Rag2^{-/-}Fra2 tg mice showed no fibrosis or Lin⁺gp38⁺ cell expansion. ECG parameters of Rag2^{-/-}Fra2 tg mice were not changed compared to control mice, indicating that inflammation is necessary to acquire Fra2-driven fibrotic phenotype and defects in the conduction system.

Conclusion: Fra2 overexpression and inflammation foster stromal cell-to-myofibroblast differentiation, leading to cardiac fibrosis and defects of the conduction system. Targeting this process might be a therapeutic strategy for SSc patients with disorders of cardiac involvement.

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OP0187

RITUXIMAB AND CYCLOPHOSPHAMIDE COMPARISON FOR EFFICACY AND SAFETY IN THE PATIENTS WITH SYSTEMIC SCLEROSIS ASSOCIATED WITH INTERSTITIAL LUNG DISEASE

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Background: Cyclophosphamide (CyP) is considered as a drug of choice for the treatment of interstitial lung disease (ILD) in the patients with systemic sclerosis (SSc). However, according to the literature, the use of CyP leads to rather limited and transient improvement of the pulmonary fibrosis. In this context the search for novel, more efficacious agents has been continued, such as attracting much attention rituximab (RTM).

Objectives: To compare the impact of CyP and RTM on SSc clinical manifestation and activity, and the safety of these agents in the open-label prospective non-randomized study.

Methods: 107 patients with the confirmed SSc diagnosis and ILD evidence based on HRCT findings were enrolled into the study. All patients received low-dose and moderate-dose prednisolone regimens. 36 patients (**Group A**) received **parenteral CyP** for 12±6 months at total dose 10.6±5 g (the average age 47±12 years, females 92%, SSc duration 5.0±4.8 years, diffused/localized forms 1.6/1). 71 patients (**Group B**) received **RTM** at total dose 1.43±0.66 g over the follow-up period 13.2±2 months (the average age 46±13 years, females 83%, SSc duration 5.6±4.4 years, diffused/localized forms 1.4/1); to 32 (45%) of them RTM was added to immunosuppressants due to inadequate efficacy of the latter. The time courses FVC(%), modified skin count (mRss, points), activity index (EScSG, points), left ventricle ejection fraction (LVEF,%), mean pulmonary arterial pressure (EchoCG), and cardiac rhythm and conductivity disorders (ECG) were evaluated.

Results: In Groups A and B the therapy was associated with significant decrease in mRss (p=0.009 and 0.001, respectively) and EScSG (p=0.000165 and 0.001, respectively). Increase in LVEF (61.8±7.3 и 63.6±7.3. p=0.02) was observed only in RTM-treated patients.

Evaluation of FVC time course in Groups A and B revealed significant FVC increase (p=0.034 and 0.000045, respectively), with median increment about 5%. In Group A FVC 10% FVC increase was found in the third of the patients thus exceeding respective parameter in Group B (p=0.2). The patient percentage with FVC decrease by ≥10% was similar in both groups.

During the follow-up period no change of the other studied parameters was observed.

The therapy was better tolerated in RTM-treated group: during RTM therapy adverse reactions emerged in significantly lower proportion of the patients (11/14%) compared with CyP-treated group (19/53%), p=0.0000.

Parameters	Group A	Group B
EScSG 1	2.8±2*	2.8±1.8*
M ± SD		
EScSG 2	1.4±1.17*	1.3±1.1*
M ± SD		
mRss 1	11.2±9.8 *	11.3±9.6 *
M ± SD		
mRss 2	7.9±6.8. *	8.0±6.6*
M ± SD		
FVC 1	80.5±20.1*	77.3±20 *
M ± SD		
FVC 2	85.9±20.5*	82.6±21.*
M ± SD		
Δ FVC%	5.4	5.3
	[-0.6; 12.3]	[0.1; 10.2]
FVC increment by ≥10%, n/%	11/31	14/19.7
FVC decrement by ≥10% n/%	2/5.6	4/5.6

Notes: in Parameters column 1 = before treatment, 2 = after treatment; M ± SD = mean value and standard deviation; * = significant difference between the values measured before and after the treatment

Conclusion: Both agents effectively alleviated skin induration and EScSG, and significantly improved FVC. However, CyP use for a year slightly more frequently resulted in clinically significant FVC increase, probably due to low RTM cumulative dose. RTM was better tolerated compared to CyP. The study findings substantiate potential use of anti-B-cell therapy both as a first-line agent for ILD treatment in the patients with SSc, and in the event of CyP inefficacy of poor tolerability, especially in the patients with cardiopathy.

Disclosure of Interests: None declared

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OP0188

PATHOGENICITY OF FUNCTIONAL AUTOANTIBODIES AGAINST AT1R IN A MOUSE MODEL OF SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) is an autoimmune connective tissue disease featured by autoimmunity, fibrosis and vasculopathy. Although many autoantibodies have been detected in the sera of patients with SSc, it is not clear whether they play a role in the pathogenesis of disease. It has been reported that autoantibodies against the angiotensin-II receptor type 1 (AT1R) are present in the sera of SSc patients and are associated with several clinical symptoms of the disease, suggesting that these autoantibodies may act as pathogenic drivers. Recently, our group has developed a novel mouse model for SSc by immunizing mice with human AT1R (hAT1R). From this model we were able to generate functional monoclonal antibodies agonizing AT1R.

Objectives: In the current study, we aim to clarify, whether B cells and antibodies directed against AT1R are involved in the pathogenesis of experimental SSc *in vivo*.

Methods: To investigate the role of B cells in the hAT1R-induced mouse model of SSc, we immunized B-cell deficient mice with hAT1R. Nine weeks after the first immunization, mice were sacrificed and sera and tissues were collected for further evaluation. To investigate the pathogenicity of anti-AT1R antibodies in the disease, monoclonal autoantibodies against hAT1R were applied to the ear of C57Bl/6 mice by single or repetitive injection. Mice were sacrificed 24 hours or 14 days after the first injection for single and repeated application, respectively, and ear and lung tissues were collected for further evaluation.

Results: Compared to the wild type C57Bl/6 mice, hAT1R-immunized B-cell deficient mice were resistant against experimental SSc with regard to autoantibody production, inflammation in the lung and skin, and skin fibrosis. Furthermore, both single and repetitive injection of monoclonal antibodies against hAT1R induced inflammation in ears of mice. Despite this local effect, repetitive injection of anti-AT1R monoclonal antibodies provoked also inflammation in the lung of mice.

Conclusion: Our data demonstrate that i) B cells are indispensable for the pathogenesis of the hAT1R-induced mouse model for SSc and ii) monoclonal antibodies against hAT1R can induce inflammation in mice. Therefore, our results support a role of autoantibodies against AT1R in the pathogenesis of SSc.

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