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An open-label study to evaluate biomarkers and safety in systemic sclerosis (SSc) patients treated with paquinimod (ABR-215757)

Roger Hesselstrand [1], Jörg H. Distler [2], Gabriela Riemekasten [3], Marie Törngren [4], Helén C. Nyhlén [4], Martin Stenström [4], Fredrik Andersson [4], Helena Eriksson [4], Birgitta Sparre [4], Helén Tuvesson [4], Oliver Distler [5]

[1]Skåne University Hospital, Lund, Sweden, [2]University of Erlangen-Nuremberg, Erlangen, Germany, [3]Charité Universitätsmedizin Berlin, Berlin, Germany, [4]Active Biotech AB, Lund, Sweden, [5]University Hospital Zurich, Zurich, Switzerland

Conclusions

- Effects on biomarkers relevant for SSc were observed during paquinimod treatment:
  - Reduced number of myofibroblasts in the skin
  - Reduced expression of several pro-fibrotic genes in skin
  - Reduced type I IFN-responsive activity in skin and plasma
- Results suggest that the mechanism for paquinimod is via modulation of the innate immune system rather than a direct effect on fibrosis
- Mainly mild and expected Adverse Effects (AEs) reported

Objective

To evaluate changes in disease related biomarkers and safety in SSc patients treated with paquinimod

Background

Paquinimod (ABR-215757) is an oral small molecular compound belonging to a class of quinoline-3-carboxamide derivatives. It is in development for treatment of systemic sclerosis (SSc), with orphan designation granted in the EU and US.

Paquinimod binds S100A9 and inhibits its interaction with the pro-inflammatory receptors RAGE and TLR4 (1). Mechanistic studies show reduced recruitment of myeloid cells into inflammatory sites (2, 3) and paquinimod effectively inhibits disease in various experimental autoimmune/ inflammatory models including an SSc model (**Poster FRI0516**).

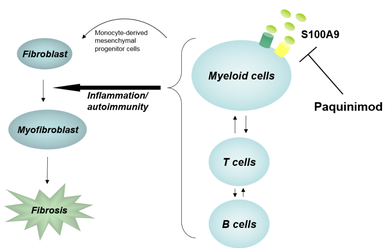


Figure 1. Proposed mechanism of action of paquinimod in SSc

Methods

- Open label, single arm multi-centre study in 9 SSc patients with rapidly progressive disease*
- Daily oral treatment for 8 weeks at 3 mg/day followed by additionally 4 weeks of follow-up
- Biomarkers were measured in blood and biopsies from lesional skin on the forearm, taken at baseline and week 8

* Skin Thickness Progression Rate ≥ 40 (4) or worsening of mRSS within the last 6 months as defined by protocol

Baseline characteristics

Patient Number	Baseline mRSS score*	Duration since onset of Raynaud's phenomenon (months)	Type of SSc-specific antibody
101/F	46	17	RNA polymerase III
102/F	40	10	RNA polymerase III
301/F	19	65	Topoisomerase I
302/F	22	29	Topoisomerase I
303/M	27	3	Topoisomerase I
304/F	35	120	Topoisomerase I
305/M	19	6	RNA polymerase III
401/F	21	18	Topoisomerase I
501/F	25	24	Unknown**

* Maximum mRSS score: 51 ** Unknown - No specific antibodies measured. All patients were ANA-positive.

Biomarkers

Reduced number of myofibroblasts in the skin

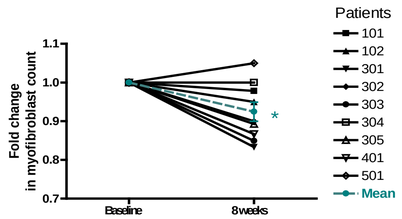


Figure 2. The number of myofibroblast in the skin was reduced in treated patients. Myofibroblasts were characterized by the expression of α-smooth muscle actin (anti-αSMA) in paraffin embedded tissue sections of skin biopsies. The mean reduction was 8% (p=0.023, Wilcoxon signed rank test).

Downregulation of pro-fibrotic genes in the skin

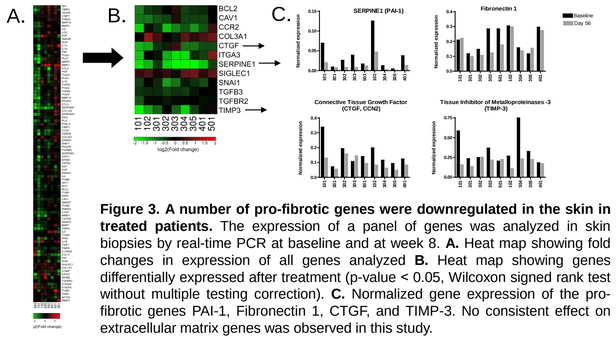


Figure 3. A number of pro-fibrotic genes were downregulated in the skin in treated patients. The expression of a panel of genes was analyzed in skin biopsies by real-time PCR at baseline and at week 8. **A.** Heat map showing fold changes in expression of all genes analyzed **B.** Heat map showing genes differentially expressed after treatment (p-value < 0.05, Wilcoxon signed rank test without multiple testing correction). **C.** Normalized gene expression of the pro-fibrotic genes PAI-1, Fibronectin 1, CTGF, and TIMP-3. No consistent effect on extracellular matrix genes was observed in this study.

Reduced type I IFN activity in skin and plasma

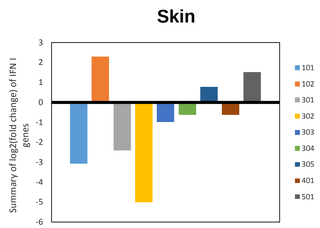


Figure 4. The expression of five type I interferon (IFN) responsive genes (IFI44, IFI44L, IFI6, IFI27 and RSAD2), selected according to Higgs et al (5), were analyzed in skin biopsies by real-time PCR at baseline and at week 8. Composite score of fold changes of the five genes is shown. Although statistical significance was not reached **a reduction of type I IFN activity in the skin was observed in 6 out of 9 patients**.

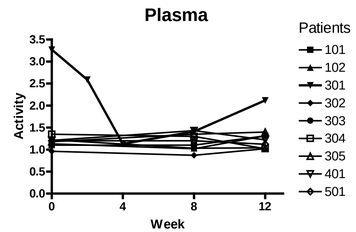


Figure 5. Interferon (IFN) type I activity in plasma was measured by using a functional reporter cell assay (6). **A reduction in type I IFN activity was evident in the patient (301) with elevated plasma activity at baseline.** Reduction of type I IFN activity has also been observed in previous clinical studies in SLE-patients (7).

Reduced level of the chemokine CCL2 in serum

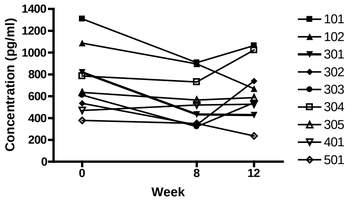
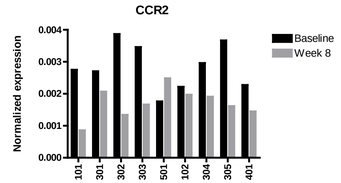


Figure 6. CCL2 in serum was analyzed by using an enzyme-linked immunoassay. **A reduced level of CCL2 at week 8 was evident in 7 out of 9 patients** (p=0,07, Wilcoxon signed rank test).

Reduced level of the chemokine receptor 2 (CCR2)

- Targeting of the myeloid cell compartment -

A.



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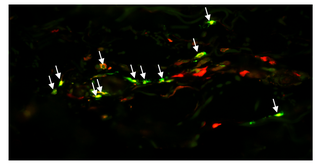

Figure 7. The level of CCR2 gene expression was reduced after treatment. A. Normalized gene expression of CCR2 in skin, the mean fold change was 0.59 (p=0.019, Wilcoxon signed rank test) **B.** Colocalization of CCR2 with CD68-expressing monocytes/macrophages in paraffin embedded tissue section in skin biopsy from one SSc patient.

Disease Activity and Safety

- No change in mRSS and QoL measures were observed in this short-term clinical trial
- Mainly mild and expected AEs reported, all patients (n=9) completed the 8 weeks of treatment
- Most common AEs were arthralgia (n=3) and headache (n=3)
- One severe, serious AE (unlikely related), peripheral ischaemia reported
- Increases, generally transient, in acute phase reactants (C-reactive protein and erythrocyte sedimentation rate) observed

References

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