OP0245

## PRESERVATION OF LUNG FUNCTION OBSERVED IN A PHASE 3 RANDOMIZED CONTROLLED TRIAL OF TOCILIZUMAB FOR THE TREATMENT OF EARLY SSC

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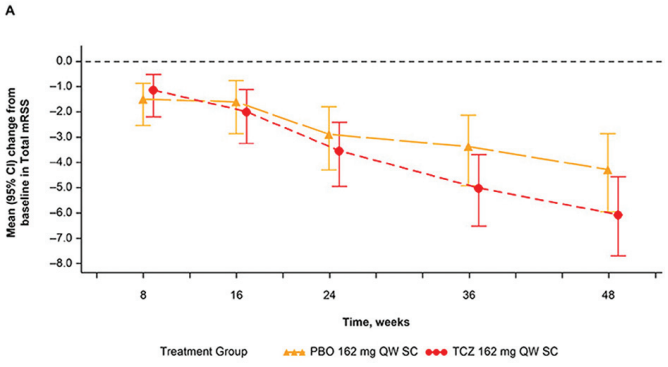
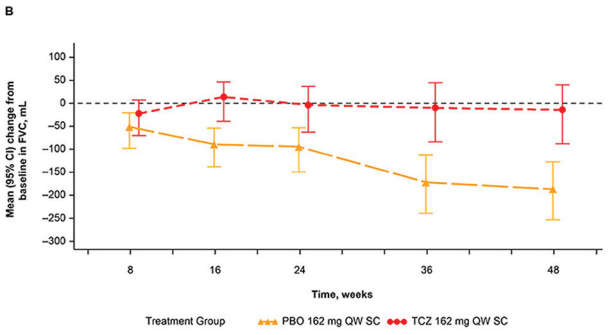
**Background:** The anti–IL6 receptor-α antibody tocilizumab (TCZ) demonstrated numerical improvement in modified Rodnan skin score (mRSS) and clinically relevant preservation of lung function (LF) (assessed by forced vital capacity [FVC]) in systemic sclerosis (SSc) patients (pts) in a ph 2 trial.[1]
**Objectives:** Report the efficacy and safety (sft) of TCZ vs placebo (PBO) in SSc pts from the double-blind period of ph 3 trial (NCT02453256).
**Methods:** SSc pts were randomly assigned 1:1 to weekly subcutaneous TCZ 162 mg or PBO for 48 wks. Primary endpoint was mean difference (diff) in change (Δ) from baseline (BL) to wk 48 in mRSS for TCZ vs PBO. Key secondary endpoints were ΔBL%-predicted FVC (ppFVC) and time to Tx failure (time from first study treatment (Tx) to first occurrence of death, decline in FVC >10%, increase in mRSS >20% and mRSS ≥5, or occurrence of predefined SSc-related Cx). Chest high-resolution computed tomography (HRCT) and ACR Combined Response in SSc (CRISS) were exploratory endpoints.
**Results:** Of 106 PBO- and 104 TCZ-treated pts, 81% were women and 31% had previous or concurrent interstitial lung disease based on history. BL mean values were age 48 yrs, SSc duration 23 mts, mRSS 20.4, ppFVC 82.1%, and ppDLCO 75.6%. Mean BL computer-assisted quantitative lung fibrosis of the most affected lobe (QLF-LM) was 4.7% for the PBO group and 5.5% for the TCZ group. At wk 48, the primary endpoint was not significant (ΔBL mRSS: PBO, −4.4; TCZ, −6.1; adjusted least squares mean diff, −1.7 [95% CI: −3.8, 0.3]; $p$=0.098) (Fig 1A). All $p$ values for other endpoints were nominal. The cumulative distribution of wk 48 ΔBL ppFVC favored TCZ over PBO (median [IQR]: PBO, −3.9 [−7.2, 0.6] vs TCZ, −0.6 [−5.3, 3.9]; van Elteren nominal $p$=0.0015). The diff in mean ΔBL FVC at wk 48 between Tx groups was 167 mL (95% CI: 83, 250), favoring TCZ (Fig 1B). At wk 48, 5 (5.4%) TCZ-treated pts experienced ≥10% absolute decline in ppFVC compared with 15 (16.5%) for PBO. The HR (95% CI) for time to Tx failure was 0.6 (0.4, 1.1), numerically favoring TCZ (Cox proportional hazards model; $p$=0.082). ACR CRISS scores favored TCZ over PBO at wk 48: median (IQR), 0.89 (0.09-1.00) vs 0.25 (0.00-0.99) ($p$=0.023). HRCT showed less progression of lung fibrosis for TCZ than for PBO, which supports the FVC results. Sft results were consistent with Cx of SSc and the established TCZ sft profile; SAEs were reported by 17% of PBO pts and 13% of TCZ pts; serious infections were reported by 7% and 2% of pts, respectively.

**Figure 1. Change from baseline in (A) mRSS and (B) FVC**




A mixed model for repeated measures analysis was implemented.
The analysis included the fixed, categorical effects of treatment, visit, the stratification factor IL-6 level (<10; ≥10 pg/mL) at screening, IL-6 level at screening-by-visit interaction, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction. Includes 22 pts in the PBO group and 9 pts in the TCZ group who received immunomodulators from week 16 if they had FVC decline or from week 24 if they experienced worsened mRSS or worsened SSc complications.

**Conclusion:** The primary mRSS endpoint was not met; however, TCZ Tx resulted in clinically relevant differences in FVC with preservation of LFS and improvement in fibrosis, measured by HRCT, in SSc pts.
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## SLE news

### OP0246 ATTAINMENT OF THE LUPUS LOW DISEASE ACTIVITY STATE IS ASSOCIATED WITH PROTECTION FROM DAMAGE ACCRUAL IN PATIENTS WITH ACTIVE DISEASE AT BASELINE

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**Background:** The recently validated Lupus Low Disease Activity State (LLDAS) definition has been shown to have utility as a treat to target endpoint in SLE, whereby LLDAS attainment is associated with reduction in permanent damage accrual. Robust evaluation is required to ensure this protective association is not simply reflective of milder disease phenotypes being over-represented among LLDAS attainers.
**Objectives:** To assess the effect of attainment of LLDAS on damage accrual in patients with active disease at baseline. SLEDAI-2K≥6 was chosen as this reflects clinical trial entry criteria.
**Methods:** A prospective multinational cohort study was undertaken in 13 centres between 2013-2017. Patients with SLE were recruited, SLEDAI-2k, SELENA flare index, PGA, and medication data collected at every visit, and damage score (SLICC-ACR damage index (SDI)) collected annually. Subgroup analyses were performed to assess the effect of LLDAS on damage accrual in patients who had active disease at baseline (SLEDAI-2K≥6). Time-dependent hazards regression models were used to assess the association of attainment of LLDAS at any time point, and proportion of time in LLDAS at the 50% observed time cut-off, with accrual of irreversible end-organ damage.
**Results:** 1,735 patients were followed for (mean ± SD) 2.2 ± 0.9 years, totalling 12,717 visits. LLDAS attainment was less frequent in patients with active disease at baseline (901 of 3835 visits in LLDAS, 23.5%), compared to patients with SLEDAI2-K<6 at baseline (5190 of 8845 visits in LLDAS, 58.7%), p<0.001. In contrast, compared to those with baseline SLEDAI-2K<6, patients with active disease at baseline demonstrated a stronger association of LLDAS attainment with reduction in risk of damage accrual, in visit by visit analysis (HR 0.49, 95% CI 0.28-0.86, p 0.01 vs HR 0.72, 95% CI 0.52-0.99, p 0.05), and in analysis of cumulative time spent in LLDAS (HR 0.52, 95% CI 0.33-0.83, p 0.01 vs HR 0.65, 95% CI 0.47-0.91, p 0.01).
**Conclusion:** Despite lower attainment of LLDAS in patients with higher disease activity at baseline, the magnitude of association of LLDAS attainment with lower damage accrual was greater in this subgroup of patients compared to those less active baseline disease. This supports the validity of LLDAS as an outcome measure, in a population similar to that typically selected into clinical trials, and further highlights the potential impact of achieving a target outcome in SLE patients with active disease.
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### OP0247 EFFECT OF IMMUNOSUPPRESSIVE DRUG WITHDRAWAL ON DAMAGE PROGRESSION AND FLARE OCCURRENCE IN SLE PATIENTS IN REMISSION

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**Background:** Patients with Systemic Lupus Erythematosus (SLE) are often treated with prolonged maintenance therapy with immunosuppressants (ISs) after remission achievement, with the aim of avoiding disease flares and subsequent organ damage. Data on the risk of flare after IS discontinuation and the effect of IS discontinuation on damage accrual are scanty.
**Objectives:** Our aims were to analyze damage progression in remitted SLE patients who did or did not discontinued ISs, to assess flare rate after IS withdrawal and to compare damage accrual in patients who did or did not flare after IS discontinuation.
**Methods:** We considered all SLE patients included in our lupus database, diagnosed between 1990 and 2018 (ACR criteria), treated with immunosuppressants over their disease course, who discontinued IS due to remission. IS discontinuation was defined as complete withdrawal of any immunosuppressive drug, and remission as clinical SLE Disease Activity Index (SLEDAI)-2K=0. Flares were defined according to SLEDAI Flare Index, and damage according to SLICC damage Index (SDI).
**Results:** Eligible patients ever treated with ISs were 319 out of 456 (69.9%) currently in follow-up. Remission lasting at least 6 months was achieved by 206 patients treated with IS (64.6%) (Table 1); among them 105 (51%) discontinued ISs during the follow-up. Mean±SD follow-up after IS withdrawal was 91±71 months (range 6-372). No difference in damage accrual between remitted patients who discontinued or did not discontinue ISs was observed at the end of follow-up, after adjusting for disease duration: median (range) SDI 1 (0-6) and 0 (0-4), respectively. Accordingly, the proportion of remitted patients who accrued damage during the follow-up was similar between those who did or did not discontinue ISs (55% vs. 48%). Among patients who discontinued ISs, 26 (24.7%) experienced a flare after a median (range) of 57 (6-264) months from IS discontinuation. Flares were severe in 50% of cases (Table 2). No difference in damage progression between patients who flared and did not flare after IS withdrawal was found at the end of follow-up: median (range) SDI 1 (0-5) and 1 (0-6), respectively. Moreover, the proportion of patients with damage accrual was similar among patients with and without flare after IS discontinuation (56% vs. 54%).

**Table 1**. Characteristics of remitted patients according to the discontinuation of ISs. Data are expressed as mean±SD or number (%).

| | Remitted patients | | P value |
|---|---|---|---|
| | IS discontinued (105) | IS not discontinued (101) | |
| Female, N (%) | 93 (88.6) | 85 (84.1) | n.s. |
| Age at 2018, years | 44±11 | 40±12 | 0.035 |
| SLE duration at 2018, years | 19.5±9.2 | 12.3±8.7 | 0.027 |
| SLE duration at remission, years | 5.2±6.1 | 6.3±4.2 | n.s. |
| Remission lasting at IS discontinuation > 2 consecutive years, N (%) | 66 (63) | 36 (35.6) | 0.001 |
| **Reason for IS therapy, N (%)** | | | |
| Lupus Nephritis | 68 (64.8) | 57 (56.4) | n.s. |
| Skin involvement | 6 (5.7) | 7 (6.9) | |
| Arthritis | 12 (11.4) | 15 (14.4) | |
| Haematological involvement | 5 (4.7) | 8 (7.9) | |
| Neuropsychiatric involvement | 3 (2.9) | 2 (1.9) | |
| Vasculitis | 3 (2.9) | 1 (0.9) | |
| Multisystemic involvement | 8 (7.6) | 11 (11) | |
| **Type of last IS*, N (%)** | | | |
| Mycophenolate | 48 (45.7) | 73 (72.2) | 0.001 |
| Azathioprine | 30 (28.6) | 18 (17.8) | 0.04 |
| Methotrexate | 14 (13.3) | 5 (4.9) | 0.008 |
| Cyclosporine | 7 (6.7) | 4(3.9) | n.s. |
| Cyclophosphamide | 6 (5.7) | 1 (0.9) | 0.001 |

* last IS used before withdrawal or at last visit. Multisystemic: involvement of more than 2 organs requiring IS therapy.