None declared, Alexander Kreuter: None declared, Georg Schett Speakers bureau: AbbVie, BMS, Celgene, Janssen, Eli Lilly, Novartis, Roche and UCB, Jörg Distler Grant/research support from: Boehringer Ingelheim, Consultant of: Boehringer Ingelheim, Paid instructor for: Boehringer Ingelheim, Speakers bureau: Boehringer Ingelheim, Andreas Ramming Grant/research support from: Pfizer, Novartis, Consultant of: Boehringer Ingelheim, Novartis, Gilead, Pfizer, Speakers bureau: Boehringer Ingelheim, Roche, Janssen
DOI: 10.1136/annrheumdis-2020-eular.5745

OP0142

FIBROBLAST GROWTH FACTOR RECEPTOR 3 REGULATES THE ACTIVITY OF PROFIBROTIC CYTOKINE AND GROWTH FACTOR PATHWAYS TO DRIVE FIBROBLAST ACTIVATION AND TISSUE FIBROSIS IN SYSTEMIC SCLEROSIS

D. Chakraborty¹, H. Zhu^{2,3}, A. Juengel⁴, L. Summa², Y. N. Li², C. Bergmann², A. E. Matei², T. Trinh-Minh², C. W. Chen², C. Dees², A. Ramming², G. Schett², O. Distler⁴, J. Distler². ¹Friedrich-Alexander University (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, ²Department of Internal Medicine 3 - Rheumatology and Immunology, Erlangen, Germany; ³Friedrich-Alexander University (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, Department of Internal Medicine 3 - Rheumatology and Immunology, Erlangen, Germany; ⁴Xiangya Hospital, Central South University, Department of Rheumatology, Changsha, Hunan, China; ⁵University of Zurich, Zürich, Switzerland

Background: Fibroblast growth factor receptor 3 (FGFR3) is a member of the family of different fibroblast growth factor receptors with several ligands called fibroblast growth factors (FGFs) in humans. Each FGFR has different isoforms resulting from natural alternative splice variants. Upon binding FGF ligands, fibroblast growth factor receptors (FGFRs) trigger various intracellular signaling pathways to regulate important biological processes. Systematic evaluation of FGF/FGFR signaling in the context of SSc has not been performed so far.

Objectives: The aim of this study was to characterize FGFR3/FGF9 signaling in the context of fibroblast activation and to evaluate FGFR3 as a potential molecular target for antifibrotic treatment in SSc.

Methods: Differential expression profiling of dermal cells from SSc patients and healthy volunteers were performed employing GEArray cDNA microarray. Real-time PCR, Western Blot, immunohistochemistry and immunofluorescence were done in skin tissues and fibroblasts from SSc patients. Selective inhibitors in conjunction with genetic knockdown and knockout strategies were used to target FGFR3 signaling *in vitro* and in mouse models of SSc: skin fibrosis induced by bleomycin and by overexpression of a constitutively active transforming growth factor receptor 1 (TBR) and tight skin-1 (TSK) mice. Affymetrix gene arrays in dermal fibroblasts from mice with constitutive FGFR3 signaling and mice lacking FGFR3.

Results: Expression of FGFR3, specifically the isoform FGFR3IIIb and its ligand FGF9, was significantly upregulated in the dermis and dermal fibroblasts of SSc patients as compared to healthy volunteers. Furthermore, an increase of FGFR3 IIIb/FGF9 expression comparable to that in SSc fibroblasts could also be obtained by stimulating normal healthy dermal fibroblasts with transforming growth factor (TGFβ) *in vitro* and in mice constitutively overexpressing active TGFβ receptor type I.

Transcriptome profiling, *in silico* analysis and functional experiments revealed that FGFR3 synergistically induces multiple profibrotic pathways including Endothelin-, Interleukin-4- and CTGF-signaling in a CREB-dependent manner. FGFR3 exerts profibrotic effects by modulating phosphorylation of CREB by ERK-, AKT-, CAMK2- and p38-kinases. Activation of FGFR3 in healthy or SSc dermal fibroblasts by stimulation with recombinant FGF9 was sufficient to induce resting fibroblast-to-myofibroblast differentiation along with increased collagen secretion and alpha-SMA production.

Genetic knockout of Fgfr3 abrogates myofibroblast differentiation *in vitro* and ameliorates skin fibrosis in TSK and TBR mice and in bleomycin-induced fibrosis. Further confirming the translational potential of these findings in the preclinical models of SSc, we demonstrate that pharmacological inactivation of FGFR3 by PD173074 could induce the regression of experimental fibrosis *in vitro* and in bleomycin-challenged, TSK and TBR mice.

Conclusion: Our findings characterize FGFR3 as an upstream regulator of a network of profibrotic mediators in SSc and thus, we could demonstrate successfully that the targeted inhibition of FGFR3 could inhibit multiple signaling pathways *in vitro* and ameliorated fibrosis in different preclinical models of SSc. These findings may have direct translational implications as FGFR3 inhibitors are currently in development.

Disclosure of Interests: Debomita Chakraborty: None declared, Honglin Zhu: None declared, Astrid Juengel: None declared, Lena Summa: None declared,

Yi-Nan Li: None declared, Christina Bergmann: None declared, Alexandru-Emil Matei: None declared, Thuong Trinh-Minh: None declared, Chih-Wei Chen: None declared, Clara Dees: None declared, Andreas Ramming: None declared, Georg Schett Speakers bureau: AbbVie, BMS, Celgene, Janssen, Eli Lilly, Novartis, Roche and UCB, Oliver Distler Grant/research support from: Grants/Research support from Actelion, Bayer, Boehringer Ingelheim, Competitive Drug Development International Ltd. and Mitsubishi Tanabe; he also holds the issued Patent on mir-29 for the treatment of systemic sclerosis (US8247389, EP2331143)., Consultant of: Consultancy fees from Actelion, Acceleron Pharma, AnaMar, Bayer, Baecon Discovery, Blade Therapeutics, Boehringer, CSL Behring, Catenion, ChemomAb, Curzon Pharmaceuticals, Ergonex, Galapagos NV, GSK, Glenmark Pharmaceuticals, Inventiva, Italfarmaco, IQvia, medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Roche, Sanofi and UCB, Speakers bureau: Speaker fees from Actelion, Bayer, Boehringer Ingelheim, Medscape, Pfizer and Roche, Jörg Distler Grant/research support from: Boehringer Ingelheim, Consultant of: Boehringer Ingelheim, Paid instructor for: Boehringer Ingelheim, Speakers bureau: Boehringer Ingelheim
DOI: 10.1136/annrheumdis-2020-eular.2915

Vasculitis

OP0143

CANCER IN GIANT-CELL ARTERITIS PATIENTS: A LARGE NATIONWIDE STUDY

N. Ben-Shabat¹, L. Dar^{2,3}, S. Tiosano^{2,3}, A. Wadat^{1,2,3}, D. Comanesther⁴, A. Cohen⁴, H. Amital^{1,2,3}. ¹Tel-Aviv University, Sackler Faculty of Medicine, Tel-Aviv, Israel; ²Sheba Medical Center, Medicine B, Ramat-Gan, Israel; ³Sheba Medical Center, The Zabudowicz Center for Autoimmune Diseases, Ramat-Gan, Israel; ⁴Clalit Health Services, Chief Physician's Office, Tel-Aviv, Israel

Background: The association between giant-cell arteritis (GCA) and malignancy is controversial.

Objectives: To assess malignancy rates and risk in GCA patients in a large-scale population-based study.

Methods: We utilized the medical database of Clalit-Health-Services for this retrospective cohort study. Follow-up was from January 1, 2002 and continued until death or end of follow-up on September 1, 2018. Incident GCA patients were compared with age-and-sex-matched controls. Hazard-ratios for subtypes of malignancies were obtained by the Cox proportional-hazard model, adjusted for socio-demographic variables and cancer risk factors.

Results: The study population included 7,213 GCA patients and 32,987 age- and sex-matched controls who were not diagnosed with the disease. The mean age of GCA diagnosis was 72.3±9.9 years (median 73.1 years) and 69.1% were women. At Kaplan-Meier survival analysis, assessing cumulative cancer-free survival in GCA patients and controls, GCA patients had worse curve than controls (chi-squared = 49.84; degrees of freedom = 1; p < 0.0001; Figure 1). At the cox-survival analysis adjusted for age, sex, SES and cancer risk factors GCA patients showed increased risk for overall cancer (HR 1.29 [95%CI 1.20-1.39]),

Table 1. Cox survival analysis assessing crude and adjusted hazard for cancer in GCA patients compare to controls

Type of malignancy	Adjusted HR	
	HR	95% CI
Any malignancy	1.29	1.20, 1.39
Oropharyngeal cancer	0.96	0.69, 1.35
Thyroid cancer	1.20	0.66, 2.16
Breast cancer	0.93	0.75, 1.14
Lung cancer	1.26	0.99, 1.59
Esophagus cancer	1.86	0.93, 3.75
Stomach Cancer	0.61	0.37, 0.98
Colorectal Cancer	1.12	0.93, 1.36
Liver and bile ducts cancer	1.06	0.69, 1.62
Kidney cancer	1.60	1.15, 2.23
Bladder cancer	1.15	0.88, 1.50
Uterus cancer	0.85	0.55, 1.30
Cervical cancer of the uterus	0.45	0.37, 1.46
Ovary Cancer	0.96	0.58, 1.59
Prostate Cancer	1.07	0.80, 1.43
Sarcoma	2.14	1.41, 3.24
Melanoma	1.11	0.80, 1.55
Acute Leukemia	1.81	1.06, 3.07
Chronic Leukemia	1.82	1.19, 2.77
Myelodysplastic syndrome	1.84	0.94, 3.60
Hodgkin's Lymphoma	2.42	1.12, 5.20
Non-Hodgkin's Lymphoma	1.66	1.21, 2.29
Multiple Myeloma	2.40	1.63, 3.53

kidney cancer (HR 1.60 [95%CI 1.15-2.23]), sarcoma (HR 2.14 [95%CI 1.41-3.24]), acute-leukemia (HR 1.81 [95%CI 1.06-3.07]), chronic-leukemia (HR 1.82 [95%CI 1.19-2.77]), Hodgkin's lymphoma (HR 2.42 [95%CI 1.12-5.20]), non-Hodgkin's lymphoma (HR 1.66 [95%CI 1.21-2.29]) and multiple myeloma (HR 2.40 [95%CI 1.63-3.53]) (Table 1). The time (mean [months] $\pm$ SD) to the diagnosis of any malignancy was significantly shorter in GCA patients (48.6 ± 41.3) compared to controls (58.1 ± 43.6 ; $p < 0.001$).

Figure 1. Kaplan-Meier cancer-free survival curve

Conclusion: GCA patients are at increased risk for sarcoma, kidney cancer, hematological malignancies and overall malignancies compared to age-and-sex matched controls from the general population.

References:

- [1] Watad A, McGonagle D, Bragazzi NL, Tiosano S, Comaneshter D, Shoenfeld Y, et al. Autoantibody status in systemic sclerosis patients defines both cancer risk and survival with ANA negativity in cases with concomitant cancer having a worse survival. *Oncoimmunology* 2019;8:e1588084.
- [2] Ben-Shabat N, Tiosano S, Shovman O, Comaneshter D, Shoenfeld Y, Cohen AD, et al. Mortality among patients with giant-cell arteritis: A large-scale population-based cohort study. *J Rheumatol* 2019;

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.6710

OP0144 EFFECT OF TOCILIZUMAB ON VASCULAR INFLAMMATION BY ¹⁸F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY: A PROSPECTIVE, LONGITUDINAL STUDY

K. A. Quinn^{1,2}, H. Dashora¹, M. Ahlman¹, P. Grayson¹. ¹National Institutes of Health, Bethesda, United States of America; ²MedStar Georgetown University Hospital, Washington, DC, United States of America

Background: Two randomized controlled trials have demonstrated clinical efficacy of tocilizumab for the treatment of giant cell arteritis (GCA)(1, 2). In these trials, clinical and laboratory measures were used to define the outcome measures. The direct effect of tocilizumab on vascular inflammation remains poorly characterized.

Objectives: To prospectively evaluate vascular inflammation as measured by ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in a longitudinal cohort of patients with GCA treated with tocilizumab over a several year follow-up period.

Methods: Patients with GCA were recruited into a prospective, observational cohort. All patients fulfilled modified 1990 American College of Rheumatology (ACR) Classification Criteria for GCA. All patients underwent FDG-PET computed tomography (CT) prior to initiation of tocilizumab. A single reader reviewed all PET scans, blinded to clinical data. Qualitative assessment of FDG uptake relative to liver uptake by visual assessment (scale 0-3) was assessed in 9 arterial territories. A summary score, PET Vascular Activity Score (PETVAS), was calculated (scale 0-27).

Patients underwent imaging at 6-12 month intervals per a standardized imaging protocol. In a subset of patients in whom tocilizumab was discontinued due to established remission, a repeat FDG-PET scan was obtained within 6 months of drug discontinuation.

Change in PET activity over time was measured by linear regression. PET activity during established remission was compared to PET activity after discontinuation of tocilizumab. For some patients, tocilizumab was added to the existing treatment regimen without a substantive change in concomitant glucocorticoid dose. In a secondary analysis, patients were stratified by prednisone dosing (high dose prednisone >10mg/day prednisone, low dose prednisone $\leq$ 10mg/day prednisone during the imaging interval) to determine if tocilizumab had an effect on vascular inflammation independent of glucocorticoids.

Results: 22 patients were included in the study. All patients had clinically active disease at baseline with median baseline PETVAS 24.5 (23-27). There was a significant reduction in PETVAS over 2 years follow up ($p < 0.01$ for linear trend) (Figure). Of note, there was continued progressive improvement in PETVAS in both year 1 and year 2 of treatment. Eight patients received concomitant high dose glucocorticoids and 14 patients remained on low dose glucocorticoids with the addition of tocilizumab. In patients who only received low dose prednisone, significant reduction in PETVAS was still observed with addition of tocilizumab (PETVAS 25.5 to 19.5, $p = 0.04$). In a subset of 5 patients who discontinued tocilizumab due to established remission [median PETVAS 19 (17.5-22) at time of remission], a repeat FDG-PET scan within 6 months after treatment discontinuation showed worsening PET activity in 4 out of 5 patients [median PETVAS 23 (20-23)]. Two of these patients subsequently experienced a clinical disease relapse.

Conclusion: Tocilizumab was associated with improved vascular inflammation as assessed by FDG-PET. There was continued improvement of vascular inflammation at both year 1 and year 2 of treatment, and early evidence suggests a rebound of vascular inflammation when tocilizumab was discontinued. These data provide rationale for long-term tocilizumab therapy in patients with GCA and for consideration of FDG-PET as an outcome measure in future clinical trials.

References:

- [1] Stone JH, et al. *N Engl J Med* 2017;377:317-28.
- [2] Villiger PM, et al. *Lancet* 2016;387:1921-7.

Figure. XXX

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.2840

OP0145 MALIGNANCY IN ANCA-ASSOCIATED VASCULITIS AND POLYARTERITIS NODOSA: AN AUSTRALIAN POPULATION-BASED STUDY

J. Tieu^{1,2,3,4}, S. Lester^{1,2}, W. Raymond⁵, H. Keen^{5,6}, C. Hill^{1,2,4}, J. Nossent^{5,7}. ¹Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia; ²Basil Hetzel Institute, Adelaide, Australia; ³Lyell McEwin Hospital, Adelaide, Australia; ⁴The Queen Elizabeth Hospital, Adelaide, Australia; ⁵University of Western Australia, Rheumatology, Perth, Australia; ⁶Fiona Stanley Hospital, Rheumatology Dept, Perth, Australia; ⁷Sir Charles Gairdner Hospital, Rheumatology Dept, Perth, Australia

Background: The increased risk of malignancy in patients with ANCA-associated vasculitis (AAV) and polyarteritis nodosa (PAN) has been attributed to late