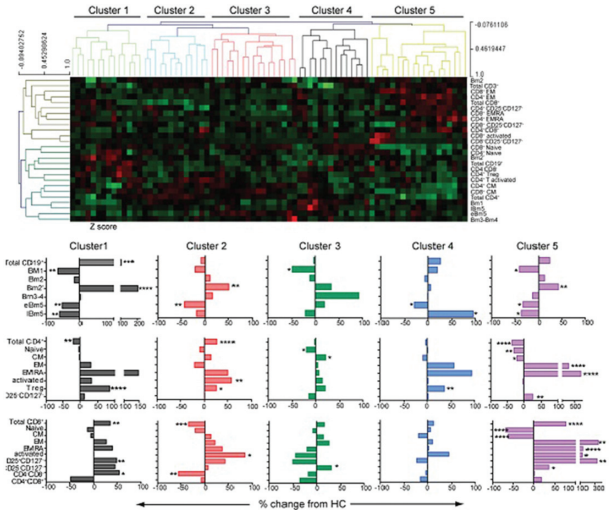

Conclusions: The results demonstrated that immune cell biomarkers could be used to re-classify patients in a manner that reflects their underlying immunopathogenesis. Characterisation of a patient's endotype could lead to better stratification of patients for selection of therapeutic targets in clinical trials.

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THU0024 TREATMENT WITH IMMUNE CHECKPOINT INHIBITORS AND THE BREAK OF B-CELL TOLERANCE TO AUTOANTIGENS

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Background: The field of autoimmunity may benefit from the knowledge gained by studying immune checkpoint inhibitors. These agents, which have proven remarkably successful in treating various types of cancer, inhibit negative costimulatory signals to T-cells, thereby enhancing anti-tumour T-cell responses. This can come at the cost of severe immune-related adverse effects (irAEs) including arthritis, colitis, endocrine diseases, hepatitis, and various skin abnormalities. However, it is currently unknown to which extent or to which autoimmune disease-associated autoantigens autoantibodies are formed (as a reflection of breaking of tolerance to self-antigens) under checkpoint inhibitor therapy and whether this is associated with irAEs.

Objectives: To investigate whether patients treated with immune checkpoint inhibitors develop autoantibodies, and whether this trait is associated with irAEs.

Methods: In pre- and (12 weeks) post-treatment sera of 133 patients with Stage III or IV melanoma treated with ipilimumab (anti-CTLA-4), we determined antibodies associated with rheumatoid arthritis (RF IgM, anti-CCP2), autoimmune hepatitis (anti-smooth muscle, anti-mitochondria, anti-liver-kidney-microsome), thyroiditis (anti-thyroid peroxidase (TPO), anti-thyroglobulin (TG)), Coeliac's disease (anti-endomysium, anti-gliadine IgG), adrenal insufficiency (anti-adrenal cortex), and autoimmune connective tissue diseases (anti-nuclear antibodies, anti-dsDNA, anti-ENA, and specific ENA tests: anti-SSA, anti-SSB, anti-RNP70, anti-U1RNP, anti-Sm, anti-Jo1, anti-CENP, anti-PMSCL, anti-RNA polymerase 3, anti-Scl70). We used McNemar's exact test for paired data to test whether autoantibody positivity increased post-treatment, and investigated by Fisher's exact tests whether developing autoantibodies was associated with system-specific (Grade 3 or 4) irAEs.

Results: In total, post-treatment positivity for any autoantibody was seen in 19.2% (19/99) of patients that were fully autoantibody-negative pre-treatment ($p<0.0001$). A significant association was observed between development of any autoantibodies and any irAEs: 14/19 (73.7%) patients that developed autoantibodies had irAEs, versus 37/80 (46.3%) patients that did not develop autoantibodies (OR: 3.3 [95% CI: 1.1 to 9.9]). Regarding specific autoantibodies, predominantly anti-TPO (4.8%, 6/125) and anti-TG antibodies (6.0%, 8/132) developed in patients negative for these autoantibodies at baseline ($p=0.03$ and $p=0.008$, respectively). However, development of these antibodies was not associated with development of thyroid disease. For most other autoantibodies, including RA-associated antibodies, post-treatment positivity increased only marginally and was not associated with occurrence of irAEs in the organ system related to the specificity of the autoantibody.

Conclusions: Breaking of humoral tolerance as measured by development of autoantibodies is relatively common under treatment with ipilimumab and is associated with the development of irAEs. The nature of the autoantigens towards which tolerance is broken is not reflected in the phenotype of the irAEs.

Disclosure of Interest: None declared

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THU0025 FLORID SYNOVITIS AFTER PD1 ANTAGONIST THERAPY IS CHARACTERISED BY A MARKED ABSENCE OF PD1+ INFILTRATING T CELLS

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Background: Although immunological blockade of checkpoint inhibitors (CIs) for cancer therapy is known to be associated with exacerbated inflammation recapitulating many features of autoimmunity[1], including synovitis resembling rheumatoid arthritis (RA)[2], no reports have investigated cellular infiltrates in synovial tissue (ST) of these patients. Here we provide the first report on ST cell infiltration, in particular PD1 expressing T cells, after a PD1 inhibitor-induced (Nivolumab) immune related adverse event (irAE) and severe synovitis.

Objectives: To characterise ST cellular infiltration in PD1 inhibitor induced arthritis with particular reference to PD1 positive T cells and compare these changes with active early RA ST.

Methods: Arthroscopic ST biopsies, parallel synovial fluid (SF) and PBMCs were collected from a DMARD-naïve nivolumab-treated small cell lung cancer (SCLC) patient with severe peripheral inflammatory polyarthritis (negative RF and ACPA; no axial or extra-articular irAE); 3 DMARD-naïve patients with seropositive early RA (<12 months duration; fulfilling 2010 ACR/EULAR criteria) were used as comparators.

Serial sections from fresh-frozen ST blocks were stained with H and E, CD3, CD45RO, CD55 and CD68 and semi-quantitatively scored as described[3]. ST, SF and PBMC cell suspensions were stained with Zombie UV (BioLegend), CD45RO, PD1, CD3, ICOS, CD8, CD4, CD20 (all BD) prior to flow cytometry. Cells were gated on live, singlet, lymphocytes, CD3+ and CD4+ T cells, and CD20+ and CD8+ T cells were excluded from endpoint PD1+, ICOS+ and CD45RO+analysis.

Results: CD68 +macrophage, CD20+ B cell and CD3+ T cell and CD45RO +memory T cell infiltration in IC-irAE was comparable to RA ST on semi-quantitative scoring, while TNF; staining was markedly elevated in CI-irAE compared to RA (CI-irAE-TNF; 4, RA-TNF; 2). Flow cytometry identified a striking absence of PD1+ ICOS+ CD4+T cells in IC-irAE SCLC in all compartments (CI-irAE: ST; 0.06, SF; 0.01, PBMCs; 0.00) compared to RA (RA: ST mean and SEM; 22.13 ±3.63: SF; 45.95±1.85: and to a lesser extent in PBMCs; 0.41±0.13: n=3 for each), despite comparable CD4 +T cell frequency in each compartment (frequency of CD3 +cells, CI-irAE: ST; 57.8, SF; 64.7, PBMCs; 38.2, RA: ST; 45.9 ±15.3, SF; 49.5±11.2, PBMCs; 62.2±13.8, figure 1).

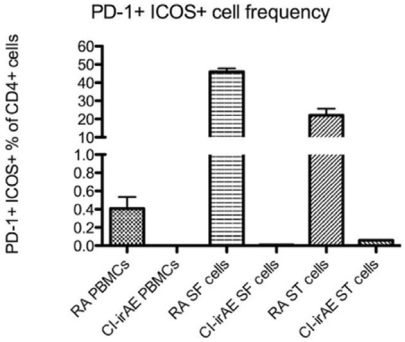

Figure 1 PD-1 +ICOS + T cells are absent in CI-irAE. Showing the PD-1 +ICOS + frequency of CD4 +T cells gated on live, singlet, lymphocytes, and

CD3+, CD20- and CD8-cells. (RA: ST mean and SEM; 22. 13±3.63: SF; 45.95 ±1.85 n=3 for each, CI-irAE: ST; 0.06, SF; 0.01, PBMCs; 0.00, n=1 for each).
Conclusions: While ST infiltration in CI-irAE SCLC recapitulates many features of RA histopathology, PD1 expression principally distinguishes RA from irAE ST T-cell infiltration. Despite abundant CD4 and CD45RO memory T cell infiltration in CI-irAE comparable with RA, we found a conspicuous absence of PD1 positive T-cells. Further research is needed to fully understand the nature of reduced PD1 expression in this setting and the source of elevated TNF, which could shed light on the pathogenesis of CI-irAE and guide CI-irAE management.

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THU0026 ORGANISED B CELLS AND PLASMA CELLS IN THE AORTA OF GIANT CELL ARTERITIS PATIENTS

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Background: Giant cell arteritis (GCA) is the most common type of systemic vasculitis. Currently, two forms of GCA are described: a cranial(C)-GCA and a systemic, large-vessel (LV)-GCA. LV-GCA frequently occurs without specific symptoms and late complications are aortic aneurysms or aortic rupture. Based on the analysis of temporal artery biopsies (TAB), GCA is postulated to start at the adventitial site and to be T cell-mediated. In the temporal artery infiltrates, T cells clearly outnumber B cells. Interestingly, we recently documented decreased numbers of B cells and elevated BAFF levels in newly diagnosed GCA patients prompting further research into the pathogenic role of B cells in GCA. Recent work in TAB of C-GCA patients demonstrated the presence of B cells and their organisation into artery tertiary lymphoid organs (ATLOs).
Objectives: Our objective was to investigated the presence and organisation of B cells in the aorta of patients with
LV-GCA:
Methods: Aorta tissue samples of 9 histologically-proven LV-GCA patients who underwent surgery due to an aortic aneurysm were studied by immunohistochemistry. Staining was performed with antibodies detecting CD20 (B cells), CD3 (T cells), CD21 (follicular dendritic cells (FDC)), PNAd (high endothelial venules (HEV)), bcl6 (germinal centre B cells), CD138 (plasma cells) and adipophilin (atherosclerotic plaque/macrophages). None of the patients received immunosuppressive treatment at the time of surgery. For comparison, 22 aorta samples from age- and sex-matched atherosclerosis patients with an aortic aneurysm were included.
Results: Aorta tissues of LV-GCA patients showed massive infiltration of B cells. The infiltrating B cells were mainly found in the adventitia and were frequently organised into high density B cell areas. In contrast to the temporal artery, B cells clearly outnumbered T cells in the aorta. ATLOs contained co-localised high density B cells and T cells, a FDC network, HEV and sometimes a germinal centre. ATLOs were observed in 77.8% of LV-GCA patients as opposed to only 36.4% of atherosclerosis patients. The number of ATLOs per patient was significantly higher in the LV-GCA group. Strikingly, ATLOs in aortas of LV-GCA patients contained more plasma cell niches and these niches also contained more plasma cells compared to aorta's of the atherosclerosis group. No association between the number of ATLOs and the number of atherosclerotic plaques was observed.
Conclusions: In conclusion, aorta tissues from patients with histologically-proven LV-GCA showed massive B cell infiltrates, predominantly located in the adventitia, that were organised into ATLOs. Moreover, these ATLO's frequently contained plasma cell survival niches. The predominance of organised B cells and plasma cells at the site of inflammation in LV-GCA suggests an involvement of B cell-mediated immune mechanisms in LV-GCA to be further explored.
Disclosure of Interest: None declared
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THU0027 NON-RESPONSE TO RITUXIMAB THERAPY IN REUMATOID ARTHRITIS ASSOCIATES WITH INCOMPLETE DISRUPTION OF THE B-CELL RECEPTOR REPERTOIRE IN THE PERIPHERAL BLOOD

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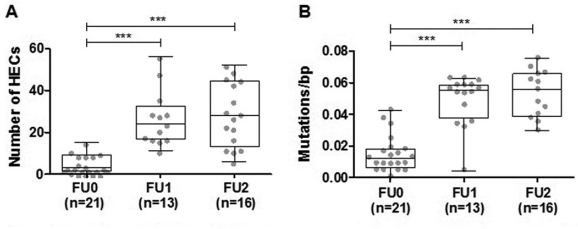
Background: Rituximab (RTX) induces more than 98% depletion of the CD20 +B cells in blood after a single injection, yet 35% to 50% of RA treated patients show a poor response to the therapy[1]. Despite the identification of many different biomarkers, mostly in the B cell compartment[2], adequate prediction of response to RTX treatment is still quite challenging.
Objectives: To test the hypothesis that non-response to rituximab can be predicted by analysing B-cell receptor (BCR) repertoire characteristics before and shortly after rituximab therapy.
Methods: Paired peripheral blood (PB) samples and synovial tissue (ST) samples were available from a total of 21 patients before therapy with RTX, and at 4 and 16/24 weeks after treatment. Next-generation sequencing was used to analyse the BCR repertoire, and asses the frequency of high expanded clones (HECs:>0.5% of the sequenced reads)[3] and load of somatic hypermutation (SHM). Clinical response was evaluated at 6 month following EULAR response criteria.
Results: In spite of the complete depletion of B cells (measured using CD19) with conventional flow cytometry, we detect a complete BCR repertoire at week 4 and 16/24 after RTX treatment. The post-treatment PB BCR repertoire is composed of fewer, but more expanded and more mutated clones compared to baseline (figure 1). Non-response associates with a higher number of HECs at week 4 ($p<0.01$) and with a higher overlap in the top-50 clones between the baseline and week 4 repertoire ($p=0.03$). In fact, in all non-responders some of the HECs detected at week 4 were already present at baseline. In these persisting clones the SHM load was higher than the median in the total repertoire. In the synovial tissue BCR repertoire the number of clones and HECs does not significantly change after RTX treatment. Like in PB, an increase in SHM load is observed after treatment but at the later time point (week 16). In ST the overlap within the top-50 clones with baseline is largely maintained at week 4, but then decreases at week 16. No baseline predictors of response to RTX treatment were identified.



Abstract THU0027 – Figure 1. HECs (A) and SHM load (B) in PB BCR repertoire before (FU0) and after (FU1 and FU2) treatment with RTX.

Conclusions: Incomplete depletion of the baseline BCR clonal repertoire in peripheral blood within the first month of treatment predicts poor clinical response at 6 months, revealing the persistence of "rituximab-resistant" BCR clonal signatures associated with treatment failure. In all patients the PB BCR repertoire at 4 weeks after rituximab is dominated by few but highly expanded and highly mutated BCR clones, most likely CD20-negative plasmablasts, while less pronounced and delayed effects are observed in the ST BCR repertoire.

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