FRI0583 IGG4-RELATED DISEASE AMONG PATIENTS PREVIOUSLY DIAGNOSED WITH IDIOPATHIC RETROPERITONEAL FIBROSIS. A NATIONWIDE DANISH STUDY

N. Lomborg¹, M. Jakobsen², C.S. Bode³, P. Junker⁴. ¹Department of Rheumatology; ²Department of Pathology, Vejle Hospital, Vejle; ³Department of Pathology; ⁴Department of Rheumatology, Odense University Hospital, Odense, Denmark

Background: IgG4-related disease (IgG4-RD) is a recently recognized systemic disease of unknown etiology and prevalence [1]. Retrospective single center series have provided evidence that 13–63% of patients with idiopathic retroperitoneal fibrosis (IRPF) could be reclassified as IgG4-RD. Since immunosuppressants or B-cell targeted therapies may halt or reverse progression, early diagnosis and treatment is important to prevent terminal fibrosis.

Objectives: To estimate the occurrence of IgG4 related retroperitoneal fibrosis (RPF) in Danish patients diagnosed with IRPF.

Methods: The National Danish Pathology Register was searched for biopsy codes relating to retroperitoneal tissue and inflammation from 01.01.2004 through 31.12.2013. Patients below 18 years of age, secondary causes, malignancies, infections, and specimens with multinucleated giant cells or granulomas were excluded. Among 724 candidate cases 68 were identified with IRPF. Among these 25 were left out due to small tissue samples, unavailable patient files or lack of consent. Clinical, laboratory data and imaging were reviewed. Paraffin-embedded tissue blocks were retrieved from 18 pathology departments. Four sections were prepared and stained with hematoxylin-eosin, Weigert's elastin and IgG4 immunostaining. Histopathologic features suggesting an IgG4-RD background were recorded (table). Cut-off levels for IgG4 positive cells at ≥ 30 per HPF and IgG4: total IgG ratio at $\geq 40\%$ were applied. Patients were categorized as IRPF, definite or possible IgG4-RD according to international consensus [2]. Intergroup comparisons were done using Mann-Whitney U test or Chi square test.

Results: Forty three patients (29 males), median age 56 years were included among which 19 (44%) met the criteria for IgG4-RD comprising 7 with definite, 12 with possible IgG4-RD and 24 with IRPF. Biopsies were available from all participants. Extraretroperitoneal manifestations, standard laboratory measures and serum IgG4 (in 5 individuals) did not differ significantly between RPF subsets. Patients with an IgG4: total IgG ratio $\geq 40\%$ had significantly more histopathologic features of IgG4-RD compared to a ratio $< 40\%$ (table). Patients with ≥ 30 IgG4 positive cells per HPF had higher numbers of tissue eosinophils than those with lower IgG4+ cell counts.

Table 1. Histopathologic findings in RPF biopsies (N=43) according to IgG4: total IgG ratio

	IgG4/IgG ratio $\geq 40\%$ N=21	IgG4/IgG ratio $< 40\%$ N=22	p-value
Lymphoplasmacytic infiltrate	21	13	0,002
Storiform fibrosis	12	3	0,004
Obliterative phlebitis	5	1	0,078
Phlebitis without obliteration	4	2	0,378
Increased numbers of eosinophils	13	6	0,030

Conclusions: A total of 44% of IRPF patients was diagnosed with IgG4-RD, 16% with definite and 28% with possible IgG4-RD. This estimate may be conservative because specimens with multinucleated giant cells or granulomas were excluded. The closer association of IgG4: total IgG ratio $\geq 40\%$ vs. lower ratios with histopathologic findings supports a direct pathogenic role by IgG4 bearing cells or IgG4 in IgG4 RPF.

References:

- Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;366: 539–51.
- Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012;25: 9: 1181–92.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.2597

FRI0584 RHEUMATIC AND MUSCULOSKELETAL DISORDERS RELATED TO IMMUNE CHECKPOINT INHIBITORS IN CANCER PATIENTS: A PROSPECTIVE SINGLE-INSTITUTION STUDY

K. Marie¹, L. Rouxel¹, R. Veillon², F. Martin², C. Dutriaux³, A. Pham-Ledard³, S. Prey³, M. Beylot-Barry³, M. Gross-Goupil⁴, B. Bannwarth¹, C. Richez¹, N. Mehsen-Cetre¹, T. Schaevebeke¹. ¹Rheumatology, Hôpital Pellegrin; ²Pneumology, Hôpital Haut-Lévêque; ³Onco-dermatology; ⁴Medical Oncology, Hôpital Saint-André, Bordeaux, France

Background: Immune checkpoint inhibitors (ICI) targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) axis have been a major advance in cancer immunotherapy. By enhancing T cell activity, unprecedented long-lasting tumour responses are observed in selected cancers but some patients experience immune related adverse events (irAE).

Objectives: To evaluate the prevalence and type of rheumatic and musculoskeletal disorders in patients receiving ICI at a single institution (University Hospital of Bordeaux, France).

Methods: All cancer patients with musculoskeletal disorders while receiving

ICI were referred to our rheumatology department. For each referred patient, an experienced rheumatologist performed a comprehensive clinical evaluation. Blood tests (inflammatory markers, serum creatine kinase, autoantibodies) and imaging (X-rays, ultrasound) were obtained according to clinical findings. HLA-DR phenotyping was also performed for some patients to search for shared epitope.

Results: From September 2015 to December 2016, 329 patients received ICI (anti CTLA-4: n=38; anti PD-1: n=251; anti PD-L1: n=29; combination anti CTLA-4/anti PD-1: n=11) and 21 patients were referred to our rheumatology department (6.4%). Mean age was 65 years and cancer types included melanoma (n=10), non small cell lung cancer (n=9), Merkel carcinoma (n=1) and renal carcinoma (n=1). All musculoskeletal disorders occurred in patients receiving anti PD-1 (nivolumab: n=12; pembrolizumab: n=6) or anti PD-L1 (avelumab: n=2; atezolizumab: n=1), with a median exposure time of 90 days (range: 1–650 days). There were two distinct clinical presentations: 1) inflammatory arthritis (IA) mimicking either rheumatoid arthritis (n=5) or polymyalgia rheumatica (n=8) and, 2) non-inflammatory musculoskeletal conditions (n=8). Of note, one patient was anti-CCP positive but negative for RF. Shared epitope HLA-DRB1 *01:01 was present in 4 patients. Eleven patients required corticosteroid therapy with a median dose of 15mg/day (range: 7–30 mg/day). Non-inflammatory disorders were easily managed with NSAIDs, analgesics and/or physiotherapy. ICI treatment was temporarily discontinued in one patient only, in line with the clinical trial protocol. To date, there was a partial or complete tumour response to ICI in 10 patients whereas 3 had stable disease and 7 had progressive disease. Tumour response or stable disease was observed in 11 of 12 patients with IA but only in 2 of 8 patients with non-inflammatory conditions.

Conclusions: In our series, patients with immune-related IA mimicking rheumatoid arthritis and polymyalgia rheumatica were responsive to low-to-moderate dose of prednisone and did not require ICI discontinuation. Furthermore, tumour response was frequently observed in such patients.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.6703

FRI0585 FREQUENT, UNUSUALLY SEVERE, LONG LASTING, LOCAL AND SYSTEMIC PNEUMOCOCCAL VACCINE REACTIONS IN PATIENTS WITH CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS): RESULTS OF A PROSPECTIVE REGISTRY BASED STUDY

V.K. Jaeger¹, H.M. Hoffmann², T. van der Poll³, H. Tilson⁴, J. Seibert⁵, A. Speziale⁵, G. Junge⁵, K. Franke⁶, E. Vritzali⁵, P.N. Hawkins⁷, J. Kuemmerle-Deschner⁸, U.A. Walker¹. ¹University Hospital Basel, Basel, Switzerland; ²University of California at San Diego and Rady Children's Hospital, San Diego, United States; ³University of Amsterdam, Amsterdam, Netherlands; ⁴University of North Carolina, Chapel Hill, United States; ⁵Novartis Pharma AG, Basel, Switzerland; ⁶QuintilesIMS, Real World Insights, NC, United States; ⁷University College London, London, United Kingdom; ⁸University Hospital Tübingen, Tübingen, Germany

Background: Pneumococcal, tetanus and influenza vaccinations are recommended for patients with Cryopyrin-Associated Periodic Syndromes (CAPS) when treated with immunosuppressive medication.

Objectives: This study aims to report the safety of pneumococcal and other vaccinations administered to CAPS patients.

Methods: All CAPS patients followed in the β -CONFIDENT (Clinical Outcomes and Safety Registry study of Ilaris® patients) registry between 07/2010 and 12/2015 were analysed if they had received a vaccination. The β -CONFIDENT registry is a global, long-term, prospective, observational registry, capturing and monitoring CAPS patients treated with canakinumab [1].

Results: 68 CAPS patients (56% female, age range 3.5–73 years) had received a total of 159 vaccine injections, 107 injections against influenza, 19 pneumococcal vaccinations (15 pneumococcal polysaccharide vaccines [PPV], 2 pneumococcal conjugate vaccines [PCV], 2 unknown), 12 against tetanus/diphtheria antigens and 21 other vaccinations.

A reaction was observed in 22 vaccine injections (14%) administered to 18 patients. 13 vaccine reactions (68% of all pneumococcal vaccine injections) occurred in 12 patients receiving pneumococcal vaccines. 12 PPV injections (80% of all PPV injections) elicited a vaccine reaction while none was elicited by the PCV injections. The high frequency of pneumococcal vaccine reactions contrasted with that of the reactions to other vaccine types: only 17% and 7% of the tetanus/diphtheria and influenza vaccinations, respectively, elicited a vaccine reaction. The odds ratios to react to the pneumococcal vaccines compared to influenza and tetanus/diphtheria vaccines were 31.0 (95% confidence interval (CI) 8–119) and 10.8 (95% CI 2–74).

Vaccine reactions after pneumococcal vaccinations were more severe and lasted significantly longer compared to the reactions after other vaccinations. Fever was elicited by almost half of all PPV injections. All symptoms after pneumococcal vaccination were observed very rapidly, usually within hours. Unlike the symptoms observed after influenza and tetanus/diphtheria vaccination, which resolved rapidly, the symptoms related to PPV were much more prolonged and in some cases lasted more than 3 weeks. In 2 patients, pneumococcal vaccination also elicited symptoms consistent with systemic inflammation due to CAPS reactivation. All 5 vaccine related serious adverse events were associated with pneumococcal vaccination.

Conclusions: Pneumococcal vaccines, unlike other vaccines, frequently trigger severe local and systemic inflammation in CAPS patients. Clinicians must balance potential benefits of pneumococcal immunisation against safety concerns.

References:

- [1] Kuemmerle-Deschner JB, et al. Safety and Efficacy of Canakinumab in Patients with CAPS: Interim Results from the Beta-Confident Registry [abstract]. *Arthritis Rheumatol.* 2015;67(suppl 10).

Acknowledgements: The β -CONFIDENT registry was supported by Novartis Pharma AG, Basel, Switzerland.

Disclosure of Interest: V. Jaeger: None declared, H. Hoffmann Consultant for: the steering committee of the β -CONFIDENT registry and in this function received consulting fees from Novartis., T. van der Poll Consultant for: the steering committee of the β -CONFIDENT registry and in this function received consulting fees from Novartis., H. Tilson Consultant for: the steering committee of the β -CONFIDENT registry and in this function received consulting fees from Novartis., J. Seibert Employee of: Novartis Pharma AG, Basel, Switzerland, A. Speziale Employee of: Novartis Pharma AG, Basel, Switzerland, G. Junge Employee of: Novartis Pharma AG, Basel, Switzerland, K. Franke Employee of: QuintilesIMS who served as the CRO that conducted the β -CONFIDENT registry., E. Vrizali Employee of: Novartis Pharma AG, Basel, Switzerland, P. Hawkins Consultant for: the steering committee of the β -CONFIDENT registry and in this function received consulting fees from Novartis., J. Kuemmerle-Deschner Consultant for: the steering committee of the β -CONFIDENT registry and in this function received consulting fees from Novartis., U. Walker Consultant for: the steering committee of the β -CONFIDENT registry and in this function received consulting fees from Novartis.

DOI: 10.1136/annrheumdis-2017-eular.1513

FRI0586 INTERLEUKIN (IL)-1 INHIBITION WITH ANAKINRA AND CANAKINUMAB IN BEHÇET'S DISEASE RELATED UVEITIS: A MULTICENTER RETROSPECTIVE OBSERVATIONAL STUDY

C. Fabiani¹, A. Vitale², G. Emmi³, G. Lopalco⁴, L. Vannozzi³, S. Guerriero⁴, S. Gentileschi², D. Bacherini³, R. Franceschini², B. Frediani², M. Galeazzi², F. Iannone⁴, G.M. Tosi², L. Cantarini². ¹Humanitas Research Hospital, Rozzano, Milan; ²University of Siena, Siena; ³University of Florence, Florence; ⁴University of Bari, Bari, Italy

Objectives: To evaluate the role of interleukin (IL)-1 inhibitors anakinra (ANA) and canakinumab (CAN) in the treatment of Behçet disease (BD)-related uveitis

Methods: multicenter retrospective observational study including 19 consecutive BD patients (31 affected eyes) receiving treatment with anti-IL-1 agents. Data were analyzed at baseline, at 3 and 12 months. Primary end-point: reduction of ocular inflammatory flares (OIF). Secondary end-points: improvement of Best Corrected Visual Acuity (BCVA); reduction of macular thickness defined by optical coherence tomography (OCT) and of vasculitis identified with fluorescein angiography (FA); evaluation of statistically significant differences between patients treated with IL-1 inhibitors as monotherapy, subjects also administered with disease modifying anti-rheumatic drugs (DMARDs) and/or corticosteroids as well as between patients administered with IL-1 inhibitors as first line biologic treatment and those previously treated with TNF- α inhibitors

Results: at 12 months OIF significantly decreased from 200/100 patients/year to 48.87/100 patients/year ($p < 0.0001$). The frequency of retinal vasculitis identified by FA significantly decreased between baseline, 3-month and 12-month follow-up visits ($p < 0.0001$ and $p = 0.001$, respectively). OIF rate was significantly higher in patients co-administered with DMARDs (81.8/100 patients/year) than in patients undergoing IL-1 inhibitors as monotherapy (0.0/100 patients/year) ($p = 0.03$). No differences were identified on the basis of corticosteroid use and between patients administered with IL-1 inhibitors as first-line biologic approach or second-line. Steroid dosage was significantly decreased at 12-month visit compared to baseline ($p = 0.02$).

Conclusions: treatment with IL-1 inhibitors is effective in the management of BD-related uveitis and provides a long-term control of ocular inflammation in refractory and long-lasting cases.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.1119

FRI0587 DIFFERENT FACTORS ARE RELATED TO RECURRENCE OF EXISTING ORGAN INVOLVEMENT AND NEW DEVELOPMENT OF ORGAN INVOLVEMENT IN IGG4-RELATED DISEASE

I. Mizushima, S. Tsuge, Y. Fujisawa, S. Hara, F. Suzuki, K. Ito, H. Fujii, K. Yamada, M. Kawano. *Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Kanazawa, Japan*

Background: IgG4-related disease (IgG4-RD) is a recently recognized systemic inflammatory disorder that can affect many organs [1]. In IgG4-RD, relapse including recurrence of existing organ involvement (REOI) and new development of organ involvement (NDOI) easily occurs during the clinical course, and its predictors have been suggested [2, 3]. However, differences between risk factors of REOI and those of NDOI have not been clarified.

Objectives: This study aimed to clarify the respective risk factors of REOI and NDOI in IgG4-RD.

Methods: We retrospectively investigated factors related to REOI and NDOI in 86 IgG4-RD patients whose follow-up period was more than 12 months. For assessment of factors related to REOI and NDOI, we performed uni- and multivariate Cox regression analysis. On stepwise multivariate analysis, we applied the variables with $P < 0.1$ in univariate analysis and the predictors of relapse suggested in past reports (age, sex, serum IgG4, IgG, and IgE levels, eosinophil counts, and RF positivity) [2, 3], and used the forward selection method (including factors presenting with $P < 0.05$).

Results: The patients comprised 57 men and 29 women (mean age 65.9 years). Mean follow-up period was 63.1 months (range 14–150). At diagnosis, their mean serum IgG4 level was 718 mg/dL (range 10.7–3,610). Seventy-one patients were treated with glucocorticoid (GC). REOI was detected at 52.3 months (range 1.0–120) after the diagnosis in 20 patients, including 4 not receiving GC at that time. On the other hand, NDOI was detected at 37.6 months (range 5.0–120) after the diagnosis in 15 patients, including 8 not receiving GC then. In multivariate Cox regression analysis, blood eosinophil counts [per 100/ μ L, hazard ratio (HR) 1.072, 95% confidence interval (CI) 1.018–1.129, $P = 0.008$] and continuation of GC (vs discontinuation or observation without GC, HR 0.245, 95% CI 0.076–0.793, $P = 0.019$) had a significant impact on the time to NDOI, whereas age (per year, HR 0.942, 95% CI 0.899–0.986, $P = 0.011$) and ANA positivity (vs negativity, HR 6.632, 95% CI 1.892–23.255, $P = 0.003$) had a significant impact on the time to REOI.

Conclusions: The present study suggests that the risk factors of REOI and NDOI in IgG4-RD are different.

References:

- [1] Stone JH et al. IgG4-related disease. *N Engl J Med.* 2012 Feb 9;366(6):539–51.
[2] Yamamoto M et al. Identification of relapse predictors in IgG4-related disease using multivariate analysis of clinical data at the first visit and initial treatment. *Rheumatology (Oxford).* 2015 Jan;54(1):45–9.
[3] Wallace ZS et al. Predictors of disease relapse in IgG4-related disease following rituximab. *Rheumatology (Oxford).* 2016 Jun;55(6):1000–8.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.2425

FRI0588 INTERIM RESULTS OF A PHASE 2 STUDY OF XMAB®5871, A REVERSIBLE B CELL INHIBITOR, IN IGG4-RELATED DISEASE

J.H. Stone¹, Z.S. Wallace¹, C.A. Perugino¹, A.D. Fernandes¹, P.S. Patel¹, P.A. Foster², D.J. Zack². ¹Massachusetts General Hospital Rheumatology Unit, Harvard, Boston; ²Clinical Development, Xencor Inc., Monrovia, United States

Background: IgG4-related disease (IgG4-RD) is an immune-mediated condition causing fibro-inflammatory lesions that can lead to irreversible organ damage. No approved therapies for IgG4-RD exist. We report the use of a novel monoclonal antibody, XmAb5871, in IgG4-RD. XmAb5871 is a humanized anti-CD19 antibody with an Fc portion engineered for increased affinity (up to 400-fold over native IgG₁) to Fc γ R1b, the only Fc receptor on B cells. Co-ligation of CD19 and Fc γ R1b leads to inhibition of B lineage cells bearing these targets. Reversible inhibition of B cell function without B cell ablation is one potential advantage of this approach.

Methods: The trial is an open-label investigation of XmAb5871 in active IgG4-RD, defined by an IgG4-RD Responder Index (RI) of ≥ 3 . XmAb5871 (5 mg/kg) is administered IV every 14 days for 12 doses. The primary outcome measure is the proportion of patients on day 169 (2 weeks following the last dose) with a decrease in the IgG4-RD RI of 2 or more points compared to baseline. Glucocorticoids are permitted but not required at entry and must be discontinued by two months. Other immunosuppressive medications are not allowed. Imaging and mechanistic studies are performed at baseline and at selected intervals.

Results: Fifteen patients were enrolled between March 2016 and January 2017. As of October 31, 2016, 12 patients had received at least one infusion of XmAb5871. The median age of the 12 patients is 58 years (range: 43 to 78 years). Two-thirds of the patients are male. Nine of the 12 patients had elevated serum IgG4 concentrations at baseline with a mean serum IgG4 of 499 mg/dL (range: 25–2415; normal < 86 mg/dL). The median baseline IgG4-RD RI score was 10 (range: 2–30), with active inflammatory disease in at least one organ system (median 4, range: 1–10). The organs most commonly affected were lymph nodes (75% of patients), submandibular glands (67%), parotid glands (58%), and lacrimal glands (50%). Four patients (33%) had kidney involvement and 3 (25%) had heart/pericardium findings. Nine of 11 patients (82%) have had an initial response to XmAb5871 therapy of at least a three-point reduction in the IgG4-RD RI within two weeks of the first dose. As of Oct 31st, 2016, five patients attained disease remission (an IgG4-RD RI of 0 and no prednisone treatment after 2 months) during the study. Efficacy outcomes will be updated as more patients complete the study. One patient had been on glucocorticoid treatment for 2 years and was on prednisone of 15 mg/day at baseline, but was able to discontinue prednisone by 2 months after starting treatment. Three patients experienced minor, transient gastrointestinal side-effects during the 1st infusion. One patient had infusion-related GI symptoms on the 5th infusion and subsequently developed rash and arthritis. She was found to have anti-drug antibodies and has discontinued the study. Mechanistic studies show that both peripheral B cells and plasmablasts decrease substantially following therapy in the majority of patients. Studies of the mechanism of this decrease and functional B cell assays are under way.

Conclusions: XmAb5871 is tolerated well in patients with active IgG4-RD and is a promising treatment approach for IgG4-RD.