stage (10). These data are not in agreement with those obtained, in a retrospective study, on 40 SSc patients with fibrosing alveolitis, treated with i.v. CYC pulses for 6 and 15 months, respectively: only in the group treated for 15 months, a greater increase of FVC was observed. This prompted the authors to suggest that longer treatment with i.v. CYC might achieve a better overall result on lung function than a shorter course (11).

Recently, the effects of pulses and oral CYC on SSc-ILD have been reported. In a double-blinded randomized trial, 45 SSc patients were treated for 6 months with monthly i.v. CYC pulses (600 mg/m^2) and 20 mg oral prednisolone on alternate days, followed by azathioprine (AZA) (2.5 mg/kg/day) as maintenance therapy for 6 months. A favourable trend for FVC of 4.19% was detected without any improvement of DLCO and other secondary outcome measures (HRCT, dyspnea score). This suggested that CYC is moderately helpful in stabilizing lung function, as corroborated by effect size (ES): the improvement of FVC was mild (ES = 0.35) and none for DLCO and TLC (ES -0.01 and 0.06, respectively) (12). In a blinded RCT vs placebo, oral CYC (2mg/kg), over a 12-month period, obtained a significant increase of FVC and TLC ($p < 0.03$ and 0.026 , respectively) but with a mild ES (0.14 and 0.19, respectively) but DLCO remained unchanged. The authors concluded that CYC had a modest beneficial effect on lung function, dyspnea, skin thickening and quality of life (13).

An unblinded randomised controlled trial (RCT), with oral CYC for 12 months compared to AZA, demonstrated that FVC deteriorated in the AZA group, achieving a final picture of ES

= 7.38 at 18 months. This demonstrates that CYC may stabilise lung fibrosis significantly better than AZA (14).

Mycophenolate mofetil (MMF), used for the prevention of organ transplant rejection and graft versus host disease, has recently been introduced for the treatment of autoimmune diseases.

MMF is derived from the fungus Penicillium stoloniferum and metabolised in the liver to the active moiety mycophenolic acid. It inhibits inosine monophosphate dehydrogenase, the enzyme which controls the rate of synthesis of guanine monophosphate in the de novo pathway of purine synthesis used in the proliferation of B and T lymphocytes (15).

The effect of MMF in SSc has been reported in few retrospective and prospective uncontrolled studies. Recently, a prospective study on 16 early SSc patients treated with MMF, i.v. methylprednisolone pulses and low-dose glucocorticoids (16) has shown that ground-glass and consolidation areas were less prominent after 1 year of treatment: however, statistical significance was not reached with a moderate effect of the treatment confirmed by ES (ES = 0.52 and 0.58, respectively). VC improved significantly only as an absolute value but not as a percentage predicted, while a significant improvement of FEV1 and DLCO was indeed obtained (p = 0.0009 for both parameters) with a favourable ES (ES = 0.93 and 1.18, respectively). This may suggest a potential capacity of MMF to modify functional parameters in SSc-ILD.

A retrospective controlled study on a larger cohort of patients, compared the efficacy and safety of MMF with different immunemodulators: out of 109 patients, 46 were on MMF (2 g daily) and 63 on CYC (47.6%), anti-thymocyte globulins (31.7%), AZA (39.7%), D-penicillamine (30.2%), α-interferon (12.7%) and methotrexate (11.1%) (17). Patients on MMF developed significantly less ILD with a better survival rate at 5 years compared to controls (95.4% versus 85.7%). Two other prospective studies on MMF provide evidence for a stabilisation of lung function in all 13 patients enrolled (18), for a significant improvement of DLCO and a reduction of ground glass opacities in 5 early ILD patients (19).

Table. I.

Outcome measures	Intravenous		Oral	
	Hoyles *et al.*	Airò *et al.*	Tashkin *et al.*	Nadashkevich *et al.*
Type of study	Randomised placebo controlled	Open prospective	Randomised placebo controlled	Randomised unblinded (vs AZA)
FVC	No change	Improved (p = 0.05)	Improved (p < 0.03)	No change
DLCO	No change	Stable/tend to decline	No change	No change
HRCT	Only trend toward/ to improvement	-	-	-
Duration	6 months (followed by AZA for 6 months)	18 months	12 months	18 months (2g/Kg for 12 mo. then 1g/Kg for 6 mo.)
Adverse events	3 withdrawals on CYC Intolerable nausea, abnormal liver function tests on AZA	1 *Herpes zoster* 2 withdrawals for disease progression	20 withdrawals on CYC, 13 on pl. Leucopenia, anemia, hematuria, pneumonia, malignancies (3)	NO withdrawals Hair loss, nausea, dyspepsia,dyspepsia, leucopenia

An overall view of these data on MMF for SSc ILD may suggest a beneficial effect as it may stabilise lung function, have a trend towards radiological improvement of ground-glass and achieve a better survival rate when compared to other immunemodulators in a retrospective analysis.

The lower toxicity profile of MMF has suggested, as in lupus nephritis (20), its use as an alternative to CYC also in SSc. The most common side effects of MMF are opportunistic infections (in particular in the first months of treatment), diarrhea, nausea, vomiting and leukopenia. MMF is considered as a safe treatment according to the data that emerged from the first studies (18, 19). However, in a larger cohort of patients, GI tract disturbances and infections were reported in 12% with a withdrawal rate of 8% (17). There are also concerns about CYC toxicity, which in short term studies induces leukopenia and infections while in long-term use may provoke mainly infertility, cumulative bone marrow toxicity and carcinogenesis.

Considering the short term adverse events, both randomized controlled trials (RCT) published in this issue show a good safety profile as only few withdrawals were reported, and also both reached a low number needed to harm of 11.

In conclusion, the present studies and the body of literature indicate that both CYC and MMF have a mild beneficial effect on SSc-ILD. For CYC, this may be true for a cohort of patients with advanced ILD, but we know now that CYC should be used as a treatment of early lung involvement, in order to avoid progression to ILD and fibrosis. It seems encouraging that MMF seems to determine an improvement of ILD in early SSc. However, RCTs are needed to evaluate the efficacy and the safety of MMF.

To sum up, the fight against the giant SSc-ILD is still in a very premature phase in which David still has not found the right stone and cannot lift a strong arm that will target Goliath in a final fight for victory.

References

1. STEEN VD, CONTE C, OWENS GR, MEDSGER TA JR: Severe restrictive lung disease in systemic sclerosis. *Arthritis Rheum* 1994; 37: 1283-9.
2. WHITE B, MOORE WC, WIGLEY FM: Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis *Ann Intern Med* 2000; 132: 947-54.
3. WHITE B, MOORE WC, WIGLEY FM, XIAO

HQ, WISE RA: Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. *Ann Intern Med* 2000; 132: 947-54.
4. GIACOMELLI R. ,VALENTINI G, SALSANO F *et al*.: Cyclophosphamide pulse regimen in the treatment of alveolitis in systemic sclerosis. *J Rheumatol* 2002; 29: 731-6.
5. JING ZHANG, QUAN TIAN, SHU-FENG ZHOU: Clinical Pharmacology of Cyclophosphamide and Ifosfamide *Current Drug Therapy* 2006; 1: 55-84.
6. BODDY AV, YULE SM: Metabolism and pharmacokinetics of oxazaphosphorines. *Clin Pharmacokinet* 2000; 38: 291-304.
7. GRIFFITHS B, MILES S, MOSS H, ROBERTSON R, VEALE D, EMERY P: Systemic sclerosis and interstitial lung disease: a pilot study using pulse intravenous methylprednisolone and cyclophosphamide to assess the effect on high resolution computed tomography scan and lung function. *J Rheumatol* 2002; 29: 2371-8.
8. DAVAS EM, PEPPAS C, MARAGOU M, ALVANOU E, HONDROS D, DANTIS PC: Intravenous cyclophosphamide pulse therapy for the treatment of lung disease associated with scleroderma. *Clin Rheumatol* 1999; 18: 455-61.
9. PAKAS I, IOANNIDIS JPA, MALAGARI K, SKOPOULI FN, MOUTSOUPOULOS HM, VLACHOYIANNOPOULOS PG: Cyclophosphamide with low or high dose prednisolone for systemic sclerosis lung disease. *J Rheumatol* 2002; 29: 298-304.
10. AIRÒ P, DANIELI E, ROSSI M *et al*.: Intravenous Cyclophosphamide for interstitial lung disease associated to Systemic Sclerosis: results with an 18-month long protocol including a maintenance phase. *Clin Exp Rheum* 2007; 25: 293-6.
11. DASS S, FERNANDES C, GRIFFITHS B, EMERY P: Safety and efficacy of prolonged treatment of fibrosing alveolitis in scleroderma with cyclophosphamide (abstract). ACR Annual Scientific Meeting. San Diego, November, 12-17, 2005 *Arthritis Rheum* 2005; 52: S165.
12. HOYLES RK, ELLIS RW, WELLSBURY J *et al*.: 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; 54: 3962-70.
13. TASHKIN DP, ELASHOFF R, CLEMENTS PJ *et al*.: Cyclophosphamide versus Placebo in Scleroderma Lung Disease. *N Engl J Med*. 2006; 354: 2655-66.
14, NADASHKEVICH O, DAVIS P, FRITZLER M, KOVALENKO W: A randomized unblinded trial of cyclophosphamide versus azathioprine in the treatment of systemic sclerosis. *Clin Rheumatol*. 2006; 25: 205-12.
15. INGLE GR, SHAH T: Enteric-coated mycophenolate sodium for transplant immunosuppression. *Am J Health Syst Pharm*. 2005 1; 62: 2252-9.
16. VANTHUYNE M, BLOCKMANS D, WESTHOVENS R *et al*.: A pilot study of mycophenolate mofetil combined to intravenous methylprednisolone pulses and oral low-dose glucocorticoids in severe early systemic sclerosis. *Clin Exp Rheum* 2007; 25: 287-92.
17. NITHYANOVA SI, BROUGH GM, BLACK CM, DENTON CP: Mycophenolate mofetil in diffuse cutaneous systemic sclerosis - a retrospective analysis. *Rheumatology (Oxford)*. 2007; 46: 442-5.
18. STRATTON RJ, WILSON H, BLACK CM: Pilot study of anti-thymocyte globulin plus mycophenolate mofetil in recent-onset diffuse scleroderma. *Rheumatology (Oxford)*. 2001; 40: 84-8.
19. LIOSSIS SN, BOUNAS A, ANDONOPOULOS AP: Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease. *Rheumatology (Oxford)*. 2006; 45: 1005-8.
20. GINZLER EM, DOOLEY MA, ARANOW C *et al*.: Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005; 353: 2219-28.