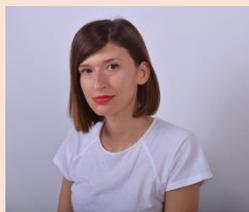


EULAR 2018 Systemic Sclerosis Highlights – Clinical Practice

A EUSTAR Young Investigator Group Report

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A large amount of new clinical research was presented at the EULAR 2018 annual meeting. Here we present a brief summary of some selected abstracts focusing on new potential therapeutic approaches for Systemic Sclerosis (SSc) and its complications.

Skin and systemic involvement

Anabasum is a oral, synthetic, non-immunosuppressive, small molecule that selectively acts as agonist of type 2 Cannabinoid Receptor. The long-term open-label safety and efficacy data in diffuse cutaneous (dcSSc) subjects who had received lenabasum in a previous phase 2 trial (JBT-101) were presented by Dr. Spiera (1). In this study 36 dcSSc patients received lenabasum 20 mg BID. Seven (19%) subjects had adverse events (AEs) related to lenabasum, all classified as minor. Improvement in multiple efficacy outcomes was observed: ACR CRIS score=56%; modified Rodnan Skin Score=-8.6; HAQ-DI=-0.14, Physician Global Assessment=-0.9, and 5-D Itch Questionnaire=-2.3. Forced vital capacity (FVC) predicted was stable from study start. These data supported Phase 3 testing of lenabasum for treatment of dcSSc.

Although the effects of both oral and iv cyclophosphamide (CYC) are well-recognized for the treatment of SSc-related interstitial lung disease (ILD), little is known on the efficacy of iv CYC on skin involvement. Dr. B. Kersten presented a study about this topic including dcSSc patients treated with at least 6 pulses of CYC (2) and a follow-up of at least 12 months. Unfortunately, although iv CYC is considered a standard treatment for skin involvement, only 43% of patients experienced a significant skin improvement. Interestingly though, the response at 6 month was the predictor for response on month 12.

The contribution of vascular injury to fibrosis formed the basis of LeRoy's Hypothesis. An Italian group (3) investigated the efficacy of Bosentan on skin involvement through means of high-frequency ultrasound. They found that after 4 years of treatment, Bosentan in combination with Iloprost (ILO), was associated with a significant decrease in dermal thickness in contrast to ILO treatment alone.

Exercise Therapy

The efficacy of exercise therapy as single intervention in SSc treatment was also discussed at the EULAR. A systemic review of

the literature was presented by dr. Liem (4). Six studies (2 randomized controlled trials, 3 observational studies and 1 single subject experimental design) were selected. The study on hand exercises reported a greater improvement of hand function using the telemedicine intervention. The RCT on mouth exercises showed only short-term efficacy at 3 months. Aerobic exercise was found to improve patient's exercise tolerance and aerobic capacity. Unfortunately though, as the literature on exercise therapy was scanty, no clear conclusions could be drawn.

Lung involvement

A large amount of studies focused on the role of B cell depletion therapy in the treatment of SSc-related ILD. The largest one was a retrospective longitudinal multicentre observational study performed by the European Scleroderma Trial and Research (EUSTAR), reporting data on 248 patient, the vast majority being dcSSc anti-topoisomerase I positive, and treated with Rituximab (RTX). ILD was the primary indication for RTX in 56% of cases. The results showed that FVC significantly improved after RTX therapy, especially in patients with baseline predicted FVC <70%. The mean follow-up was 2.4 years. Infections and other severe adverse events were frequently reported (5). Currently, a comparative study including control patients from EUSTAR centres is ongoing. A similar French retrospective study on 53 SSc patients showed a significant improvement of mean predicted FVC from 71% at baseline to 84% after 12 months (p=0.01), and of mean predicted DLCO from 58% at baseline to 63% at month 12 (p=0.04) (6).

RTX treatment was also compared to iv CYC in an open label, randomized controlled trial. Sixty early SSc patients affected by ILD were randomly assigned to monthly CYC pulses (500 mg/sq. m) or to RTX (1 g x 2). In the RTX group the mean FVC improved from 61.30% to 67.52%, while in the CYC group it declined from 59.25% to 58.06% at 6 months (p 0.003) (7). The authors concluded that RTX can be considered a safe and effective alternative to CYC as first-line treatment in patients with early SSc-related ILD.

Dr Bruni reported a similar efficacy of 1 year treatment with oral and iv CYC. Data on 322 SSc patients were obtained from the EUSTAR database and the Scleroderma Lung Studies I and II. The AEs observed with the 2 different regimens significantly differed. Leukopenia

and haemorrhagic cystitis were observed more commonly in the oral CYC group (1.6% vs 1.2%, and 5.5% vs 0%, respectively). Conversely though, more serious AEs (9% vs 19%), need for oxygen supplementation (5% vs 14%) and SSc-related cardiomyopathy onset (2% vs 9%) were observed in the iv CYC group (8).

A retrospective cohort study about the treatment of SSc-related pulmonary arterial hypertension (PAH) was also presented. It included 67 PAH patients from the Spanish Scleroderma Registry. The patients were divided into 3 groups: monotherapy (45%) vs. sequential combination therapy (33%) vs. upfront combination therapy (22%). Primary end-point was mortality from any cause. Sequential combination therapy was found to be a protective factor (HR=0.11). Survival rates in the 3 groups were: 78% vs. 95.8% vs. 94.1% at 1 year, 40.7% vs. 81.5% vs. 51.8% at 3 years and 31.6% vs. 56.5% vs. 34.5% at 5 years (p=0.007). Side effects were not significantly different among groups (9). These results need to be definitely confirmed in prospective studies.

Vascular complications

New insights into the treatment of SSc vascular complications emerged for both traditional drugs and new techniques. Schioppo et al. (10) highlighted the role of ILO, an anchor drug for the treatment of digital ulcers (DU) in SSc: the acute and chronic effects of two different ILO regimens were reported in this single centre pragmatic non-randomised trial. 96 SSc patients were divided into 3 groups: no ILO, iv ILO once monthly and iv ILO for 5 consecutive days 3-monthly. ILO could induce acute effects as observed with power Doppler ultrasound (PDUS) parameters, especially in the "iv ILO once monthly" group, but these effects were not maintained (10). These results raise the issue of how ILO infusions should be scheduled. This topic was analysed by the same Author (11) in a three rounds Delphi exercise, which highlighted the necessity of sound data from controlled studies and the need for a personalization of the ILO scheme according to patients' needs. Most of the experts agreed on a 1-3 days monthly regimen for RP and DU healing and a 1 day monthly for DU prevention. Although these suggestions are intended for clinical setting use, it will be necessary to formally validate the present suggestions in future clinical trials.

The value of a new instrument in topical therapy for DU was reported by Del Papa et al. (12) in a randomized controlled trial aimed to confirm previous preliminary data on Adipose

Tissue Grafting (AT-G), a lipofilling technique based on Adipose-derived stromal/stem cells (ADSCs). SSc patients suffering from a DU lasting for at least 6 weeks prior to enrolment time and showing no tendency to heal, were randomised to be blindly treated with AT-G or a sham procedure (SP): DU healing was observed in 23/25 patients receiving AT-G versus 1/13 receiving the SP (p<0.0001); the 12 patients who unsuccessfully received SP, were afterward successfully treated with a rescue AT-G. Furthermore, AT-G treatment was able to significantly reduce pain intensity and increase capillary numbers in the affected fingers (p<0.0001).

Gastrointestinal involvement

Based on the emerging role of microbiota in SSc and GI manifestations, the results of a proof-of-concept double-blind randomised placebo-controlled trial of probiotics in SSc related gastrointestinal disease were presented by Low et al. (13). Forty patients were randomized to receive placebo (n=21) or probiotics (n=19). The primary endpoint, identified as the improvement in GI symptoms as assessed by UCLA Gastrointestinal tract questionnaire (GIT 2.0) at 60 days, was not achieved. However, at 120 days a greater improvement in GIT-reflux subdomain was observed (p=0.0037). Furthermore, a possible positive association between greater alpha diversity of microbiota and lower GIT scores emerged in the probiotic group. Despite being preliminary, these data could provide justification for a larger definitive trial of probiotics in SSc.

Conclusions

The selection of abstracts reported here provides a synopsis of some of the exciting and influential research presented at the 2018 EULAR Congress. Inevitably, an exercise such as this is inherently subjective and will inadvertently omit important research. Nonetheless, we hope to have compiled a selection of the meeting's highlights whose manuscripts we eagerly await.

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