SESSION 13

TREATMENT

S.13.1 SAFETY AND EFFICACY OF RITUXIMAB IN SSc: AN ANALYSIS FROM THE EUROPEAN SCLERODERMA TRIAL AND RESEARCH GROUP

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Objectives. Objective of this multicentre, observational study was to assess effects and safety of rituximab (RTX) using the European Scleroderma Trial and Research Group (EUSTAR) cohort.
Methods. EUSTAR centres were asked to provide specific data about SSc patients treated with RTX. Primary endpoints were predefined for different disease manifestations and compared between baseline and follow-up. Normally distributed data, analysed by paired *t*-test, are shown as mean (S.D.), and non-parametric data, analysed by Wilcoxon matched paired signed-rank test, are shown as median and interquartile range.
Results. Data on 72 SSc patients treated with RTX were captured from 27 EUSTAR centres (51 females/21 males, 52 diffuse/19 limited, age 51 (44–60) years, disease duration 6 (3–10) years, 47 anti-Scl-70 positive).
The most frequent RTX application scheme was 1000 mg $\times$ 2 within 2 weeks (57/72 patients). Co-treatment with other immunosuppressive drugs was reported in 28 patients.
The modified Rodnan skin score (mRSS) significantly decreased *vs* baseline at 7 (5–9) months follow-up ($n = 47$, $18.2 + 10.9$ *vs* $14.5 + 9.9$, $P = 0.0002$). This was true for both patients with later disease stages and also for patients with earlier, extended skin fibrosis (dSSc with mRSS >16 at baseline, $n = 26$; $26.5 + 6.8$ *vs* $20.4 + 8.9$, $P < 0.0001$, reduction by 29.9%). S-HAQ was unchanged, but the European SSc activity score improved after rituximab treatment [$n = 10$; 3.7 (2.6–6.4) *vs* 1.7 (0.9–2.5), $P = 0.01$]. RTX had no effects on lung fibrosis (FVC, DL_{CO}, TLC, HRCT score) in $n = 11$ patients with evidence for SSc-ILD.
In SSc-polyarthritis patients, the DAS-28 declined at 6 months follow-up without reaching statistical significance [$n = 8$; 4.8 (2.5–7.5) *vs* 3.7 (2.6–6.6); $p = 0.3$]. Of 8, 5patients were RF and/or anti-CCP antibody positive. Similar results were obtained for secondary outcome measures (tender and swollen joint count, VAS, CRP, ESR).
Additional positive effects of RTX were seen on SSc-related myopathy (CK levels, $273 + 177$ *vs* $184 + 139$; $n = 12$, $P = 0.03$) and on digital ulcers [total number per patient 1 (1–3) *vs* 0 (0–1); $n = 23$; $P = 0.0086$].
During RTX treatment 14 patients had infections, 3 serum sickness, 2 allergic reactions and 1 lung fibrosis aggravation, 29 fatigue and 9 nausea. Four patients died, one possibly related to RTX treatment (pneumonia and cardiac failure 1.5 months after RTX infusion).
Conclusion. This large EUSTAR cohort study points at positive effects of RTX in particular on skin fibrosis, and suggests randomized controlled trial in SSc patients.

S.13.2 ORAL IMATINIB FOR THE TREATMENT OF SCLERODERMA PULMONARY INVOLVEMENT: PRELIMINARY RESULTS OF A PILOT STUDY

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Background. Pulmonary involvement (PI) represents a major cause of death of scleroderma patients. CYC showed a small beneficial effect in RCTs, but a large portion of patients appeared to be totally refractory. Since activation of tyrosine kinases may be involved in the pathogenesis of scleroderma, we have decided to test the effect of imatinib mesylate, a tyrosine kinases inhibitor, on pulmonary and skin fibrosis in a cohort of scleroderma patients, refractory to conventional therapy.
Materials and methods. This study, a Phase II multicentric open trial, is focused on 30 consecutive patients with active pulmonary involvement defined as: Grade 2 dyspnoea (Mahler Dyspnea Index) plus interstitial alveolitis (CT scan showing ground-glass in two lung segments OR neutrophilic/eosinophilic alveolitis), refractory to CYC ($\geq$6 g for a minimum of 3 months).
The study follows a 'Simon's two-stage design': 10 patients are enrolled in a first phase. A 'good response to the treatment' is required in at least 10% of patients before starting the second phase of enrolment (20 patients). The drug will be rejected if the final observed response rate will be in <30% of patients. Patients are treated with oral imatinib, 200 mg/day for 6 months. A 'good response' is defined as the improvement of PI measured trough predefined clinical, functional and radiological criteria in presence of a fair drug tolerance. Secondary outcomes are: cutaneous involvement (mRSS) and laboratory evidence of reduced skin fibroblast activation.
Results. In the first phase, three patients (30%) matched the criteria for a 'good response': two patients (diffuse, late SSc) have shown an increase of >15% in FVC rate and one patient (limited, early SSc) an increase of >15% of DL_{CO} and an improved CT scan pattern after 6 months of treatment. Four severe adverse effect, all judged as unrelated to the study drug, were recorded. No data about cutaneous involvement are still available and no laboratory investigation on biological samples has been performed so far. The second phase is under way and the results will be available in few months.
Conclusions. If the available data will be confirmed by the final assessment, imatinib mesylate appears effective and tolerable in a subgroup of scleroderma patients with pulmonary involvement refractory to conventional treatment. These results warrant further investigations and a randomized placebo controlled trial.

S.13.3 PHARMACOLOGICAL INHIBITION OF MPGES-1 RESULTS IN REDUCED PRO-FIBROTIC AND PRO-INFLAMMATORY SIGNALLING IN HUMAN SCLERODERMA FIBROBLASTS

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Aim. To determine the specific role of microsomal prostaglandin E synthase-1 (mPGES-1) in scleroderma (SSc) disease using skin fibroblasts isolated from normal and SSc patients.
Methods. Skin fibroblasts were isolated by punch biopsies from the forearm of healthy individuals and those with diffuse cutaneous scleroderma in DMEM containing 10% fetal bovine serum. Donors were age-, site- and sex matched. Experimental protocols were approved by the ethics committee. Cells were cultured in the presence/absence of mPGES-1 inhibitor (provided by Merck Frosst Canada) for 18 h and then the expression of pro-fibrotic markers was determined by qPCR analysis. The levels of pro-inflammatory cytokines were measure in the cell culture supernatant using LUMINEX. The expression of p-Akt, T-Akt, p-FAK, T-FAK, p-Smad3 and T-Smad were determined by western blotting.
Results. The immunohistochemical findings showed that the level of mPGES-1 was enhanced in the forearm biopsies of SSc patients *vs* normal patients (NP). Therefore, we determined the effect of mPGES-1 inhibitor (provided by Merck Frosst, Canada) on the expression of pro-fibrotic and pro-inflammatory cytokines using SSc and NP fibroblasts. Our studies showed that the expression of pro-fibrotic cytokines (α-SMA, ET-1, collagen type 1 and connective tissue growth factor [CTGF]) were significantly higher in the SSc skin fibroblasts compared with NP fibroblasts. Treatment with mPGES-1 inhibitor significantly

decreased the expression of α-SMA, ET-1 and collagen type 1 but not CTGF in SSc skin fibroblasts; only numeric reduction in the expression of pro-fibrotic cytokines was observed in NP fibroblasts with mPGES-1 treatment. As expected, the production of pro-inflammatory cytokines (IL-4, IL-8, MCP-1) was significantly higher in the supernatant of SSc fibroblasts compared with NP fibroblasts. Treatment with mPGES-1 inhibitor reduced the levels of pro-inflammatory cytokines in the supernatant of SSc fibroblasts. In addition, mPGES-1 inhibitor significantly decreased the enhanced phosphorylation of both focal adhesion kinase as well as Akt, but not Smad3 in SSc fibroblasts.

Conclusions. These results indicated that elevation of mPGES-1 during SSc could be a contributing factor in the pathology of SSc and blocking mPGES-1 could be therapeutically beneficial.

S.13.4 ORAL SILDENAFIL IN SKIN ULCERS SECONDARY TO SSc

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SSc is a chronic autoimmune disorder that affects skin and a number of internal organs. RP is a hallmark of the disease, causing frequent skin ulcers that can progress to gangrene and amputation if not adequately treated. Recently, phosphodiesterase-5 inhibitors have been advocated as an useful adjunct in patients unresponsive or failing to conventional therapy.

The aim of the present study was to retrospectively evaluate the tolerability of oral sildenafil (alone or in combination with i.v. iloprost) and its effectiveness in RP and in the healing of skin ulcerations in a case series of SSc patients.

37 SSc patients (31 females, 6 males, 23 Lc-SSc, 14 Dc-SSc), ACA: 16/37, Scl-70: 13/37, ANA: 5/37, disease duration: 21 years from RP, 15 years from the first non-RP symptom, mean age 59 (range 27–91) years were enrolled. Statistical analysis was performed by Wilcoxon signed-rank test and descriptive statistics, using Stat View software. The starting dose of oral sildenafil was between 12.5 and 60 mg in single or divided doses (maintenance dose: 12.5–120 mg). Twenty-four patients continued to perform monthly iloprost infusions and sildenafil was added on top of this treatment. Of 37, 25 patients had a mean number of 1.7 ulcers (21 patients upper limbs, 4 lower limbs).

The treatment was continued for a mean period of 14.4 months (range 1–84 months). The drug was well tolerated, side effects were frequent (15/37) but generally mild: headache, hypotension and bloating were the most frequent. In 7/37 cases, the treatment was stopped for side effects. Two patients withdrew the treatment for lack of efficacy, three patients for miscellaneous reasons (appearance of absolute contra-indication, referral to other centres).

A significant reduction in the number of ulcers was observed at the end of the treatment (beginning: 1.7, end: 0.7 $P = 0.0005$). Skin ulcers completely or partially healed in 76% of the patients.

Mean pain VAS showed a statistically significant improvement between enrolment and the end of follow-up (before treatment 60, after 39, $P = 0.02$).

Sildenafil is well tolerated in vascular involvement secondary to SSc. Its administration resulted in a beneficial effect in a significant number of patients with skin ulcers (76%) who previously failed treatments with i.v. prostanoids. Combination of iloprost and sildenafil was well tolerated. Sildenafil might represent a rescue therapy in patients unresponsive to prostanoids or alternatively the first choice in subjects in which these medications are contraindicated or difficult to access.