Conclusion: The newly described antibodies against GPCR, GF and GFR are highly correlated. Associations with morbidity- and mortality-determining organ involvement indicate their possible functional relevance and novel pathophysiological mechanisms. As new biomarkers, some of the ab have prognostic value for SSc; for other manifestations, their value should be evaluated in further studies.

REFERENCES:

- [1] Cabral-Marques, O., Marques, A., Giil, L.M. et al. GPCR-specific autoantibody signatures are associated with physiological and pathological immune homeostasis. *Nat Commun* 9, 5224 (2018). <https://doi.org/10.1038/s41467-018-07598-9>
- [2] Riemekasten G, Philippe A, Näther M, et al. Involvement of functional autoantibodies against vascular receptors in systemic sclerosis *Annals of the Rheumatic Diseases* 2011;70:530-536.
- [3] Weigold, F., Günther, J., Pfeiffenberger, M. et al. Antibodies against chemokine receptors CXCR3 and CXCR4 predict progressive deterioration of lung function in patients with systemic sclerosis. *Arthritis Res Ther* 20, 52 (2018). <https://doi.org/10.1186/s13075-018-1545-8>

Disclosure of Interests: Kristina Sterner: None declared, Césaire J. K. Fouodo: None declared, Inke König: None declared, Axel Künstner: None declared, Hauke Busch: None declared, Harald Heidecke Shareholder of: Owner of Cell-Trend, Anja Schumann: None declared, Antje Müller: None declared, Gabriela Riemekasten: None declared, Susanne Schinke Grant/research support from: UCB sponsors EULAR registration fees

DOI: 10.1136/annrheumdis-2021-eular.1504

OP0245

ANTI-S100A4 MONOCLONAL ANTIBODY TREATMENT AMELIORATES SKIN FIBROSIS IN INFLAMMATORY AND NON-INFLAMMATORY PRE-CLINICAL MODELS OF SYSTEMIC SCLEROSIS

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Background: AX-202 is a monoclonal antibody that inhibits the bioactivity of S100A4. S100A4 is an alarm signal that is released from cells in response to stress or injury and functions as an amplifying mechanism of inflammation and fibrosis in the diseased tissue microenvironment. Previous in vitro studies have found that S100A4 induces fibroblast activation, sensitizes fibroblasts to the effects of TGFβ, drives epithelial-mesenchymal transition, and stimulates monocyte cytokine release (1-3). Moreover, S100A4^{-/-} mice are protected from fibrosis in several animal models (1). In patients with systemic sclerosis (SSc), S100A4 is elevated both in lesional tissue and systemically and correlates with skin involvement, disease activity, and pulmonary function.

Objectives: The aim of this study was to assess the antifibrotic effects of murine AX-202 in two pre-clinical models of SScs reflecting both inflammation-mediated and inflammation non-mediated fibrosis and confirm the in vivo activity of humanized AX-202.

Methods: We first evaluated the effects of murine AX-202 in the bleomycin-induced skin fibrosis model and the tight-skin 1 (Tsk-1) model. In the bleomycin (BLM) model, fibrosis was induced by 3 weeks of BLM s.c. injections followed by 3 weeks of AX-202 treatment in parallel with continued BLM s.c. injections. The control groups included NaCl s.c. injections for 6 weeks, BLM s.c. injections for 6 weeks, or BLM s.c. injections for 3 weeks, followed by NaCl s.c. injections for 3 weeks. Three dosing regimens of AX-202 were tested: 3.75, 7.5, or 12.5 mg/kg i.p. every 3rd day. In the Tsk-1 model, treatment with 7.5 mg/kg i.p. every 3rd day was administered from week 5 until week 10. The control groups included pa mice, Tsk-1 mice, and Tsk-1 mice treated i.p. with isotype IgG. We subsequently evaluated the effects of humanized AX-202 in the model of BLM-induced skin fibrosis in a similar design as used for the murine AX-202 study. Three dosing regimens were tested: 8 mg/kg and 16 mg/kg i.p. every 3rd day and 24 mg/kg i.v. once weekly.

Results: In the BLM model, murine AX-202 (7.5 mg/kg) was effective both in the prevention of progression of pre-established skin fibrosis and in the induction of regression of fibrosis as assessed by the dermal thickness (-55%, p<0.0001 vs BLM for 6 weeks, and -23%, p<0.0001 vs BLM for 3 weeks), myofibroblast count and hydroxyproline content. Murine AX-202 also ameliorated fibrosis in the Tsk-1 model as assessed by the hypodermal thickness (-24%, p=0.01 vs Tsk-1 isotype control), myofibroblast count, and hydroxyproline content. In both models, the antifibrotic effects were associated with a reduction in pSMAD3 expression. Humanized AX-202 was effective in the prevention of progression of pre-established skin fibrosis in all doses tested across all endpoints (dermal thickness, myofibroblast counts, hydroxyproline content). In the two groups treated with

16 mg/kg i.p. and 24 mg/kg i.v., humanized AX-202 also induced regression of fibrosis (-83%, p<0.001, and -61%, p<0.001 vs BLM for 3 weeks, respectively). Both murine and humanized AX-202 were well tolerated in all study groups in both models.

Conclusion: We demonstrate that AX-202 confers potent antifibrotic effects in complementary models of SSc. These results confirm and expand previous data showing that inhibition of S100A4 by AX-202 is a promising potential therapeutic candidate for disease modification in SSc or other fibrotic conditions.

REFERENCES:

- [1] Tomcik M et al. S100A4 amplifies TGF-beta-induced fibroblast activation in systemic sclerosis. *Ann Rheum Dis*. 2015;74(9):1748-55.
- [2] Cerezo LA et al. The metastasis-associated protein S100A4 promotes the inflammatory response of mononuclear cells via the TLR4 signalling pathway in rheumatoid arthritis. *Rheumatology (Oxford)*. 2014;53(8):1520-6.
- [3] Fei F, et al. Role of metastasis-induced protein S100A4 in human non-tumor pathophysiology. *Cell Biosci*. 2017;7:64.

Acknowledgements: The study was supported by Arxx Therapeutics and MHCR 023728.

Disclosure of Interests: Michal Tomčík: None declared, Thuong Trinh-Minh: None declared, Cuong Tran Manh: None declared, Hana Štorkánová: None declared, Lenka Štorkánová: None declared, Ladislav Šenolt: None declared, Jörg Klingelhöfer Employee of: Arxx Therapeutics, Rizwan I Hussain Employee of: Arxx Therapeutics, Jonas Hallén Employee of: Arxx Therapeutics, Jörg H.W. Distler Shareholder of: the stock owner of 4D Science, Consultant of: Actelion, Active Biotech, Anamar, ARXX, Bayer Pharma, Boehringer Ingelheim, Celgene, Galapagos, GSK, Inventiva, JB Therapeutics, Medac, Pfizer, RuiYi and UCB, Grant/research support from: Anamar, Active Biotech, Array Biopharma, ARXX, aTyr, BMS, Bayer Pharma, Boehringer Ingelheim, Celgene, Galapagos, GSK, Inventiva, Novartis, Sanofi-Aventis, RedX, UCB

DOI: 10.1136/annrheumdis-2021-eular.1968

OP0246

PREDICTIVE VALUE OF LABORATORY AND INSTRUMENTAL FINDINGS IN THE VERY EARLY DIAGNOSIS OF SYSTEMIC SCLEROSIS. ROLE FOR CXCL4 CHEMOKINE

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Background: Systemic sclerosis (SSc) is a rare and progressive autoimmune disease, whose diagnosis is difficult in the early stages because of the lack of specific signs and symptoms. Criteria for a Very Early Diagnosis of SSc (VEDOSS) have been proposed to identify those patients affected by undifferentiated connective tissue disease (UCTD) at risk to develop SSc [1]. For the diagnosis of SSc a strict clinical and laboratory follow up is mandatory [2]. CXCL4 chemokine recently proved to be higher in early SSc [3][4][5].

Objectives: Aim of our study was to evaluate at baseline the main clinical-demographic and laboratory parameters in a group of VEDOSS patients, comparing these features during the follow-up, to detect any difference between progressors (P) and non-progressors (NP) into SSc. Furthermore, we dosed plasma levels of CXCL4.

Methods: We included 27 VEDOSS patients, defined by EUSTAR 2011 Criteria and not fulfilling the 2013 ACR/EULAR classification criteria of SSc, attending the Rheumatology Unit of Policlinico Umberto I in Rome from 2009 to 2020. Demographic, laboratory and instrumental features were analyzed, and, after a mean follow-up of 5.7±1.7 years, we compared the P to NP patients. Having obtained written informed consent, blood samples were taken at baseline to measure plasma levels of CXCL4 chemokine using an ELISA assay.

Results: At baseline the 27 VEDOSS patients (mean age 53.2±13.5 years, all females) had ANA positivity in 25 (93%) cases and Raynaud's phenomenon in 25 (93%) cases. In a mean follow-up time of 43.5 ± 23.1 weeks from the first clinical examination, 15 (55%) patients were classified as P into SSc. These P patients showed a significant association with SSc specific antibodies such as anti-Centromere, anti-Scl70 and anti-RNAPIII (p=0.014) as well as with a specific "Scleroderma pattern" at the nailfold capillaroscopy (p=0.022) respect to those NP into SSc. A group of 6 P patients evolved in less than 24 months (mean 19,6 ± 6,8 weeks) and were defined "Fast Progressor". They were also significantly associated with those autoantibodies considered as having a worse prognosis such as anti-Scl70 and anti-RNAPIII (p=0.005), and had a shorter duration of RP (88 vs 189.3 months) and a younger mean age (49.5 vs 55.4 years) respect to "Slow Progressor" (SSc evolving in >24 months). At baseline we detected significantly higher median plasma levels of CXCL4 in the 27 VEDOSS patients compared to 10 healthy subjects (9024±10559 pg/ml versus 348,5±684,3 pg/ml; p=0.0047). We also noticed a trend for lower CXCL4 levels in the "Fast Progressor" than in