Acknowledgements This work was supported by DFG (HA 8163/1–1) and STAEDTLER Stiftung (WW/eh20/17).
Disclosure of Interest None declared.

P150 IMPACT OF RADON SPA ON PAIN AND THE IMMUNE SYSTEM OF PATIENTS WITH MUSCULOSKELETAL DISORDERS

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10.1136/annrheumdis-2018-EWRR2019.133

Career situation of first and presenting author Post-doctoral fellow.
Introduction The pain reducing effects of certain natural springs containing the radioactive noble gas radon have been described for centuries. Today, one expects that small cumulative dose of radiation of about 0.3 mSv originating from radon progeny impacts on the immune system and bone metabolism of patients suffering from chronic painful degenerative and/or inflammatory diseases. However, osteoimmunological analyses of patients during radon spa were lacking.
Objectives We initiated the observational and explorative RAD-ON01 study to analyse for the first time the impact of radon spa on the immune status in the whole blood of 100 patients.
Methods Whole blood of the patients was drawn before and at weeks 6, 12 and 30 after therapy. Deep immunophenotyping was performed by multicolour flow cytometry and cytokine analyses by ELISA.
Results The RAD-ON01 study confirmed a long-lasting pain reduction. While the major immune cells were only marginally affected, in particular regulatory T cells and dendritic cells were temporarily increased and activation markers on immune cells were decreased. Further, a decrease of serum markers related to bone erosion was observed. The cytokine analyses showed that temporarily increased TGFβ following radon spa correlates with reduced pain perception of the patients. To exclude placebo effects, in November 2018 the RAD-ON02 study (EUDRACT: 2016-002085-31) started. With this prospective, temporarily placebo-controlled and double- blinded trial the evidence level of radon spa application and knowledge on osteoimmunological modes of action of radon should be improved.
Conclusions We conclude that patients with musculoskeletal disorders do benefit from radon spa and that osteoimmunological mechanisms are modulated by exposure of the patients to very low doses of radiation. Future randomized studies should improve the evidence level for radon as therapeutic option for chronic painful degenerative and/or inflammatory diseases.
Acknowledgements This work was supported by the German Federal Ministry of Education and Research (GREWIS, 02NUK017G and GREWIS-alpha, 02NUK050E), the Bayerisches Staatsbad Bad Steben GmbH, the Landesamt für Gesundheit und Lebensmittelsicherheit Bayern, and the EU (FP7 Nuclear Fission, Safety and Radiation Protection; FP7–249689).
Disclosure of Interest None declared.

P151 NOCICEPTIVE PAIN IN ACUTE EXPERIMENTAL SYNOVITIS IS PARTLY MEDIATED BY THE ALARMIN S100A9

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10.1136/annrheumdis-2018-EWRR2019.134

Career situation of first and presenting author Post-doctoral fellow.
Introduction Inflammatory mediators like S100A8 and -A9 released by the synovium have been implicated in the regulation of pain. They may regulate pain either via direct stimulation of nerve endings in the synovium or via stimulation at the site of the dorsal root ganglia (DRG), enabling an increased phagocyte infiltration and causing sensitization.
Objectives To elucidate the role of S100A9 in the pain response after induction of an acute synovitis using streptococcal cell walls (SCW) as a trigger.
Methods Acute synovitis was induced by a single i.a. injection of SCW in the knee joint of C57Bl6 (WT) mice and S100A9$^{-/-}$ mice, control mice received a saline injection. Serum S100A8/A9 levels were investigated by ELISA. Joint swelling and cell influx was assessed by ^{99m}Tc accumulation and histology. Pain response were investigated using an Incapacitance Tester (weight bearing), Catwalk (gait analysis) and von Frey's filaments (mechanical allodynia). Gene expression of inflammatory mediators and neuron activation markers in DRG were determined by q-PCR. Monocyte influx and protein expression was monitored by immunohistochemistry (IHC).
Results A single i.a. injection of SCW resulted in increased synovial and serum levels of S100A8 and S100A9 at day 1, which returned to basal levels at day 7. Joint swelling and cell influx were similar in WT and S100A9$^{-/-}$ mice at day 1 day excluding a role for S100A8/9 in synovitis. WT mice showed a marked and significant decrease in percentage of weight bearing on the SCW injected hindpaw (28%) compared to saline injection (47%, $p<0.001$) at day 1, whereas S100A9$^{-/-}$ mice did not. In addition, gait analysis showed increased 'limping' in the WT mice, whereas the S100A9$^{-/-}$ mice did not. Both mouse strains showed a similar reduction of paw withdrawal threshold, excluding a role for S100A8/9 in allodynia. DRG showed no increased phagocyte infiltration after SCW injection and no change in gene expression of MCP-1, KC, IL-1β or TNF was measured. In addition, F4/80 staining was unchanged in both WT and S100A9$^{-/-}$ mice. However, neuron activation markers NAV1.7, ATF3 and GAP43 were significantly increased at 1 day after SCW injection in WT mice, compared to saline injected mice ($p=0.022$, 0.004 and 0.030, respectively) and not in S100A9$^{-/-}$ mice, which is in line in with the reduced pain response observed earlier in S100A9$^{-/-}$ mice. The difference in NAV1.7 expression in the DRG was further confirmed at protein level with IHC.
Conclusions These findings show that S100A9 is an important mediator of inflammatory nociceptive pain response, and not of peripheral sensitization. During the acute phase of inflammation S100A8/A9 is likely involved via direct activation of nerve endings in the synovium and not via monocyte infiltration in the DRG.
Disclosure of Interest None declared.