Systemic Sclerosis

When assessed by chest micro-Ct imaging, Fra-2 mice treated with abatacept displayed a 12% decrease in lung density (10 mg/mL, p=0.037) as well as an increase in functional residual capacity as compared to IgG1-treated mice (16% for 1 mg/mL, p=0.001% and 14% for 10 mg/mL, p=0.005%). Consistent with these results, abatacept 10 mg/L decreased histological fibrosis score (Ashcroft score) as well as hydroxyproline content by 79% (p=0.009) and 31% (p=0.044) respectively, as compared to IgG1-treated mice.

Treatment with abatacept 10 mg/mL markedly reduced protein levels in the lesional lungs of Fra-2 mice of the fibrogenic markers MCP1 by 79% (p=0.043) and osteopontin by 87% (p=0.039). Levels of TGF-β were also reduced with abatacept (61% for 1 mg/mL, p=0.037% and 69% for 10 mg/mL, p=0.013). Further, abatacept decreased M1 and M2 macrophages infiltration as well as T-cell proliferation in the lesional lungs of Fra-2 mice. Upon treatment with abatacept a reduction of right ventricular systolic pressure (28.1±1.5 mmHg vs 36.0±5.1 mmHg, p=0.037 for 10 mg/mL) and right ventricular hypertrophy (0.29±0.01 vs 0.35±0.01, p=0.007 and 28±0.01% vs 0.33±0.01% for 10 mg/mL, p=0.037) was observed compared to IgG1-treated mice. Consistent with these findings, abatacept 10 mg/mL was associated with significant decrease in percent medial wall thickness and numbers of muscularized distal pulmonary arteries.

Conclusions: We demonstrate that treatment with abatacept improves digestive involvement, prevents lung fibrosis and attenuates PH in SSc pre-clinical mice models. These findings suggest that abatacept might be an appealing therapeutic approach for severe internal organ involvement in SSc beyond its already demonstrated effects on skin fibrosis.

REFERENCE:

Disclosure of Interest: None declared

Wednesday, 13 June 2018: New driving molecules in systemic sclerosis

OP0089 ABATACEPT IS EFFECTIVE IN EXPERIMENTAL DIGESTIVE AND LUNG TISSUE FIBROSIS

G Boletti1,2, C Guignabert4,5, S Pezet2, A Cauvez2, J Sadone6, L Tu3,4, C Nicco1, C Gobeaux1, F Batteux1, Y Allain1,2, J Avouac1,2.

Methods: Abatacept was given in the chronic graft-versus-host disease (cGvHD) model which is characterised by non-specific interstitial pneumonia and pulmonary hypertension (PH), mimicking severe SSc organ damage. In the Fra-2 mouse model which is characterised by non-specific interstitial pneumonia and pulmonary vascular remodelling leading to PH. Mice were treated by intraperitoneal injections of abatacept (1 mg/mL in the cGvHD model for 6 weeks; 1 mg/mL or 10 mg/mL in the Fra-2 mouse model for 4 weeks) or human IgG1 (100 mg) used as a negative control.

Results: In the cGvHD model, treatment of allogeneically mice with abatacept led to a significant reduction of alanine aminotransferase (24%, p=0.014) and aspartate aminotransferase levels (61%, p<0.001). Pathological analysis of colon revealed decreased inflammatory infiltrates and destruction of crypts in allogeneically mice receiving abatacept.

Conclusions: Although irAE occurrence is not required for treatment benefit, it strongly associates with overall survival. Optimal multidisciplinary management of irAEs, including rheumatologists when needed, is worthwhile to maintain beneficial responses.

Disclosure of Interest: None declared

OP0090 MITOCHONDRIAL DNA MUTATIONS AND RESPIRATORY CHAIN DYSFUNCTION IN LUNG FIBROSIS OF SYSTEMIC SCLEROSIS


Background: Recent data have implemented reactive oxygen species (ROS) in the etiology of interstitial lung disease (ILD) in systemic sclerosis. Objectives: To investigate a role of large-scale somatically acquired mutations in mitochondrial DNA (mtDNA) and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.

Methods: Lung biopsies from patients with diaplastic interstitial pneumonitis and systemic sclerosis (n=31) were analysed for mitochondrial functions and compared with biopsies from 13 healthy controls (HC). From 17 patients we identified simultaneous biopsies from the upper and lower lung.

Results: Malondialdehyde as a marker of ROS formation was increased in ILD patients with diaplastic interstitial pneumonitis and systemic sclerosis (n=31) were analysed for mitochondrial functions and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.

Objective: To investigate a role of large-scale somatically acquired mutations in mitochondrial DNA (mtDNA) and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.

Methods: Lung biopsies from patients with diaplastic interstitial pneumonitis and systemic sclerosis (n=31) were analysed for mitochondrial functions and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.

OP0089 ABATACEPT IS EFFECTIVE IN EXPERIMENTAL DIGESTIVE AND LUNG TISSUE FIBROSIS

G Boletti1,2, C Guignabert4,5, S Pezet2, A Cauvez2, J Sadone6, L Tu3,4, C Nicco1, C Gobeaux1, F Batteux1, Y Allain1,2, J Avouac1,2.

Methods: Abatacept was given in the chronic graft-versus-host disease (cGvHD) model which is characterised by non-specific interstitial pneumonia and pulmonary hypertension (PH), mimicking severe SSc organ damage. In the Fra-2 mouse model which is characterised by non-specific interstitial pneumonia and pulmonary vascular remodelling leading to PH. Mice were treated by intraperitoneal injections of abatacept (1 mg/mL in the cGvHD model for 6 weeks; 1 mg/mL or 10 mg/mL in the Fra-2 mouse model for 4 weeks) or human IgG1 (100 mg) used as a negative control.

Results: In the cGvHD model, treatment of allogeneically mice with abatacept led to a significant reduction of alanine aminotransferase (24%, p=0.014) and aspartate aminotransferase levels (61%, p<0.001). Pathological analysis of colon revealed decreased inflammatory infiltrates and destruction of crypts in allogeneically mice receiving abatacept.

Conclusions: Although irAE occurrence is not required for treatment benefit, it strongly associates with overall survival. Optimal multidisciplinary management of irAEs, including rheumatologists when needed, is worthwhile to maintain beneficial responses.

Disclosure of Interest: None declared

OP0090 MITOCHONDRIAL DNA MUTATIONS AND RESPIRATORY CHAIN DYSFUNCTION IN LUNG FIBROSIS OF SYSTEMIC SCLEROSIS


Background: Recent data have implemented reactive oxygen species (ROS) in the etiology of interstitial lung disease (ILD) in systemic sclerosis. Objectives: To investigate a role of large-scale somatically acquired mutations in mitochondrial DNA (mtDNA) and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.

Methods: Lung biopsies from patients with diaplastic interstitial pneumonitis and systemic sclerosis (n=31) were analysed for mitochondrial functions and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.

OP0090 MITOCHONDRIAL DNA MUTATIONS AND RESPIRATORY CHAIN DYSFUNCTION IN LUNG FIBROSIS OF SYSTEMIC SCLEROSIS


Background: Recent data have implemented reactive oxygen species (ROS) in the etiology of interstitial lung disease (ILD) in systemic sclerosis. Objectives: To investigate a role of large-scale somatically acquired mutations in mitochondrial DNA (mtDNA) and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.

Methods: Lung biopsies from patients with diaplastic interstitial pneumonitis and systemic sclerosis (n=31) were analysed for mitochondrial functions and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.

OP0090 MITOCHONDRIAL DNA MUTATIONS AND RESPIRATORY CHAIN DYSFUNCTION IN LUNG FIBROSIS OF SYSTEMIC SCLEROSIS


Background: Recent data have implemented reactive oxygen species (ROS) in the etiology of interstitial lung disease (ILD) in systemic sclerosis. Objectives: To investigate a role of large-scale somatically acquired mutations in mitochondrial DNA (mtDNA) and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.

Methods: Lung biopsies from patients with diaplastic interstitial pneumonitis and systemic sclerosis (n=31) were analysed for mitochondrial functions and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.

OP0090 MITOCHONDRIAL DNA MUTATIONS AND RESPIRATORY CHAIN DYSFUNCTION IN LUNG FIBROSIS OF SYSTEMIC SCLEROSIS


Background: Recent data have implemented reactive oxygen species (ROS) in the etiology of interstitial lung disease (ILD) in systemic sclerosis. Objectives: To investigate a role of large-scale somatically acquired mutations in mitochondrial DNA (mtDNA) and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.

Methods: Lung biopsies from patients with diaplastic interstitial pneumonitis and systemic sclerosis (n=31) were analysed for mitochondrial functions and consecutive respiratory chain dysfunction as a trigger for ROS formation and lung fibrosis.
Background: Systemic sclerosis (SSc), amongst autoimmune rheumatic disorders, shows a heterogeneous and unpredictable course from stable/mild involvement to progressive/late stage, when irreversible multorgan fibrosis occurs. Early SSc diagnosis remains a clinical challenge; a delay in diagnosis leads, in turn, to therapy delay and more severe patient disability. Earliest vascular immune-mediated alterations are critical in SSc, which, indeed, has been referred to as a ‘vascular’ disease. Recognition of biomarker(s) involved in earliest vascular derangements might represent a tool potentially useful for therapeutic approach. Blood level of chemokines IFN-γ-inducible protein 10 (IP-10/CXCL10) and IFN-inducible T cell alpha chemoattractant (I-TAC/CXCL11), both involved in endothelial dysfunction, has been shown to associate with worse SSc prognosis.

Objectives: To investigate possible modifications of circulating CXCL10/CXCL11 in the shift from very early diagnosis of SSc (VEDOSS), when vasculopathy and fibrosis are still at very low degree, to definite SSc. Associations between chemokines and capillaroscopic pattern, autoantibody positivity were evaluated.

Methods: Multiplatform luminex technology was used to analyse CXCL10/CXCL11 in total 62 sera, 34 from VEDOSS and 28 from SSc patients, fulfilling the new ACR/EULAR 2013 classification criteria; none of the subjects were treated for SSc. Within VEDOSS group, we selected 29 sera of subjects with follow up (40.67±5.46 months) and, for each patient of this subcohort, chemokine levels were assessed at follow up (T1) and compared with basal level (T0). Appropriate tests were used for sample distribution and statistical analysis.

Results: Serum CXCL10/CXCL11 were significantly lower in all VEDOSS (CXCL10: 236.00±40.09 pg/ml; CXCL11: 38.00±6.97 pg/ml) vs all SSc sera (CXCL10: 633.90±97.60 pg/ml; CXCL11: 267.70±76.10 pg/ml; p<0.001 and p<0.01, respectively). Moreover, in VEDOSS subcohort, basal chemokine values (T0) were significantly higher (p<0.001) in sera of subjects who subsequently shifted to SSc (CXCL10: 237.34±27.34 pg/ml; CXCL11: 45.12±7.18 pg/ml) vs subjects not developing SSc (CXCL10: 633.90±97.60 pg/ml; CXCL11: 267.70±76.10 pg/ml; p<0.001 and p<0.01, respectively). In VEDOSS subcohort, basal chemokine levels were higher in SSc as compared to healthy subjects where it is clearly expressed.12

Conclusions: CXCL10/CXCL11 blood level measurement in VEDOSS patients potentially represents a noninvasive biomarker associated with vascular modifications – as shown by capillaroscopic pattern – predictive of SSc.

REFERENCES:

Disclosure of Interest: None declared


Abstract OP0091 – Figure 1. Mitochondrial parameters in lung biopsies simultaneously obtained in both, upper and lower lungs, of patients with fibrotic lungs. Lines connect values of the same patients.

Conclusions: Our data support a role of mtDNA-mutations and consecutive respiratory chain dysfunction as a trigger and perpetuator of ROS formation in both, idiopathic interstitial pneumonitis and ILD of patients with systemic sclerosis.

Disclosure of Interest: None declared