(n=80), endocrine irAEs (n=67), rheumatic (n=49) and pulmonary irAEs (n=17). So far, evaluation of tumour response was available for 551 patients, including 190 responders (complete response n=36 and partial response n=154), 192 patients with stable disease and 169 with progressive disease. 122/189 responders (65%) and 107/192 with stable disease (56%) experienced at least one irAE while reported only in 40/169 non responders (24%). Patients experiencing at least one irAE had an increased overall survival (median of 1169 days versus 224 days, $p<0.0001$, figure 1), without statistical difference according to organ system. Of note, there was also no statistical difference regarding tumour response or irAEs occurrence among the 9.4% of patients with preexisting inflammatory or autoimmune disease (60/636).

Abstract OP0088 – Figure 1. Overall survival according to irAE occurrence

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

DOI: 10.1136/annrheumdis-2018-eular.3783

WEDNESDAY, 13 JUNE 2018:

New driving molecules in systemic sclerosis

OP0089 ABATACEPT IS EFFECTIVE IN EXPERIMENTAL DIGESTIVE AND LUNG TISSUE FIBROSIS

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Background: Cytotoxic T-lymphocyte associated molecule-4 (CTLA-4) is an immunoregulatory membrane receptor resulting in the down-regulation of T-cell responses. A previous report showed that abatacept (CTLA4-Ig) prevented and induced regression of inflammation-driven dermal fibrosis in two different mouse models of systemic sclerosis (SSc).¹

Objectives: We aimed to assess the effects of abatacept in two complementary mouse models reflecting digestive involvement, lung fibrosis and pulmonary hypertension (PH), mimicking severe SSc organ damage.

Methods: Abatacept was given in the chronic graft-versus-host disease (cGvHD) mouse model, characterised by digestive involvement, and 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.

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 0.33 ± 0.010 , $p=0.037$ and 29 ± 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.

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Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.2545

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

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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 of ROS formation and lung fibrosis.

Methods: Lung biopsies from patients with idiopathic 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 had simultaneous biopsies from the upper and lower lung.

Results: Malondialdehyde as a marker of ROS formation was increased in ILD ($p=0.007$). The median proportion of mtDNA containing the pathogenic common deletion was 22.5% in ILD patients, compared to 0% in HC. This translated into a 3.8-fold diminishment of mtDNA-encoded cytochrome c-oxidase (COX2), but not nucleus-encoded (COX4) respiratory chain subunits in ILD compared to controls ($p<0.0001$) and a 33% diminishment of mtDNA-encoded cytochrome c-oxidase activity ($p=0.001$ vs controls). In all patients, the more fibrotic lower lungs had significantly more malondialdehyde ($p=0.0004$), mtDNA deletions ($p=0.0006$), and cytochrome c-oxidase dysfunction ($p=0.0003$) than the less-fibrotic upper lung counterparts. Conversely, lower lungs had significantly less ($p=0.0003$) mtDNA-encoded COX2 subunits in comparison to non-mtDNA-encoded COX4 subunits (figure 1). There was no association of any mitochondrial parameter with smoking status or age, and no difference between biopsies from patients with systemic sclerosis and non-specific interstitial pneumonitis.

Abstract OP0090 – 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

DOI: 10.1136/annrheumdis-2018-eular.2960

OP0091 CXCL10/CXCL11 SERUM MEASUREMENT AS POTENTIAL PREDICTOR OF SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc), amongst autoimmune rheumatic disorders, shows a heterogeneous and unpredictable course from stable/mild involvement to progressive/late stage, when irreversible multiorgan fibrosis occurs.¹ Early SSc diagnosis remains a clinical challenge; a delay in diagnosis leads, in turn, to therapy delay and more severe patient disability.²⁻³ Earliest vascular immune-mediated alterations are critical in SSc, which, indeed, has been referred to as a 'vascular' disease.⁴ Recognition of biomarker(s) involved in earliest vascular derangements might represent a clinical 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.^{5,6}

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: Multiplexed 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 $\pm$ 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 $\pm$ 40.09 pg/ml; CXCL11: 38.00 $\pm$ 6.97 pg/ml) vs all SSc sera (CXCL10: 633.90 $\pm$ 97.60 pg/ml; CXCL11: 267.70 $\pm$ 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 $\pm$ 27.34 pg/ml; CXCL11: 45.12 $\pm$ 7.18 pg/ml) vs subjects not developing SSc (CXCL10: 140.06 $\pm$ 16.17 pg/ml; CXCL11: 20.17 $\pm$ 4.06 pg/ml). Sera analysed at follow up (T1) showed a significant increase of both chemokines vs T0 values only in patients who developed SSc (CXCL10: 536.18 $\pm$ 54.98 pg/ml; CXCL11: 250.21 $\pm$ 86.53 pg/ml; p<0.001). CXCL10/CXCL11 retained significant predictive values for SSc development with 165 pg/ml and 29.67 pg/ml cut-off values, respectively, as shown by receiver operating characteristic (ROC) analysis. Significant correlation of CXCL10/CXCL11 with nailfold capillaroscopic pattern was observed.

Chemokine serum level in VEDOSS and SSc patients and predictive chemokine value in VEDOSS subjects. A. Multiplex cytokine assay showed circulating CXCL10 higher in sera of SSc patients vs. VEDOSS subjects (SSc: 633.90 $\pm$ 97.60 pg/ml; VEDOSS: 236.00 $\pm$ 40.09 pg/ml). B. CXCL11 circulating levels were higher in SSc as compared with VEDOSS subjects (SSc: 267.70 $\pm$ 76.10 pg/ml; VEDOSS 38.00 $\pm$ 6.97 pg/ml); *p<0.01; **p<0.001. ROC curves showed that CXCL10 and CXCL11 retained good predictive power to identify VEDOSS subjects later shifting to SSc. C. Serum level of CXCL10 $\geq$ 165 pg/ml was identified as a cut-off value; the area under the ROC curve (AUC) was 0.70 (95% confidence interval-0.52-0.94, p<0.01) with 0.75 sensitivity and 0.70 specificity D. CXCL11 $\geq$ 29.67 pg/ml was the cut-off value; AUC resulted 0.80 (95% confidence interval-0.67-0.99, p<0.01) with a sensitivity of 0.75 with and a specificity of 0.88.

Correlations	Rho (p)	P
CXCL10/CXCL11	0.6 (Pearson)	<0.0001
CXCL10/NVC	0.6 (Spearman)	<0.0001
CXCL11/NVC	0.5 (Spearman)	<0.001

Serum CXCL10 and CXCL11 concentrations also significantly correlated (Pearson's Rho p=0.6; <0.0001) and correlated with capillaroscopic pattern (Spearman's p 0.6 and 0.5, respectively; p<0.001 and p<0.0001). NVC=nailfold videocapillaroscopy

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.

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Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.3697

OP0092 DECREASED DICKKOPF-1 EXPRESSION IN CLINICALLY UNINVOLVED SKIN FROM PATIENTS WITH SYSTEMIC SCLEROSIS

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Background: Evidence suggests that the Wnt pathway is a critical mediator of the fibrotic process. The activity of the pathway is tightly regulated by several soluble inhibitors such as Dickkopf-1 (Dkk-1). We, among others, have previously shown that Dkk-1 is absent from scleroderma skin in sharp contrast to skin from healthy subjects where it is clearly expressed.^{1,2}

Objectives: Up until now, Dkk-1 skin expression has only been assessed in established fibrosis, in biopsies obtained from clinically involved areas. We aimed to assess whether the striking lack of Dkk-1 skin expression is also evident in a)