declared, Charles Masson: None declared, Divi Cornec: None declared, Jean-Jacques Dubost: None declared, Laurent Marguerie: None declared, Sebastien Ottaviani: None declared, Franck Grados: None declared, Rakiba Belkhir: None declared, Olivier fain: None declared, Philippe Goupille Grant/research support from: AbbVie, Amgen, Biogen, BMS, Celgene, Chugai, Lilly, Janssen, Medac, MSD France, Nordic Pharma, Novartis, Pfizer, Sanofi and UCB, Consultant of: AbbVie, Amgen, Biogen, BMS, Celgene, Chugai, Lilly, Janssen, Medac, MSD France, Nordic Pharma, Novartis, Pfizer, Sanofi and UCB, Speakers bureau: AbbVie, Amgen, Biogen, BMS, Celgene, Chugai, Lilly, Janssen, Medac, MSD France, Nordic Pharma, Novartis, Pfizer, Sanofi and UCB, Christelle Sordet: None declared, Bruno Fautrel Grant/research support from: AbbVie, Lilly, MSD, Pfizer, Consultant of: AbbVie, Biogen, BMS, Boehringer Ingelheim, Celgene, Lilly, Janssen, Medac MSD France, Nordic Pharma, Novartis, Pfizer, Roche, Sanofi Aventis, SOBI and UCB, Peggy Philippe: None declared, Muriel PIPERNO: None declared, Bernard Combe Grant/research support from: Novartis, Pfizer, Roche-Chugai, Consultant of: AbbVie; Gilead Sciences, Inc.; Janssen; Eli Lilly and Company; Pfizer; Roche-Chugai; Sanofi, Speakers bureau: Bristol-Myers Squibb; Gilead Sciences, Inc.; Eli Lilly and Company; Merck Sharp & Dohme; Pfizer; Roche-Chugai; UCB, Olivier Lambotte Consultant of: BMS France, MSD, Astra Zeneca, Incyte, Christophe Richez Consultant of: Abbvie, Amgen, Mylan, Pfizer, Sandoz and UCB., Jérémie SELLAM: None declared, Thomas Sene: None declared, Guillaume Denis: None declared, Thierry Lequerre: None declared, Xavier Mariette Consultant of: BMS, Gilead, Medimmune, Novartis, Pfizer, Servier, UCB, Gaetane Nocturne: None declared

DOI: 10.1136/annrheumdis-2020-eular.3930

OP0126 IS IMMUNE CHECKPOINT INHIBITORS THERAPIES SAFE AND EFFECTIVE FOR PATIENTS WITH CANCER AND PREEXISTING AUTOIMMUNE DISEASE?

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Background: Immune checkpoints inhibitors (ICIs) are associated with frequent immune-related adverse events (irAEs). Most patients with preexisting autoimmune disease (PAD) have been universally excluded from clinical trials and ICIs are not recommended for patients with cancer and PAD due to the unknown safety. In this study, we aim to evaluate the safety and efficacy of ICIs in patients with PAD and cancer.

Objectives: Systematic searches were performed of PubMed, EMBASE, and the Cochrane library from inception through September 2019 for observational studies reporting safety and efficacy data among ICIs-treated patients with cancer and PAD. A random effects meta-analysis was performed to calculate pooled incidence rates of PAD flare, irAEs and response.

Methods: Systematical search of PubMed, EMBASE and Cochrane Library plus a hand search of conference proceedings were performed for observational studies that reported cancer incidence in patients with RA treated with biologics or tofacitinib with active comparator of conventional DMARDs (csDMARDs) or TNFi. The pooled relative risk (RR) and 95% confidence interval (CI) were calculated with fix-effects or random-effects model.

Results: A total of 619 ICI-treated patients with PAD in 14 publications were finally identified. In the random effects meta-analysis, pooled incidence of PAD flares, *de novo* irAEs or both of any grade was 60% (95% CI 52%-68%). Viewed separately, there were 219 and 206 patients experiencing PAD exacerbation and *de novo* irAEs of any grade, yielding a pooled incidence of 35% (95% CI 29%-41%) and 33% (95% CI 24%-42%) respectively. Of these, most of flare and *de novo* irAEs were graded as mild (grade 1-2) (pooled proportion: 82%, 95%CI 72%-91%; 65%, 95%CI 54%-76%, respectively). Rheumatoid arthritis was associated with a trend toward higher flare occurrence compared with another individual PADs (RR=1.25-1.88). With respect to efficacy, 136 patients showed complete or partial response, corresponding to a pooled response rates of 30% (95% CI 22%-39%). There were no statistical differences between patients with and without immunosuppressive therapy at ICI start regarding flare (RR: 1.08, 95% CI 0.72-1.62), but a trend towards lower response rates was observed in patients with baseline immunosuppressants (RR: 0.58, 95% CI 0.26-1.33).

Conclusion: Immune toxicities are frequent in ICI-treated patients with PAD but often mild and manageable without discontinuing therapy. Rheumatoid arthritis is associated with a trend toward more flares. ICI treatment are effective and not absolute contraindication in PAD patients, but close monitoring and multidisciplinary collaboration should be contemplated, especially for those concomitantly receiving immunosuppressant or having rheumatoid arthritis.

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Figure 1. Pooled effect estimates in ICI-treated patient with PAD (A) PAD flare, *de novo* irAEs or both; (B) PAD flare; (C) *de novo* irAEs. ICI: Immune checkpoint inhibitors; PAD: Preexisting autoimmune disease; irAEs: Immune-related adverse events.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.5054

Immunity in rheumatic disease

OP0127 TRANSCRIPTIONAL ACTIVITY OF SURVIVIN CONTRIBUTES TO MATURATION AND FUNCTION OF THE INTERFERON-GAMMA PRODUCING T CELLS IN RHEUMATOID ARTHRITIS

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Background: Interferon gamma (IFN γ) signalling and downstream effects make important contribution in pathogenesis of rheumatoid arthritis (RA). Here, we propose a mechanism by which oncoprotein survivin participates in development of IFN-dependent repertoire of T cells in RA patients.

Objectives: We study the role of survivin in the phenotype of CD4 T cells of RA patients.

Methods: CD4 cells of RA patients and healthy controls were purified from blood, activated and subjected to RNAseq, ChIPseq with antibodies to survivin (BIRC5) was performed on CD4+ cells. Histone H3 ChIPseq was performed using antibodies to H3K27ac, H3K27me3 and H3K4me3. Statistical analysis was performed in R-studio using the Bioconductor package DESeq2, clustering using Spearman and Ward.D2.

Results: Unsupervised clustering of CD4 samples by expression of 48 core Th cell markers identified subsets of CD28^{hi}CD27^{hi}IFN γ central memory cells (Tcm), CD28^{lo}CD27^{lo}IFN γ effector memory cells (Tem) and CD28^{null}CD27^{null}IFN γ terminal effector cells (Tte). Tte cells showed classical features of Th1 cells including high levels of TBX21, TNF α and IL32 and signs of activation in IFN signalling machinery. Interestingly, they combined the features of peripheral Tregs CD25^{hi}Foxp3^{hi}IKZF2^{neg} and IL10 producing cells together with type 1 regulatory cells, which rely on transcription factors BATF and IRF1 for the differentiation and produced high amounts of perforin and granzyme B. Importantly, Tte CD4 cells had also high transcription of BIRC5 (p=1.15e-18).

To study if BIRC5 is a part of IFN signalling, CD4 cells were cultured with survivin inhibitor YM155 and activated with IFN γ . RNAseq analysis revealed 2033 (FC<2.0, n=336) differentially expressed genes in the IFN stimulated cultures. Interestingly, a substantial number of these IFN-dependent genes was significantly reduced in the survivin-deficient cultures and included among others CD28, FoxP3, IKZF2, ICOS, BATF, PRDM1, CXCR3, IRF4 and IRF8. Analysis of the peak sequences identified enrichment for composite motifs for IRFs (ETS:IRF, p1.0e-124; bZIP:IRF, p=1.0e-640), indicating that survivin is important for IFN γ signalling. Numerically, the peaks containing ETS:IRF motifs were most prevalent and identified in total within 49.7% of all survivin-ChIP peaks. Frequent was co-localisation of the IRF:bZIP and IRF:ETS motifs within the survivin peaks. Among the IRF motifs dominated those suitable for IRF1 (p=1.0e-127) and IRF8 (p=1.0e-84). However, the DNA binding motifs of these two are alike.

Encouraged by the survivin ChIPseq results, we wanted to know its relation to histone marks. We observed that 50% of survivin peaks containing both IRF:bZIP and IRF:ETS motifs are co-localized with the H3K27ac marks. In total, 16 of 48 core Th cell markers used for patients clustering were identified by survivin ChIPseq, co-localized with IRF composite motifs and histone marks. They were also dependent of survivin for expression.

Conclusion: his study showed that survivin binds to DNA and regulates the core gene expression contributing to maturation and function of the IFN γ producing Th1 cells.

References: -

Disclosure of Interests: Malin Erlandsson: None declared, Karin ME Andersson: None declared, Nisha Nair: None declared, Anastasios Damdimopoulos: None declared, Sofia Töyrä Silfverswärd: None declared, Rille Pullerits: None declared, Anne Barton Consultant of: AbbVie, Maria I Bokarewa: None declared

DOI: 10.1136/annrheumdis-2020-eular.4325

OP0128 DISTINCT FEATURES OF HLA-DR+ AND HLA-DR-PD-1HI CXCR5- T PERIPHERAL HELPER CELLS IN SEROPOSITIVE RHEUMATOID ARTHRITIS

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Background: PD-1hi CXCR5- T peripheral helper (Tph) cells are newly identified pathogenic CD4+ helper T cells in rheumatoid arthritis (RA). Since Tph cells have been emerged quite recently, the characteristics of Tph cells as a biomarker of RA are not fully understood.

Objectives: The aim of the study is to evaluate how useful Tph cells in peripheral bloods are when compared to other immune cell subsets, and to clarify which Tph subset most accurately reflects the disease activity of RA.

Methods: The RA patients who visited our rheumatology department between January 2000 and February 2017, and met the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria were included. We first assessed correlation with 40 immune cell subsets and the disease activity of RA. Next, the proportions of these immune cells were compared between RA and healthy controls (HCs). We also investigated the immune cell subsets which reflected the time course change of the disease activity after the methotrexate (MTX) treatment. The study protocol was approved by the ethics committee at Keio University School of Medicine.

Results: Thirty-four seropositive RA, 12 seronegative RA and 34 HCs were included. The immune cell subsets which showed correlation with DAS28-ESR ($r > 0.2$ or $r < -0.2$) were activated CD4 T cells ($r = 0.31$), HLA-DR+Th1 cells ($r = 0.20$), HLA-DR+Th1-17 cells ($r = 0.25$), Tfh1-17 cells ($r = -0.25$), HLA-DR+Tph cells ($r = 0.22$), CD3+CD8+naïve T cells ($r = -0.25$), CD3+CD8+effector memory T cells ($r = -0.26$), plasma cells ($r = 0.40$) and CD14++CD16+intermediate monocyte ($r = 0.23$). The proportions of HLA-DR+Th1 cells (2.3% vs. 5.7%), HLA-DR+Th1-17 cells (0.7% vs. 2.2%), Tfh1-17 cells (1.7% vs. 2.0%), HLA-DR+Tph cells (0.02% vs. 0.1%), CD3+CD8+effector memory T cells (16.6% vs. 25.7%), plasma cells (0.04% vs. 0.17%) were statistically higher in the patients with RA compared to HCs. While the proportion of Tph cells showed weak correlation with DAS28-ESR ($r = 0.18$), that was extremely higher in RA (0.08% vs. 0.25%). Interestingly, when assessing the correlations with the disease activity in seropositive and seronegative RA separately, the proportions of Tph cells ($r = 0.52$) and HLA-DR+Tph cells ($r = 0.50$) were highly reflected in seropositive RA, but not in seronegative RA. Regarding the disease activity after the MTX treatment, the change of proportion of Tph cells between week 0 and 52 significantly reflected the change of DAS28-ESR ($r = 0.75$, $p = 0.025$), but not HLA-DR+Tph cells because of the non-specific reduction by the MTX treatment. Rather, HLA-DR-Tph cells significantly reflected the change of DAS28-ESR while receiving the MTX treatment ($r = 0.76$, $p = 0.021$).

Conclusion: Tph cells and HLA-DR+Tph cells highly reflected the disease activity of seropositive RA. However, after the treatment, the proportion of HLA-DR+Tph cells decreased independent from the disease activity, and that of HLA-DR-Tph cells more accurately reflected the change of the disease activity during the treatment.

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Disclosure of Interests: Hiroki Yamada: None declared, Takanori Sasaki: None declared, Katsuya Suzuki: None declared, Masaru Takeshita: None declared, Shuhei Tanemura Employee of: I am employed by Mitsubishi Tanabe Pharma Corporation, Noriyasu Seki Employee of: I am employed by Mitsubishi Tanabe Pharma Corporation, Hideto Tsujimoto Employee of: I am employed by Mitsubishi Tanabe Pharma Corporation, Tsutomu Takeuchi Grant/research support from: Eisai Co., Ltd, Astellas Pharma Inc., AbbVie GK, Asahi Kasei Pharma Corporation, Nippon Kayaku Co., Ltd, Takeda Pharmaceutical Company Ltd, UCB Pharma, Shionogi & Co., Ltd., Mitsubishi-Tanabe Pharma Corp., Daiichi Sankyo Co., Ltd., Chugai Pharmaceutical Co. Ltd., Consultant of: Chugai Pharmaceutical Co Ltd, Astellas Pharma Inc., Eli Lilly Japan KK, Speakers bureau: AbbVie GK,

Eisai Co., Ltd, Mitsubishi-Tanabe Pharma Corporation, Chugai Pharmaceutical Co Ltd, Bristol-Myers Squibb Company, AYUMI Pharmaceutical Corp., Eisai Co., Ltd, Daiichi Sankyo Co., Ltd., Gilead Sciences, Inc., Novartis Pharma K.K., Pfizer Japan Inc., Sanofi K.K., Dainippon Sumitomo Co., Ltd.

DOI: 10.1136/annrheumdis-2020-eular.5552

OP0129 AUTOREACTIVE, CITRULLINATED PEPTIDE-SPECIFIC T CELLS IN RHEUMATOID ARTHRITIS

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Background: Self-reactive CD4+ T cells are thought to play a key role in the pathogenesis of rheumatoid arthritis (RA) and represent a target for antigen-specific, tolerogenic therapies¹. Phenotyping such cells could provide the means with which to monitor these treatments. Here, we aimed to demonstrate antigen-induced T cell responses to RA relevant epitopes using peptide stimulation of peripheral blood mononuclear cells (PBMC). Several autoantigens have been described in RA, including various citrullinated peptide (cit-peptide) epitopes²; here we have used a combination of cit-peptides that will be used to load tolerogenic dendritic cells in a forthcoming experimental medicine study (AuToDeCRA II).

Objectives: To detect peripheral blood T cell proliferation in response to candidate autoantigens in RA patients and healthy controls (HCs) using flow cytometry.

Methods: PBMC from RA patients and HCs were obtained following informed consent and were cryopreserved. Prior to use, cells were thawed in medium supplemented with human serum and were labelled with a proliferation tracking dye (PTD). 2×10^5 labelled cells were plated into 96 well plates with a minimum of 7 replicates per condition and were either cultured alone or stimulated with individual peptides at varying concentrations or a peptide pool. On day 9, cells from replicate wells were harvested, pooled and stained for surface markers and viability. Samples were acquired on a BD Fortessa X20 and analysis was performed in FlowJo version 10. A manual gating strategy was used to identify CD45RO+ (memory) CD4+ T cells and amongst this population, activated/proliferated cells were defined as CD25+ PTD low. Stimulation indices (SI) were calculated as the percentage of activated/proliferated cells from stimulated wells divided by the percentage from unstimulated wells.

Results: Ten RA patients (including early and established disease) were recruited alongside seven HCs. Cit-peptides were initially titrated on an individual basis to determine the optimum concentration for use ($n = 2$). We then compared stimulation with either single peptides or a pool ($n = 2$), and found that PBMC stimulated with the pooled cit-peptides had a higher proliferative response. Both single and pooled cit-peptide induced T cell proliferation was observed in both RA and HC samples (Figure 1); the largest responses were seen amongst RA

Figure 1 Antigen-specific CD4+ CD45RO+ responses of citrullinated peptide stimulated PBMC from HCs and RA patients.