CXCL4 was effectively inhibited in activated PRP treated with the sGC activator BI 685509 whereas minimal inhibition was observed in samples treated with the sGC stimulator Riociguat. Inhibition of CXCL4 production in activated human platelet rich plasma treated with the sGC activator BI 685509

Figure 1.

Conclusion: Collectively, these results point to the use of the sGC activator BI 685509 as a novel treatment for SSC and suggests potential superior effects vs. sGC stimulators like Riociguat in this autoimmune disease.

REFERENCES:

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POS0621

EFFECTS OF B CELL DEPLETION BY CD19-TARGETED CAR-T CELLS IN A MURINE MODEL OF SYSTEMIC SCLEROSIS

Keywords: Animal models, Systemic sclerosis

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Background: Chimeric antigen receptor (CAR)-T cells represent a potentially curative strategy for B cell malignancies. A first successful clinical experience has been reported in systemic lupus erythematosus, suggesting that CD19-targeted CAR-T cell transfer was feasible and tolerable [1].

Objectives: Since systemic sclerosis (SSc) and SLE are both severe diseases sharing B cell implication in their pathogenesis, we aimed at assessing the efficacy and tolerance of two B cell depletion strategies, including one with CD19-targeted CAR-T cells, in a preclinical model mimicking the severe lung damages observed in SSc.

Methods: B cell depletion strategies were evaluated in the Fra-2 transgenic (Tg) mouse model. We considered a first group of 16 untreated mice, a second group of 15 mice receiving a single intravenous (IV) dose (50 µg) of anti-CD20 monoclonal antibody (mAb) at day 1 and a third group of 8 mice receiving 50 µg anti-CD20 mAb IV at day 1 followed by the IV injection of 2×10⁶ CD19-targeted CAR-T cells at day 3. After 6 weeks, different validated markers of inflammation, lung fibrosis and pulmonary vascular remodeling were assessed.

Results: Following treatment with anti-CD20 mAb, CD19 expression was significantly decreased in peripheral blood and lesional lungs of Fra-2 Tg mice by 59% (p<0.001) and 40% (p=0.019), respectively, compared to control Fra-2. B cell depletion was even more pronounced in mice treated with CD19-targeted CAR-T cells: CD19 expression was decreased in peripheral blood and lungs of Fra-2 Tg mice by 92% (p<0.001) and 85% (p<0.001), respectively, compared to control Fra-2. CAR-T cell infusion increased mortality in Fra-2 Tg mice (Figure 1A). In line with the above findings, mice receiving CD19-targeted CAR-T cells displayed a significant increase in lung density (mean difference of 55±28 Hounsfield Units, p=0.038) (Figure 1B-C) and a marked reduction of functional residual capacity (mean difference of 25±9%, p=0.041) as compared to control Fra-2 when assessed by chest micro-CT imaging. CAR-T cell infusion significantly increased lung collagen content (mean difference of 11.9±4.4 µg/mL, p=0.020) (Figure 1D), histological fibrosis score (mean difference 1.74±0.48, p=0.002) (Figure 1E-F) and right ventricular systolic pressure mean difference 8.52±2.70 mmHg, p=0.013) (Figure 1G). CAR-T cells accumulated in lesional lungs and promoted T infiltration and activation: a significant increase of CD4+ effector memory T cells was observed in CD19-targeted CAR-T cell-treated Fra-2 Tg mice compared to Fc control Fra-2 Tg mice (mean difference of 52±7%, p=0.001). Moreover, the fraction of CD69 and PD1+expressing cells was significantly increased within the CD4+ and CD8+ subsets in the lung of CD19-targeted CAR-T cell-treated Fra-2 Tg mice. Treatment with anti-CD20 mAb in monotherapy had no impact on lung inflammation-driven fibrosis and pulmonary hypertension.

Conclusion: B-cell therapies failed to show efficacy in the Fra2 transgenic mice. The exacerbated Fra-2 lung inflammatory burden stimulated accumulation and expansion of activated CD19-targeted CAR-T cells, secondarily inducing T-cell activation and systemic inflammation, finally leading to disease worsening.

REFERENCE:

Figure 1. Effects of B cell depletion by anti-CD20 mAb in association or not with CD19-targeted CAR-T cells in Fra-2 Tg mice.

A. Survival curves of Fra-2 mice after anti-CD20 mAb and CD19-targeted CAR-T cell infusion. Significance was determined by log rank (Mantel-Cox; p=0.031). B. Representative pictures of micro-computed tomography. C. Y-axis shows the lung density at micro-computed tomography. D. Y-axis shows the content of collagen in a lung fragment (µg) evaluated by Sircol assay. E. Representative H&E 4-µm lung sections (magnification × 8). F. Y-axis shows the Ashcroft histological score. G. Y-axis shows the right ventricular systolic pressure (RVSP). All data are shown as the mean ± SEM. * p<0.05, ** p<0.01, ***p<0.001 determined by one-way analysis of variance with Tukey’s post hoc test.

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Disclosure of Interests: None Declared.

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POS0622

BIFIDOBACTERIUM LONGUM RAPO AMELIORATES DERMAL AND PULMONARY FIBROSIS THROUGH THE MODULATION OF GUT MICROBIOTA AND IMMUNE RESPONSE IN BLEOMYCIN-INDUCED SYSTEMIC SCLEROSIS IN MICE

Keywords: Systemic sclerosis, -omics, Lungs