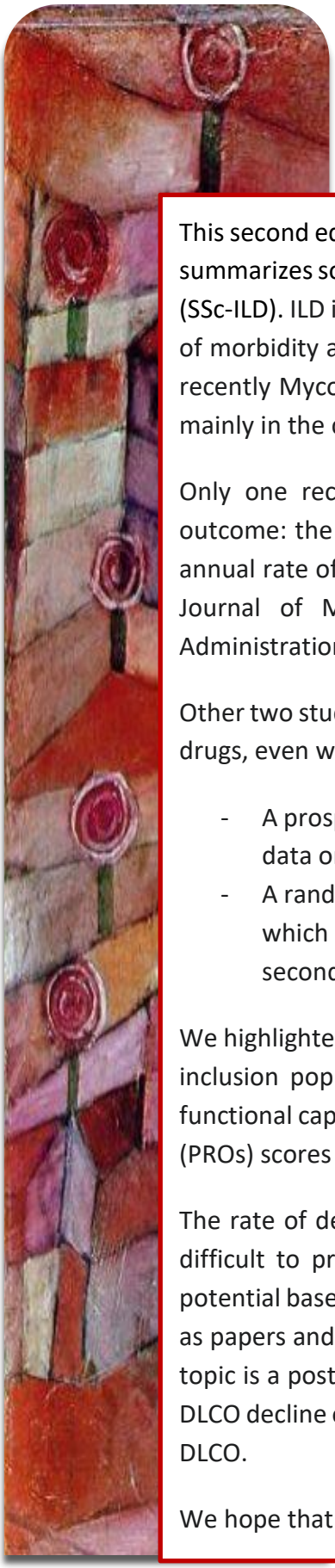

CLINICAL SCIENCE JOURNAL CLUB OF EUSTAR YIG

October 2019

This second edition of the clinical science journal club of the EUSTAR Young Investigators (YIG) summarizes some of the recent advances in Systemic Sclerosis related Interstitial Lung Disease (SSc-ILD). ILD is a relatively frequent complication in SSc, representing one of the main causes of morbidity and mortality. Current treatments for ILD include Cyclophosphamide and more recently Mycophenolate Mofetil (MMF). New therapeutic options are now on the horizon, mainly in the category of biologic drugs or small molecules.

Only one recent study was specifically focused on the SSc-ILD progression as primary outcome: the SENSCIS trial, that demonstrated the efficacy a of Nintedanib in reducing the annual rate of decline in FCV. The results have been recently published on the New England Journal of Medicine and are summarized below. Importantly, the Food and Drug Administration has approved the drug for this indication in September 2019.

Other two studies (summarized below) have been recently published, focused on two biologic drugs, even with primary endpoints other than SSc-ILD:

- A prospective observational study on Rituximab (RTX) in the EUSTAR cohort, providing data on its possible efficacy in different organ involvements
- A randomized clinical trial on Tocilizumab (TCZ) and the subsequent open-label phase, which primary endpoint was the efficacy on cutaneous involvement, but among the secondary endpoints, interesting results on ILD were provided.

We highlighted some important points to consider when discussing the recent studies on ILD: inclusion population criteria, in particular the subset of patients (limited or diffuse), the functional capacity, the concomitant treatments and the value of Patient Reported Outcomes (PROs) scores in reflecting the efficacy of the drugs.

The rate of decline of pulmonary functional capacity is a particularly relevant issue, as it is difficult to predict and define. Many studies are trying to point out which could be the potential baseline predictors, such as the one from *A.M.Hoffman-Voldt* [not already published as papers and therefore not included in this journal club]. An interesting study regarding this topic is a post-hoc analysis of the joined cohort in SLS-I and II trials, suggesting that FVC and DLCO decline over 2 years was a better predictor of long-term outcome than baseline FVC and DLCO.

We hope that you will enjoy this Journal Club!




Contributors to October issue, from left to right: Eugenia Bertoldo, Corrado Campochiaro, Kristina Clark, Maria-Grazia Lazzaroni

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

Distler O. et al, N Engl J Med 2019; 380:2518-2528

Nintedanib is a tyrosine-kinase inhibitor already approved for the treatment of idiopatic pulmonary fibrosis (IPF).
Recently, the SENSCIS trial included 576 patients with SSc-ILD and was able to demonstrate the efficacy of Nintedanib in reducing the annual rate of FVC loss, as compared to placebo. Specifically, patients on Nintedanib showed an overall rate of decline of −1.4±0.4 in FVC% predicted (%pFVC) vs. −2.6±0.4 in the placebo arm at week 52 (Figure 1).

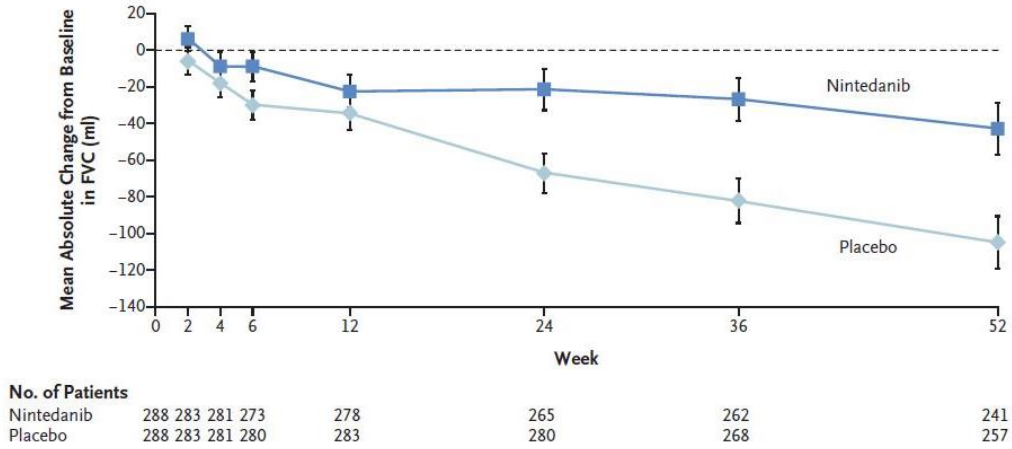

Figure 1. Observed change from baseline over 52 weeks in FVC. I bars indicate the standard error.

Concomitant immunosuppressive treatment was allowed and **interesting results come from the group that received Nintedanib plus MMF, that showed a lower FVC decline. In fact, in patients receiving MMF the FVC loss was −40.2 ml/year in the Nintedanib group and −66.5 ml/year in the placebo group, while in patients not receiving MMF at baseline was −63.9 ml/year and −119.3 ml/year.**

Nevertheless, no significant results were recorded in the secondary endopoints, such as the efficacy on skin involvement or significant improvement in patients reported outcomes PROs scores (St. George's Respiratory Questionnaire (SGRQ) and the Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnea questionnaire). Moreover, no efficacy was shown on other clinical manifestations of SSc.

The safety profile of Nintedanib was similar to that already observed for IPF patients, with gastrointestinal adverse events, including diarrhea, as the most frequently recorded adverse events.

Points to be considered in the interpretation of these results include PROs used as secondary endpoints not specifically designed for SSc and the relatively conserved lung function at the baseline in patients included (72.4±16.8 for the Nintedanib group and 72.7±16.6 for the placebo group).
In conclusion, Nintedanib was able to reduce the lung function decline in SSc-ILD patients, but further studies are needed to point out the efficacy of this drug in patients with less conserved lung function and its efficacy when combined with immunosuppressive drugs of different types and dosage in a real-life setting.

Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). *Khanna D, et al.; Ann Rheum Dis 2018;77:212.*

Efficacy and Safety of Tocilizumab for the Treatment of Systemic Sclerosis: Results from a Phase 3 Randomized Controlled Trial. *Khanna D, et al.; ACR 2018. Arthritis Rheumatol. 2018; 70 (suppl 10).*

Preservation of Lung Function Observed in a Phase 3 Randomized Controlled Trial of Tocilizumab for the Treatment of Early Systemic Sclerosis. *Khanna D, et al.; ATS Conference 2019. MeetingAbstracts.A2627*

The 48-weeks faSScinate clinical trial in patients with SSc concluded that TCZ determined a clinically meaningful, even if not statistically significant, decline in modified Rodnan Skin Score (mRSS), as compared to placebo. Moreover, in the TCZ arm a significant lower number of patients with a decline in %pFVC was reported. Subsequently the Authors presented the results of *exploratory efficacy and safety through week 96 of the faSScinate trial, including the 48-week open-label period*.

Overall, observed mean change in mRSS from baseline was –3.1 ± 6.3 for placebo and –5.6 ± 9.1 for TCZ at week 48 and –9.4 ± 5.6 for placebo-TCZ and –9.1 ± 8.7 for continuous-TCZ at week 96. **Any decline in %pFVC was observed for 42% placebo-TCZ and 46% continuous-TCZ patients in the open-label period; no patients had >10% absolute decline in %pFVC**. Serious infection rates/100 patient-years were 10.9 (3.0-27.9) with placebo and 34.8 (18.0-60.8) with TCZ during the double-blind period by week 48, while in the open-label period the rates were 19.6 (7.2 to 42.7) with placebo-TCZ and 0.0 (0.0 to 12.2) with continuous-TCZ.
Globally, this study supported the observation that the placebo and the TCZ patients similarly improved when placebo was switched to active treatment.
A subsequent double-blind phase III randomised controlled trial on TCZ in SSc (NCT02453256), whose results were presented at ACR 2018 and ATS 2019, confirmed that although the primary end point on mRSS change was not met, the difference in mean FVC change from baseline to week 48 was 167 mL (83-250) in favour of TCZ, and the preservation of lung function with TCZ was shown by change from baseline in FVC over time. Moreover, **at week 48, 5 (5.4%) TCZ-treated patients experienced ≥10% absolute decline/worsening in %pFVC versus 15 (16.5%) for placebo.** HRCT also showed improvement in lung fibrosis with TCZ versus placebo, supporting the lung function results.

In conclusion, TCZ seems to determine meaningful differences in FVC decline, with preservation of lung function in SSc patients.

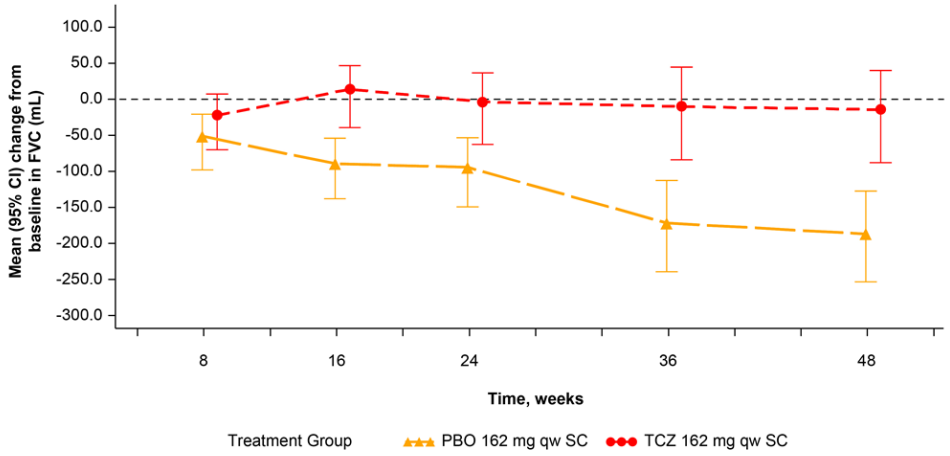

Figure 2. Decline in FVC from the baseline to week 48 in TCZ versus PBO group

Outcomes of patients with systemic sclerosis treated with Rituximab in contemporary practice: a prospective cohort study

Elhai M. et al.; Ann Rheum Dis 2019;0:1-9

Previous studies have suggested a potential role of RTX on skin involvement and ILD, but with several methodological limitations. This prospective observational study analyzed the outcome of **254 SSc patients from the EUSTAR cohort treated with RTX** (71% with ILD, 64% with dcSSc) with a median **follow-up period of 2-years**. *A propensity score model* was applied to tightly **match a control group of 9575 patients not-treated with RTX.**

The main outcomes measures were adverse events rate, mRSS improvement (decrease of 25% and $\geq$ 5 points), ILD worsening (decrease in FVC>10% and >15% in DLCO) and steroid use.

The leading indications for RTX were lung (58%), musculoskeletal (42%) and skin (32%) involvement. **No efficacy was found on lung involvement**: **FVC (OR:1.03 [0.55-1.94]; p:0.93) and DLCO were stable both in RTX treated patients and controls**. In the small subgroup with concomitant use of RTX and MMF there was a trend for a better FVC outcome as compared to the group with RTX alone (delta FVC:5.22 [0.83-9.62]; p:0.019 vs 3[0.66-5.35]; p:0.012), but not statistically significant.

A **good safety profile** (no adverse events in 70% of patients, severe in 14% and leading to discontinuation in 9%) and a significant **improvement in skin fibrosis** were recorded, together with an increased probability of **discontinuing or decreasing steroids**. Interestingly, **only 2 scleroderma renal crisis** were reported, despite of the use of i.v. steroids as premedication.

Regarding the lack of efficacy of RTX on ILD, the Authors concluded that the observational design of the study could have led to **selection biases**, including mostly ILD patients with poor predictive factors. Therefore, only a randomized trial could establish the potential role of RTX in SSc-ILD.

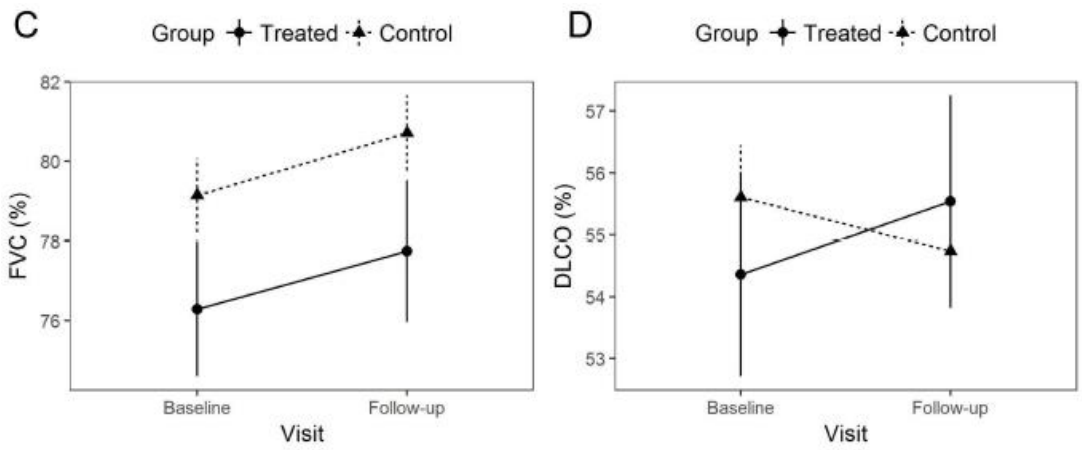

Figure 3. Evolution of PFT parameters among propensity score-matched patients treated with RTX and controls.

Short-term progression of Interstitial Lung Disease in Systemic Sclerosis Predicts Long-term Survival in Two Independent Clinical Trial Cohorts.

Volkmann E et al.; Ann Rheum Dis. 2019; 78(1): 122–130.

The aim of this study was to assess survival and identify predictors of survival in those patients who were included in the SLS I and SLS II studies.

SLS I study comprised of a randomised controlled trial of patients with SSc-ILD who received treatment for one year with either oral cyclophosphamide (CYC) or placebo. SLS II randomised patients with SSc-ILD to receive either 1 year of oral CYC followed by a year of placebo or 2 years of MMF.

The authors presented the long-term survival of patients who were included in these studies, 12 years' worth of follow up for the patients in the SLS I, and 8 years for those in SLS II. Results from both studies showed no significant difference in long term survival or time to organ failure between each treatment arm.

In both studies the analysis performed with Cox proportional hazards models, showed that increased age and increased mRSS at baseline were associated with increased mortality. Longitudinal assessment of both %pFVC and percentage predicted diffusing capacity of the lungs for carbon monoxide (%pDLCO) measured as a time-varying covariate were each independently associated with mortality.

Only in the SLS I baseline %pFVC was independently associated with mortality. In SLS II, the change in FVC from baseline to 12months was predictive of long-term survival. Utilising categorical grouping of patients in the base model of skin and age, a decline in FVC of ≥10% and ≥15% was also associated long term survival.

Limitations to this study include the fact that this was a restricted cohort of patients and may not fully reflect the patient population or current treatment practices. This is especially the case in the SLS I study, where the patients did not have a maintenance regime following induction treatment with CYC.

In summary this study looks into the outcome of SSc patients with ILD. It highlighted that higher baseline skin score and older age are predictors of a worse outcome. **They also pointed out that the course of FVC and DLCO over 24 months was a more robust predictor of survival than baseline results. The authors suggest that their results support an early decline in these lung function parameters should prompt more aggressive treatment strategies in order to impact on long term mortality.**