Effect of Nintedanib on KL-6 in Patients with Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) in the SENSCIS Trial

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INTRODUCTION

- Krebs von den Lungen-6 (KL-6), a marker of epithelial and endothelial injury, has been associated with lung involvement in patients with SSc.[1,2]
- Nintedanib is an intracellular inhibitor of tyrosine kinases that inhibits processes fundamental to the progression of fibrosis.[3]
- In the SENSCIS trial in patients with SSc-ILD, nintedanib reduced the rate of decline in forced vital capacity (FVC) over 52 weeks by 44% compared with placebo.[4]

AIM

- To assess associations between circulating levels of KL-6 and clinical variables, and the effect of nintedanib on changes in KL-6, in the SENSCIS trial.

METHODS

The SENSCIS trial

- Patients had SSc with first non-Raynaud symptom in the prior ≤7 years, extent of fibrotic ILD on HRCT ≥10%, and FVC ≥40% predicted.[4]
- Blood samples were taken at baseline and at weeks 4, 24 and 52. Levels of KL-6 were analyzed using a commercially available immunoassay.

Analyses

- Associations between KL-6 levels and clinical variables at baseline, and between changes in KL-6 and changes in clinical variables over 52 weeks, were assessed using Spearman's correlation coefficients (rho).
  - The following clinical variables were assessed:
    - » Age
    - » Lung function (FVC, DLco, SpO_2)
    - » Modified Rodnan skin score
    - » St George's Respiratory Questionnaire total score
  - Correlations with rho ≥0.25 and p<0.05 were considered notable.
- Absolute changes in KL-6 over 52 weeks in the nintedanib and placebo groups were analyzed using a mixed model for repeated measures and restricted maximum likelihood approach.
  - Data were $\log_{10}$ transformed prior to analysis and estimates of change from baseline were back-transformed to provide fold changes.
  - Subgroup analyses were performed for SSc subtype (limited cutaneous SSc [lcSSc] vs diffuse cutaneous SSc [dcSSc]) and use of mycophenolate at baseline (yes vs no).

CONCLUSIONS

- In the SENSCIS trial in patients with SSc-ILD, higher circulating KL-6 was associated with lower DLco % predicted at baseline. No notable correlations were observed between changes in KL-6 and changes in clinical variables over 52 weeks.
- Over 52 weeks, KL-6 levels decreased more in patients treated with nintedanib than placebo. Greater reductions in KL-6 with nintedanib were observed in patients who had lcSSc or who were not taking mycophenolate at baseline.

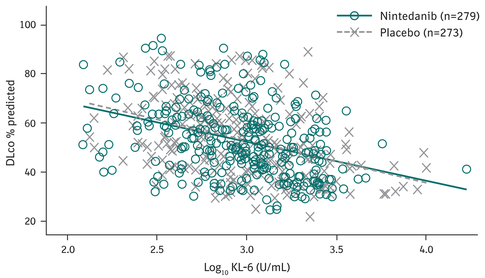
RESULTS

- Of the 576 patients treated in the SENSCIS trial, 559 (97.0%) had data on KL-6 level at baseline.
- Mean (SD) KL-6 levels at baseline were 1216 (1265) U/mL in the nintedanib group (n=282) and 1356 (1398) U/mL in the placebo group (n=277).

Associations between KL-6 and clinical variables at baseline

- There was a weak negative correlation between KL-6 and DLco % predicted at baseline (rho: −0.38 [95% CI: −0.45, −0.31]; nominal p<0.0001). No notable correlations were observed between KL-6 and other clinical variables at baseline.

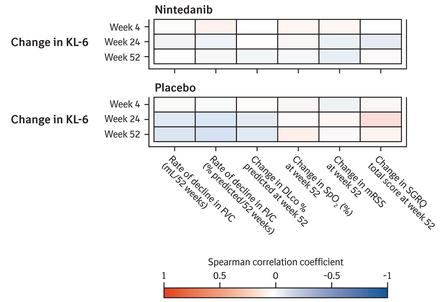
Correlation between KL-6 and DLco % predicted at baseline



Associations between changes in KL-6 and changes in clinical variables over 52 weeks

- No notable correlations were observed between changes in KL-6 and changes in clinical variables over 52 weeks.

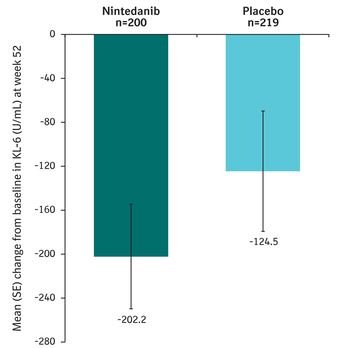
Heat map of Spearman correlation coefficients between changes in KL-6 and changes in clinical variables over 52 weeks



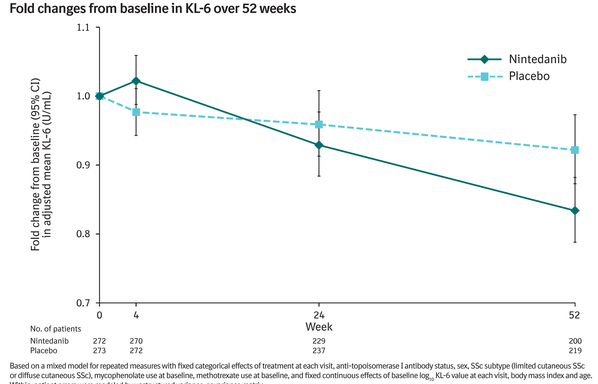
Changes in KL-6 in patients treated with nintedanib versus placebo

- There was a greater decrease in KL-6 in the nintedanib group than in the placebo group. Over 52 weeks, the difference between the nintedanib and placebo groups in fold change in KL-6 was approximately 9%. Greater reductions in KL-6 with nintedanib were observed in patients with lcSSc vs dcSSc and in patients not taking vs taking mycophenolate at baseline.

Absolute change from baseline in KL-6 at week 52



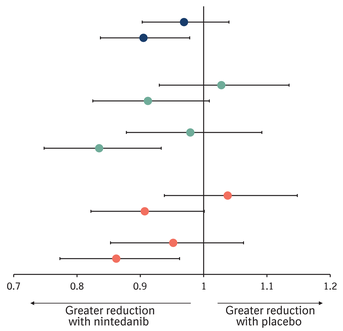
Fold changes from baseline in KL-6 over 52 weeks



Based on a mixed model for repeated measures with fixed categorical effects of treatment at each visit, anti-topoisomerase I antibody status, sex, SSc subtype (limited cutaneous SSc or diffuse cutaneous SSc), mycophenolate use at baseline, methotrexate use at baseline, and fixed continuous effects of baseline $\log_{10}$ KL-6 value at each visit, body mass index and age. Within-patient errors were modeled by unstructured variance-covariance matrix.

Ratios of fold changes from baseline in KL-6 in subgroups by SSc subtype and use of mycophenolate at baseline

	Nintedanib, n	Placebo, n	Ratio of fold changes for nintedanib vs placebo (95% CI)
Overall population			
Week 24	229	237	0.97 (0.90, 1.04)
Week 52	200	219	0.91 (0.84, 0.98)
SSc subtype			
Week 24			
dcSSc	117	118	1.03 (0.93, 1.14)
lcSSc	112	119	0.91 (0.83, 1.01)
Week 52			
dcSSc	100	111	0.98 (0.88, 1.09)
lcSSc	100	108	0.84 (0.75, 0.93)
Mycophenolate use at baseline			
Week 24			
Yes	112	115	1.04 (0.94, 1.15)
No	117	122	0.91 (0.82, 1.00)
Week 52			
Yes	101	108	0.95 (0.85, 1.06)
No	99	111	0.86 (0.77, 0.96)



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