Exagen, Bristol Myers Squibb, Medimmune/Astra Zeneca, Lilly, Immupharma, Amgen, Janssen, Sanofi, Neovacs, Anthera, Speakers bureau: UCB, GSK, EMD Serono, Bristol Myers Squibb, Medimmune/Astra Zeneca, Janssen
DOI: 10.1136/annrheumdis-2019-eular.3728

SATURDAY, 15 JUNE 2019

Lessons learned from checkpoint inhibitors

OP0335

A PROSPECTIVE CLINICAL AND MRI STUDY OF IMMUNE CHECKPOINT INHIBITOR (ICI)-INDUCED MUSCULOSKELETAL MANIFESTATIONS MYO-FASCIITIS AND NOT SYNOVITIS IS THE PROMINENT IMAGING FINDING

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Background: Immune check point inhibitors (ICI) were a breakthrough in cancer therapeutics. These agents target certain "brakes" of the immune system aiming at activating T cells to fight cancer. Taking into account their mechanism of action it is no surprise that they have been associated with immune related adverse events

Objectives: To assess the prevalence, clinical and imaging characteristics of ICI-induced musculoskeletal manifestations in a prospective manner

Methods: This is a prospective, clinical and MRI study conducted from Jan 2016 to Oct 2018. All patients treated with ICI who developed musculoskeletal manifestations were referred to the Rheumatology Department and subjected to a full clinical assessment and laboratory workup. An MRI of the involved area(s) was performed within one week of the initial clinical evaluation. In 2 patients MRI was not performed due to claustrophobia (n=1) and presence of non compatible metal implant (n=1).

Results: During the study period a total of 130 patients were treated with ICI. Of those, 10 (7.7%) developed ICI-induced musculoskeletal manifestations. They suffered from lung (n=4), bladder (n=3), renal cancer (n=2) or melanoma (n=1) and received treatment with nivolumab (n=7), pembrolizumab (n=1), durvalumab (n=1) and atezolizumab (n=1). They were mostly male (n=8) with a mean $\pm$ SEM age of 66.7 ± 2.6 years. The median (range) time from ICI treatment since development of symptoms was 2.5 (1-22) months. Autoantibodies (RF/ACPA/ANA) were negative in all patients and only 3/10 had a mild/moderate increase of inflammatory markers at disease onset. Three different patterns of musculoskeletal manifestations were found: i) Prominent joint involvement (n=3). Areas involved were the small joints of the hands (n=2) and knee/ankle (n=1). The MRI of the latter patient depicted not only synovitis but also myositis of the muscles surrounding the involved joints, ii) Prominent "periarticular" involvement (n=4). These patients had diffuse swelling of the hands (n=4) feet (n=3) or knees (n=1). Joints retained a good and relatively painless range of motion. MRI depicted mild synovitis with more prominent myositis and/or fasciitis in the surrounding tissues in all cases, iii) Myo-fasciitis (n=3). In all 3 such cases the involved area was the knee. Clinically, these patients presented with pain in the knee and either no objective signs of arthritis (n=2) or swelling with non inflammatory synovial fluid. MRI depicted myo-fasciitis of the surrounding muscles in all cases; a partial tear of the quadriceps tendon was also found in the patient with knee swelling. Overall, symptoms were mild/moderate and responded well to treatment (low dose steroids in 6 and NSAIDs/analgesics in 4) with no need for ICI discontinuation.

Conclusion: In our cohort ICI-induced musculoskeletal manifestations were not uncommon and developed in 7.7% of patients. Imaging evidence of myo-fasciitis was found in all patients indicating that the muscle/fascia is more frequently involved than the synovium. Our clinical and imaging data point to the direction that ICI-induced musculoskeletal manifestations mostly involve periarticular structures and associate mainly with myo-fasciitis and not synovium based pathology

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.5029

OP0336

COMMONLY USED DRUGS IN RHEUMATOLOGY MAY ALTER ANTI-TUMORAL RESPONSE TO IMMUNE CHECKPOINT INHIBITORS

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Background: Immune checkpoint inhibitors (ICIs) are revolutionizing the treatment of some advanced cancers. Gut microbiota has emerged as an important component of anti-tumoral response and can also be related to the occurrence of immune-related adverse events (irAEs). It has recently been shown that antibiotic treatment given at the initiation of ICI therapy had a dramatic impact on microbiota that compromised the anti-tumoral effect of ICIs (1).

Objectives: To evaluate whether co-medications known to have a potential impact on gut microbiota may alter ICI efficacy and/or irAE occurrence when given at ICI onset.

Methods: This was a retrospective cohort study including all cancer patients who received ICIs at our institution from May 2015 to September 2017. Co-medications given to the patients within one month before or one month after the first administration of ICI were extracted from medical records on the basis of a predefined list of medications known to impact gut microbiota. The tumour response, occurrence of irAEs and patient outcomes were assessed on a regular basis. Overall survival (OS) has been considered from the start of ICI therapy.

Results: 635 patients (70% male, mean age 64.5 years) were included, of whom 293 had melanoma, 150 had advanced non-small cell lung cancer and 83 had renal carcinoma. A previous autoimmune disorder was present in 8% of patients, mainly rheumatic and endocrine diseases. Psychotropic drugs (41.1%), proton pump inhibitors (PPIs) (37.3%), angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) (32%), glucocorticoids (GC) (24.2%), antibiotics (21.4%), statins (20.8%) and morphine (20.6%) were the most co-prescribed medications. Baseline GC use, when ≥ 10 mg of prednisone equivalent, was associated with a significant decrease in OS (median 4.5 months versus 24.3 months; $p<0.0001$) and a less frequent tumour response (55% versus 73%; $p=0.0001$). When given after ICI onset for the management of irAEs, GC did not influence ICI efficacy (Figure A). Baseline PPIs use also altered both OS (median 10.9 versus 24.3 months; $p<0.0001$) and tumour response (62% versus 71%; $p=0.02$) (Figure B). We confirmed the detrimental impact of antibiotics when given at ICI onset, and also found worse outcomes for patients receiving baseline psychotropic drugs (median OS 9.3 versus 19.4 months; $p=0.0001$). No significant difference was observed with baseline use of NSAIDs, aspirin, statins and ARBs/ACE. Furthermore, co-medication with antibiotics, GC, PPIs, morphine, NSAIDs, aspirin and psychotropic drugs was associated with decreased occurrence of irAEs.

Conclusion: As many of these treatments are used by rheumatologists, one should be aware of their potential detrimental effect when used at ICI initiation, that sometimes could have been avoided.

REFERENCE:

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.7470