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OP0183

EFFICACY AND SAFETY OF RIOCIQUAT IN PATIENTS WITH EARLY DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS AND INTERSTITIAL LUNG DISEASE (SSC-ILD): RESULTS FROM THE PHASE IIB RISE-SSC STUDY

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Background: Diffuse cutaneous systemic sclerosis (dcSSc) is an autoimmune connective tissue disease characterised by fibrosis and, in some patients, interstitial lung disease (ILD). Riociguat is a soluble guanylate cyclase (sGC) stimulator with vasoactive, anti-proliferative and anti-fibrotic effects. We hypothesised that riociguat may preserve lung function in patients with dcSSc.

Objectives: To evaluate the effect of riociguat on lung function in patients with early dcSSc from the multicentre, randomised, double-blind, placebo-controlled Phase IIB RISE-SSc study (NCT02283762).

Methods: Patients had dcSSc of duration ≤ 18 months, modified Rodnan skin score (mRSS) 10–22 units, forced vital capacity (FVC) $\geq 45\%$ predicted (%pred) and lung diffusion capacity for carbon monoxide (DLCO) $\geq 40\%$ pred at screening. Patients were randomised to riociguat (n=60) or placebo (n=61) in individually adjusted doses of 0.5 mg up to 2.5 mg tid. The primary endpoint was the change in mRSS from baseline to Week 52. Secondary endpoints included change in FVC%pred from baseline to Week 52. Effects on lung function (FVC%pred) were assessed in the overall population and in post-hoc analyses in patients with FVC %pred 50–75% or medical history of ILD at baseline. Between groups, differences were in least-squares [LS] means.

Results: Although the study did not meet its primary endpoint, there was a reduction in mRSS with riociguat vs placebo (–2.34; 95% CI: –4.99 to 0.30; p=0.08). There were no significant differences between treatment groups in the changes in FVC%pred (–0.20; 95% CI, –3.40 to +3.00; p=0.90) or DLCO%pred (2.01; 95% CI: –4.99 to 6.25; p=0.35) which included all patients irrespective of the presence of SSC-ILD. However, differences between riociguat and placebo were observed when patients with SSC-ILD were analysed: At baseline, 11/60 (18%) patients in the riociguat group and 12/61 (20%) in the placebo group had medical history suggesting ILD (SSc-ILD); 11/60 (18%), and 7/61 (11%), respectively, had restrictive lung disease (FVC%pred 50–75%). Results in subgroups were expressed as within-group mean change (SD). In patients with SSC-ILD, the decline in FVC%pred between baseline and Week 52 was smaller in the riociguat group (–2.7[4.0]) than the placebo group (–8.9[13.1]). The changes in DLCO%pred were –0.11 (0.22) and +0.87(0.71), respectively. In patients with restrictive lung disease, FVC %pred decreased by –8.7 (14.0) at Week 52 with placebo but was almost unchanged (+0.7[5.7]) with riociguat. The changes in DLCO%pred were +0.42 (0.85) and –0.27(0.39), respectively.

Patients with SSC-ILD receiving riociguat had lower incidences of adverse events and serious adverse events [82% (n=9) and 9% (n=1) respectively] compared with placebo [92% (n=11) and 25% (n=3) respectively] with no differences between treatment groups in the incidence of respiratory adverse events. No deaths occurred in the SSC-ILD subgroup, and no new safety signals were observed.

Conclusion: These results suggest that in an exploratory analysis, riociguat may be associated with preservation of lung function and good tolerability in patients with dcSSc and evidence of ILD on medical history.

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OP0184

PROFIBROTIC LNCRNA H19X: UNRAVELLING THE EFFECTS ON CHROMATIN REMODELING IN SYSTEMIC SCLEROSIS FIBROBLASTS

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Background: Long noncoding RNAs (lncRNAs) are noncoding transcripts involved in the regulation of gene expression in health and disease. lncRNAs function via different mechanisms either acting cis, regulating the expression of nearby genes, or in trans, modulating the expression of distant genes. We identified a novel TGF β regulated lncRNA, H19X, which was strongly upregulated in a wide variety of fibrotic disorders. Moreover, we were able to demonstrate that H19X is a key driver of myofibroblast formation and extracellular matrix (ECM) overproduction.

Objectives: To define the mode of action of H19X (cis or trans) and to assess H19X function on chromatin rearrangements that may drive myofibroblast differentiation and ECM production.

Methods: The function of H19X was investigated in SSC dermal fibroblasts (n=5) by knocking down H19X with locked nucleic acid oligonucleotides followed by TGF- β stimulation and microarray analysis with Illumina HT-12 arrays. In situ hybridization for H19X was performed using Stellaris FISH probes. Chromatin remodeling was investigated by Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq).

Results: As analyzed by microarray, none of the 16 genes belonging to the same genomic region as H19X locus was affected by its downregulation, indicating that in-cis regulation is not a major mechanism of H19X activity. Cellular localization can give a first indication about lncRNA trans function: FISH staining of SSC fibroblasts stimulated with TGF- β revealed tightly localized nuclear foci in TGF- β treated cells. H19X nuclear localization was confirmed by cell fractionation, where H19X expression was peaking in the nucleus of cells after 6h of treatment with TGF- β . We next hypothesized that H19X nuclear expression might induce chromatin rearrangements. We assessed whether chromatin changes caused by H19X knockdown might be correlated with changes in expression profile seen by microarray. Therefore, we analyzed the differences in the chromatin conformation flanking transcription start sites (TSSs) by ATAC-seq. A clear separation between the two experimental groups (scrambled vs H19X knockdown) was observed and 450 differentially accessible regions were identified (p<0.05, Log2FC>0.5).

After focusing on genes that displayed significant variations and Log2FC>0.5 for both the array and ATAC-seq analysis, eight candidate genes were found both upregulated by microarray and showed increased accessibility at their TSSs by ATAC-Seq. Similarly, three candidate genes were identified as being downregulated by microarray and showed decreased TSS accessibility by ATAC-Seq. These genes included histones HIST1H2BD and HIST1H1C, suggesting a direct regulation of chromatin organization as a mode of action for H19X. Moreover, the cell cycle progression inhibitors FABP3 and PTTG1 were pointing to a role of H19X in proliferation.