Immune events with checkpoint inhibitors

**Background:** The pathogenesis of rheumatic immune-related adverse events (irAEs) from checkpoint inhibitor cancer immunotherapy directed against programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) remains unknown, even though they are a consequence of pharmacologic inhibition of a specific immune mechanism. Given that some irAEs resemble polymyalgia rheumatica (PMR) or giant cell arteritis (GCA), a disease whose pathogenesis is poorly understood, observations regarding the pathogenesis of PMR-like or GCA-relevant anatomical site interrogated. Latent class analysis did not reveal potential influence on scoring of uptake. Quantification of 18F-FDG uptake by maximum standardized uptake values (maximum standard unit value, SUVmax) was performed at sites relevant to PMR or GCA (17 sites relevant to PMR, 17 sites relevant to GCA) in paired scans, and the difference calculated. 

**Objectives:** This study investigated whether such changes occurred in patients receiving immunotherapy who did not develop clinically evident rheumatic irAEs. 

**Methods:** Consecutive patients exposed to PD-1 or PD-L1 inhibitor immunotherapy at a single center had scintigraphic uptake calculated by a nuclear medicine physician experienced in assessment of vasculitis. Patients were included if they had had 18F-fluorodeoxyglucose (18F-FDG) PET/CT imaging both within the two weeks prior to immunotherapy initiation and after at least eleven weeks of immunotherapy. Patients who went on to develop a rheumatic irAE were excluded, as were patients with scintigraphic evidence of liver metastases owing to their potential influence on scoring of uptake. Quantification of 18F-FDG uptake by maximum standardized uptake values (maximum standard unit value, SUVmax) was performed at sites relevant to PMR or GCA (17 sites relevant to PMR, 17 sites relevant to GCA) in paired scans, and the difference calculated.

**Results:** Twenty-four patients receiving nivolumab, pembrolizumab or avelumab met the inclusion criteria, primarily for melanoma, non-small cell lung cancer, or lymphoma. The mean age was 67 at the time of the first scan, 71% were male, and 66% had a complete or partial oncological response at best response. No statistical or clinically significant difference in SUVmax was noted at any PMR or GCA-relevant anatomical site interrogated. Latent class analysis did not reveal clusters identifiable by cancer type, best response, or presence of combination therapy.

**Conclusion:** Patients treated with PD-1/PD-L1 inhibitors without clinically evident rheumatic irAEs do not develop subclinical PMR or GCA-like changes on PET/CT. This supports the proposition that PMR-like and GCA-like irAEs are a distinct entity with stochastic onset, and do not simply represent generalized immune activation induced by immunotherapy.

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**Objectives:** In this study we aimed to assess the checkpoint proteins in childhood SLE patients.

**Methods:** Forty-nine jSLE patients together with 15 age- and gender-matched controls were included. Clinical features, disease activity scores and laboratory parameters were recorded both retrospectively and at the time of sampling. Patient samples were collected at their last visit, Plasma CD25 (IL-2Rα), 4-1BB, B7.2 (CD86), TGF-β1, CTLA-4, PD-1, PD-1, Tim-3, Lag-3. Gaeñit-9 levels were studied by the cytometric bead-based multiplex assay panel according to manufacturer’s instruction (LEGENDXplex HU Immune Checkpoint Panel 1 (10-plex); catalogue number 740962, Biolegend) and analysed by Novocyte 3005 flow cytometer. Two-step cluster analysis procedure was conducted over the chosen 7 symptom status and 3 clusters were chosen for the final analysis.

**Results:** A total of 49 patients (71.4% female) diagnosed with SLE according to the SLICC criteria and 15 healthy controls (73.3% female) were included in the study. The mean age of the patients was 17.7 ± 2.6 years and the controls was 13.3±1.4 years. The median disease duration was 5.7 years. At the time of sampling fifteen of the patients had a SLEDAI score of zero (no activity), 21 of them had between 1-5 (mild activity), 7 of them had between 6-10 (moderate activity), 5 of them had between 11-19 (high activity), 1 of them had >20 (very high activity).

**Conclusion:** Gaeñit-9 and PD-L1 were significantly higher in SLE patients. Other checkpoint proteins and IL-2Rα were also higher but did not reach statistical significance. There were significant correlations between SLEDAI and IL-2Rα, Gaeñit-9 and PDL1. Figure 1 There were three clinical clusters: Cluster 1 included patients with no major organ involvement, cluster 2 had predominantly haematological involvement (n=16) and cluster 3 (n=11) had predominantly renal involvement. Checkpoint proteins were not different among these three clusters.

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