Methods: Demographic and clinical data of patients with SSc, DM and ASS were retrospectively recorded from January 2015 for the purpose of this study. The baseline time was a diagnosis of ILD confirmed by computed tomography (CT) scan of the chest. The IFP cohort was used as control group. Progressive lung disease was defined when the patient presented within 24 months after the diagnosis of ILD with at least one of these characteristics: a) a relative decline in FVC of at least 10% of expected value; b) a relative decline in FVC from 5% to less than 10% of the expected value and a worsening of respiratory symptoms or an increase in the extent of lung fibrosis on high-resolution CT scan; c) a worsening of respiratory symptoms and an increase in the extent of lung fibrosis on high resolution CT scan. All data were reported and analyzed with standard descriptive statistics, as appropriate. The 5-year survival was assessed with the Kaplan-Meyer method; univariate and multivariate Cox-regression models were built to look for possible risk factors. Data were analyzed with SAS/STAT Statistics version 9.4 (SAS Institute, Cary, NC, USA).

Results: The overall cohort included 177 CTD-ILD patients (99 SSc, 25 DM, 53 ASS) and 153 IFP patients. At ILD diagnosis, as expected, CTD patients were younger [median age (IQR); IFP: 68 (63-73) years, SSc 58 (46-66) years, DM 54 (51-65) years and ASS: 59 (60-67) years; p<0.001 vs IFP] and predominantly female (IFP: 23%, SSc 83.5%, DM 81% and ASS 65%; p<0.001 vs IFP). Usual interstitial pneumonia was observed in a low number of CTD patients, evidenced in 11 (11.5%) SSc, 7 (12.9%) ASS and 4 (16.6%) DM patients. At ILD diagnosis, the median (IQR) value of forced vital capacity (FVC) was similar between IFP [75% (64-91)], DM [79% (60-90)] and ASS [77.5% (64-93)], while was significantly higher in SSc patients [94% (78-106), p<0.001 vs IFP]. At baseline, all CTDs showed a higher mean (SD) value of diffusing capacity for carbon monoxide (DLCO%) than IFP [56% (30-83%), DM: 62% (23), ASS: 63% (22)] vs IFP [50% (15); p<0.001]. During follow-up, 10 (9.7%) patients with SSc, 4 (16%) with DM and 3 (8%) with ASS showed a progressive subset of ILD. CTDs showed better 5-year survival compared to IFP (log rank: p=0.001) (Figure 1). Multivariate Cox analysis highlighted that male gender (HR: 2.29, 95% CI 1.25-4.18), age at diagnosis (HR: 1.07, 95% CI 1.04-1.10) and DLCO at baseline (HR: 0.95, 95% CI 0.94-0.97) were independent prognostic factors in CTD-ILD.

Conclusions: The prognosis of CTD patients with lung fibrosis appears to be significantly better than those with IFP. The early detection of lung involvement in at-risk patients like SSc, DM and ASS, and the availability of effective immunosuppressive treatment may explain this discrepancy. Of note male patients, older age and compromised DLCO at baseline represent poor prognostic factors.

References:

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SUSTAINED COMPLETE B CELL DEPLETION IS ASSOCIATED WITH RITUXIMAB EFFICACY IN CONNECTIVE TISSUE DISORDERS - ASSOCIATED INTERSTITIAL LUNG DISEASE

Keywords: Lungs, Systemic sclerosis

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Background: The benefit of RTX has been suggested for interstitial lung disease (ILD) associated with connective tissue disorders (CTD). Preliminary data have suggested that B cell depletion measured 2 weeks after the first RTX infusion was predictive of short-term treatment response at 6 months in systemic sclerosis (SSc)-ILD.

Objectives: To determine whether the quality of B cell depletion was associated with therapeutic response to RTX in CTD-ILD.

Methods: Retrospective monocentric study including all patients treated at least 1 year with RTX for SSc- or MCTD-ILD. The observation period was defined by the time from the first to the last RTX infusion. ILD was identified based on high-resolution CT. The results of forced vital capacity (FVC) and carbon monoxide diffusion capacity (DLCO) were collected at the time of the first RTX infusion, at month 12 and at the time of the last RTX infusion. B cell immunophenotyping was performed the day of each RTX infusion (Aquios, Beckman Coulter). B cell depletion was defined by CD19 <18/µL. The primary outcome was the absolute change from baseline of FVC (L) at 12 months and at the last RTX infusion according to complete or incomplete B cell depletion within the observation period. Secondary outcomes were the course of DLCO at the same time points according to B cell depletion and the analysis of the % of good RTX responders at 12 months and at the last RTX infusion, defined by at least 5% improvement in %FVC compared to baseline.

Results: 17 patients (12 SSc and 5 MCTD) were included, with a median age of 59 years (95% confidence interval, CI, 48-63 years) and a median disease duration of 8 years (95% CI 5-11 years). The median duration of RTX exposition was 45 months (95% CI 19-90 months), the median number of infusions was 8 (patient 95% CI 5-14) and the cumulative RTX dose was 7g (95% CI 5-14g). These parameters were similar in the 9 patients with complete B cell depletion (CD19: 15µL, 95% CI 14-18µL, Figure 1A-B) and the 8 patients with incomplete B cell depletion (CD19: 70µL, 95% CI 18-126µL, Figure 1A-B) during RTX exposure. The absolute change from baseline of the FVC was different according to B cell depletion during the observation period. In the subset of patients who maintained complete B cell depletion (Figure 1C), median FVC increased from 2.58L (95% CI 1.13-4.08L) to 3.08L (95% CI 1.34-6.4L) at month 12 (p=0.004) and 3.22L (95% CI 1.57-4.19L) at the last RTX infusion (p<0.019) (Figure 1D). Conversely, in the subset of patients with constant incomplete B cell depletion (Figure 1C), FVC initially increased from 2.04L (95% CI 0.9-3.24L) to 2.23L (95% CI 0.83-3.35L) at month 12 (p=0.039) before decreasing to 1.89L (95% CI 1.00-3.24L) at month 12 (p=0.37) (Figure 1D). The absolute change from baseline of DLCO did not significantly differ according to B cell depletion. However, the percentage of patients with any FVC improvement was higher in the subset of patients who maintained complete BC depletion at 1 year (6/9, 67% vs. 4/8, 50%) and at the last RTX infusion (8/9, 89% vs. 4/8, 50%). Conversely, median DLCO did not significantly differ according to BC depletion.

Conclusion: These results highlight the importance of obtaining and maintaining B cell depletion to gain clinically relevant efficacy of RTX in CTD-ILD. CD19 measurement at each infusion is a relevant tool to monitor RTX efficacy in daily practice.

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