Increased risk of ischaemic heart disease and immune-related adverse events of cancer

Conclusions: Exploratory analyses from the VISUAL III trial demonstrated that efficacy in adalimumab-treated patients was sustained or improved through 78 weeks of treatment, irrespective of IMM use. AE rates were consistent with previous VISUAL trials, although numerically higher rates for a subset of AEs were observed in patients taking IMM.

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Background: Immune checkpoint inhibitors (ICI) represent a new standard of care for the treatment of selected advanced cancers and are still being investigated in many other tumour types. By enhancing the T-cell activation, a unique spectrum of inflammatory side effects has emerged, also known as immune-related adverse events (irAEs), including various well-described rheumatic manifestations. Data regarding the association between irAEs and patient outcomes are conflicting.

Objectives: To evaluate the incidence and characteristics of irAEs in patients receiving ICI, as well as the correlation with tumour response and patient survival.

Methods: This was a single-centre prospective observational study including all cancer patients receiving ICI. The occurrence of irAEs, tumour response and patient outcomes were assessed on a regular basis. Overall survival has been considered from the start of ICI.

Results: From May 2015 to September 2017, 636 patients (70% male, mean age 64 years) have been included in this cohort while receiving anti PD-1 (n=435), anti PD-L1 (n=66) or anti CTLA-4 (n=3) as single agent or as sequential (n=100) or combined (n=32) therapies. Cancer types were mainly melanoma (n=293), non-small cell lung cancer (n=150) and renal carcinoma (n=83). Overall, 274/633 patients (43%) experienced irAEs, either 1 irAE (n=162), 2 irAEs (n=78), 3 irAEs (n=34), with a median exposure time of 52 days (IQR 30–96). 18/633 (2.8%) patients had an irAE requiring hospitalisation, and 6/633 (0.9%) died due to irAE.

Conclusions: ICI is associated with worse prognosis among FMF patients compared to controls. Proper screening methods are recommended to assess whether early identification and treatment may improve life expectancy.

REFERENCES:

Disclosure of Interest: None declared


OP0088 IMMUNE-RELATED ADVERSE EVENTS OF CANCER IMMUNOTHERAPY – WHEN INFLAMMATORY SIDE EFFECTS ARE ASSOCIATED WITH SURVIVAL: A SINGLE-CENTRE PROSPECTIVE COHORT STUDY

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Background: Immune checkpoint inhibitors (ICI) represent a new standard of care for the treatment of selected advanced cancers and are still being investigated in many other tumour types. By enhancing the T-cell activation, a unique spectrum of inflammatory side effects has emerged, also known as immune-related adverse events (irAEs), including various well-described rheumatic manifestations. Data regarding the association between irAEs and patient outcomes are conflicting.

Objectives: To evaluate the incidence and characteristics of irAEs in patients receiving ICI, as well as the correlation with tumour response and patient survival.

Methods: This was a single-centre prospective observational study including all cancer patients receiving ICI. The occurrence of irAEs, tumour response and patient outcomes were assessed on a regular basis. Overall survival has been considered from the start of ICI.

Results: From May 2015 to September 2017, 636 patients (70% male, mean age 64 years) have been included in this cohort while receiving anti PD-1 (n=435), anti PD-L1 (n=66) or anti CTLA-4 (n=3) as single agent or as sequential (n=100) or combined (n=32) therapies. Cancer types were mainly melanoma (n=293), non-small cell lung cancer (n=150) and renal carcinoma (n=83). Overall, 274/633 patients (43%) experienced irAEs, either 1 irAE (n=162), 2 irAEs (n=78), 3 irAEs (n=34), with a median exposure time of 52 days for the first irAE. Dermatological irAEs were by far the most frequent (n=160), followed by digestive
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


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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 67% (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±1.5 mmHg vs 36±0.5 mmHg, p=0.037 for 10 mg/mL) and right ventricular hypertrophy (0.29±0.01 vs 0.35±0.01, p=0.037 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 mouse 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


OP0090 MITOCONDRIAL 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 diaphasic 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 (COX), but not COX2, compared to HC. Compared to HC, the median proportion of mtDNA-containing the pathogenic common deletion was 22.5% in ILD patients, compared to 0% in HC.

Conclusion: We demonstrated effects on skin fibrosis.