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 tertiary lymphoid organs (ATLOs).

Objectives: Our objective was to investigate 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)), PNA^{ad} (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.

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THU0027

NON-RESPONSE TO RITUXIMAB THERAPY IN RHEUMATOID 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 therapy¹. Despite the identification of many different biomarkers, mostly in the B cell compartment², 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 assess 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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