Sanofi Aventis, Inventiva, CSL Behring, Boehringer Ingelheim, Bayer, Robert Lafatis: None declared, David Fox: None declared, Dinesh Khanna Shareholder of: Eicos Sciences, Inc, Grant/research support from: Bayer, BMS, Pfizer, Horizon, Consultant for: Actelion Acceleron, Arena, Bayer, BI, BMS, CSL Behring, Corbus, Cytos, GSK, Genentech/Roche, Galapagos, Employee of: Elcos Sciences, Inc, Michael Whitfield Shareholder of: Scientific Founder, Celdara Medical LLC, Grant/research support from: Dr. Whitfield has received research contracts from Celdara Medical LLC and UCB Biopharma, Consultant for: Bristol Myers Squib, Celdara Medical, Corbus, and Boehringer Ingelheim

DOI: 10.1136/annrheumdis-2019-eular.7661

THU0355 IGURATIMOD MIGHT TREAT SCLERODERMA WITH INTERRUPTED EGR1/TGF- β LOOP

Qingran Yan¹, Lichong Shen¹, Daniel Morales-Cano¹, Xiaoxiang Chen¹. ¹Renji Hospital, Shanghai Jiaotong University, School of Medicine, Department of Rheumatology, Shanghai, China

Background: Systemic sclerosis (SSc) is an autoimmune disease characterized with multiple organ fibrosis. Previous studies showed transcription factor early growth response 1 (Egr1) overexpressed in the lesional skin of SSc patients, as well as Egr1 inducible genes¹. Egr1 forms a positive feedback loop with master pro-fibrotic cytokine TGF β and thus promotes fibrosis.

Objectives: To investigate the anti-fibrotic effect of a novel DMARD iguratimod in scleroderma models and patient skin grafts.

Methods: We used iguratimod to treat TGF β -stimulated human skin fibroblast, bleomycin induced mice, tight skin 1 (TSK-1) mice and SSc skin grafts. The bleomycin model contained pre-establish fibrosis and late onset treatment. The skin grafts came from three SSc patients and was planted into irradiated nude mice.

Results: Iguratimod down-regulated egr1 expression in human skin fibroblast, with decreased collagen production and α -SMA expression. Knocking down Egr1 in fibroblast could mimic these effects. Both oral and topical iguratimod could reduce dermal thickening and collagen deposition in bleomycin induced skin fibrosis. α -SMA (+) myofibroblast counts, as well as Egr1 (+) and/or TGF β (+) fibroblast counts in iguratimod treated groups were significantly less than the controls. Similarly, topical iguratimod ameliorated fibrosis with deduced dermal thickening in TSK-1 mice. Of note, 5-week iguratimod local injection remarkably reduced collagen content in skin grafts from three SSc patients. Staining of Egr1 and TGF β in skin tissue were inhibited after iguratimod treatment simultaneously.

Conclusion: We found the potential of iguratimod to treat SSc, which was characterized as an Egr1 inhibitor. Further clinical investigation is needed to establish its safety and efficacy.

REFERENCES

- [1] Bhattacharyya S, Sargent JL, Du P, et al. Egr-1 induces a profibrotic injury/repair gene program associated with systemic sclerosis. *PloS one* 2011;6(9):e23082 doi: 10.1371/journal.pone.0023082
- [2] Chen SJ, Ning H, Ishida W, et al. The early-immediate gene EGR-1 is induced by transforming growth factor-beta and mediates stimulation of collagen gene expression. *The Journal of biological chemistry* 2006;281(30):21183-97 doi: 10.1074/jbc.M603270200
- [3] Wu M, Melichian DS, de la Garza M, et al. Essential roles for early growth response transcription factor Egr-1 in tissue fibrosis and wound healing. *The American journal of pathology* 2009;175(3):1041-55 doi: 10.2353/ajpath.2009.

Acknowledgement: This work is supported by National Natural Science Foundation of China (81601401).

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.2421

THU0356 STAPHYLOCOCCUS AUREUS REGULATES FIBROBLAST FUNCTIONS – IMPLICATIONS FOR TISSUE REPAIR IN CHRONIC DIGITAL ULCERS IN SYSTEMIC SCLEROSIS

Masaya Yokota¹, Matthew Kassier¹, Nicola Häfner², Matthias Brunner¹, Janine Schniering¹, Oliver Distler¹, Annelies S. Zinkernagel², Britta Maurer¹. ¹Center of Experimental Rheumatology, Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland; ²Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Background: Chronic digital ulcers (DU) are a major complication in systemic sclerosis (SSc). Non-healing wounds are characterized by persistent inflammation, defective re-epithelialization and impaired matrix remodeling,

and are often accompanied by bacterial colonization. In DU, the breach of the basement membrane exposes tissue and cell layers to commensal skin bacteria.

Objectives: To investigate whether interactions between commensal skin bacteria and dermal fibroblasts affect tissue repair mechanisms.

Methods: Dermal fibroblasts isolated from healthy controls (HC) and patients with diffuse cutaneous SSc (dcSSc) (n=3, each) were co-cultured with *Staphylococcus aureus* (SA) for 3 h at using a lower inoculum rather representing colonization (1×10^5 CFU/ml) and a higher inoculum reflecting infection (1×10^7 CFU/ml). Thereafter, fibroblasts were cultured with flucloxacillin-containing medium to kill extracellular and adherent bacteria. For mechanistic studies, a fibroblast cell line (BJ-5ta) was used. IL-6, IL-8, pro-collagen α , and interferon (IFN)- β proteins in culture supernatants were measured by ELISA. Gene expression was assessed by quantitative PCR. Contractility was analyzed by collagen gel contraction assay. Wound closure assay was performed on a confluent cell layer with a uniform cell-free gap, generated by a cell culture insert. Expression of alpha-smooth muscle actin (α -SMA) was evaluated by Western blotting, cell proliferation with a colorimetric assay. Cell death was analyzed by live cell real time assay. Bacterial invasion was assessed by immunofluorescence staining using confocal microscopy and CFU recovery. Gene knockdown was performed using siRNA.

Results: Exposure to 1×10^7 CFU/ml of SA influenced fibroblast function. In brief, exposure to SA increased the secretion of IL-6 and IL-8 in dermal fibroblasts by 1571/455-fold (HC/dcSSc; $p=0.08<0.05$) and by 325/1402-fold (HC/dcSSc; $p<0.05$ each) respectively. In addition we observed upregulation of the expression of MMP1 by 8.2/5.7-fold (HC/dcSSc; $p<0.05$ each) and MMP3 by 5.1/5.7-fold (HC/dcSSc; $p=0.06<0.05$). There was a trend towards decreased secretion of pro-collagen α . TGF- β -induced α -SMA expression was completely inhibited. Cell contraction was impaired by 22.0/31.6% (HC/dcSSc; $p=0.08<0.05$), wound closure by 18.8/14.9% (HC/dcSSc; $p<0.05$ each), and proliferation by 30.5/44.3% (HC/dcSSc; $p=0.24<0.05$). SA induced apoptosis and necrosis. SA invaded fibroblasts via endocytosis (25-50% of inoculated live SA). IFN- β secretion was induced 8.4/31.7-fold (HC/dcSSc; $p<0.05$ each). The genes of cytosolic dsDNA sensor molecules such as cyclic GMP-AMP synthase (cGAS) were upregulated 11.9/8.6-fold (HC/dcSSc; $p<0.05$ each). TLR9, an endosomal DNA sensor, was constitutively expressed. Knockdown of STING or MyD88, downstream mediators of cGAS and TLR9 respectively, reduced the induction of IFN- β (down to 68.2/66.2%; $p=0.20/0.16$), IL-6 (down to 57.2/55.2%; $p<0.05$ each), and IL-8 (down to 45.3/36.0%; $p<0.05$ each). Furthermore, inhibition of endocytosis with cytochalasin D decreased the expression of IFN- β (down to 24.6%; $p<0.05$), IL-6 (down to 34.9%; $p<0.05$), and IL-8 (down to 27.6%; $p<0.05$). In contrast, inhibition of endocytosis did not affect induction of apoptosis. This suggests that the invasion of fibroblasts by SA and the subsequent intracellular DNA sensing are crucial for the induction of these genes independently of apoptosis.

Conclusion: Invasion of dermal fibroblasts by SA with activation of the STING and TLR9-MyD88 pathways is a key element in the impairment of tissue repair responses.

THU0357 VENTRICULAR-ARTERIAL COUPLING AS A PREDICTOR OF CARDIOVASCULAR EVENTS IN SYSTEMIC SCLEROSIS

Elisabetta Zanatta¹, Pamela Polito¹, Giulia Famoso², Franco Cozzi¹, Andrea Doria¹, Francesco Tona². ¹Rheumatology Unit, Department of Medicine – DIMED, Padova, Italy; ²Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy

Background: Standard Transthoracic Echocardiography (TTE) parameters have shown a low sensitivity in the detection of primary myocardial involvement (PMI) in systemic sclerosis (SSc). Arterial-ventricular coupling (VAC) is calculated by TTE as the ratio between arterial elastance (Ea) and ventricular end-systolic elastance (Ees), which reflects left ventricle stiffness. VAC is a central determinant of cardiovascular performance.

Objectives: We aimed to assess TTE-derived measures of cardiac mechanics and the prognostic role of VAC in SSc.

Methods: 75 patients affected by SSc without symptoms of cardiac involvement and 10 controls matched for sex and age were retrospectively evaluated. We considered the first TTE available after SSc diagnosis. Determinants of cardiac mechanics were calculated by TTE¹: end systolic elastance (Ees), arterial elastance (Ea), ventricular arterial coupling (VAC=Ees/Ea), end diastolic elastance (Eed). A value of VAC > 0.62 was considered indicative of altered VAC (i.e. uncoupling), whereas a lower value as normal (i.e. coupling). Finally, we considered the hospitalization for cardiovascular event during a mean follow-up of 10.8 $\pm$ 1.8 years.

Results: Among the 75 patients 42 (59.2%) had a diffuse cutaneous form of SSc (dSSc) and 64 (85.3%) were female; in SSc patients the mean age was 53±12.1 yrs and the mean disease duration 10.1± 2.3 yrs. 36 (52.2%) patients had positive SCI70, 31 (44.9%) ACA, and 2 (2.9%) anti-RNA pol III. Compared to controls, SSc patients had higher Ea (2.28 vs 0.95 mmHg/ml, $p=0.003$) and Ees (3.95 vs 2.98 mmHg/ml, $p=0.05$), and increased diastolic stiffness (Eed) (0.210 vs 0.146 mmHg/ml, $p=0.01$). VAC was consequently comparable to controls. SSc patients affected with dcSSc had a lower Ees (2.90 vs 4.367, $p<0.001$) and Eed (0.24 vs 0.17, $p=0.032$) and a higher VAC (0.52 vs 0.70, $p=0.01$) compared to ISSc. No differences were found between patients with anti-SCI70 and ACA. At 10 years, 23% of patients was hospitalized for at least one cardiovascular event. The analysis of survival free hospitalization or death in all SSc patients demonstrated a worse outcome and poor prognosis in patients with an altered VAC (31, 47.7%) compared to those with a normal VAC (34, 52.3%) (Figure 1).

Abstract THU0357 – Figure 1

Conclusion: Our study suggests that both ventricular and arterial stiffness may be increased in SSc patients without signs and symptoms of heart disease. Since VAC seems to have a prognostic role in the prediction of cardiovascular events in SSc, it could be helpful to define an early therapeutic strategy to prevent or delay cardiac manifestations in these patients.

REFERENCE:

1. Sagawa K et al, Am J Cardiol 1977;40:748-753.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.7479

20. Spondyloarthritis – clinical aspects (other than treatment)

THU0358 DEVELOPMENT OF A SET OF ASAS QUALITY STANDARDS FOR ADULTS WITH AXIAL SPONDYLOARTHRITIS

Uta Kiltz^{1,2}, Robert B.M. Landewé³, Désirée van der Heijde⁴, Martin Rudwaleit⁵, Maxime Dougados⁶, Nurullah Akkoc⁷, Annelies Boonen⁸, Jan Brandt-Juergens⁹, Philippe Caroon¹⁰, Laure Gossec¹¹, Meryn Jongkees¹², Pedro Machado¹³, Helena Marzo-Ortega¹⁴, Anna Moltó⁶, Victoria Navarro-Compán¹⁵, Karin Niedermann Schneider¹⁶, Percival D. Sampaio-Barros¹⁷, Gleb Slobodin¹⁸, Filip van den Bosch¹⁹, Astrid van Tubergen⁸, Salima van Weely²⁰, Michael Weisman²¹, Dieter Wiek²², Juergen Braun¹². ¹Rheumazentrum Ruhrgebiet, Herne, Germany; ²Ruhr-University, Bochum, Germany; ³ARC, Amsterdam, Netherlands; ⁴Leiden University Medical Center, Leiden, Netherlands; ⁵Klinikum Bielefeld, Bielefeld, Germany; ⁶Hôpital Cochin, Paris, France; ⁷Rheumatology, Izmir, Turkey; ⁸Maastricht University Medical Center, Maastricht, Netherlands; ⁹Rheumapaxis, Berlin, Germany; ¹⁰Ghent University, Ghent, Belgium; ¹¹Sorbonne Université, Hôpital Pitie-Salpêtrière, Paris, France; ¹²Seayn Medical, The Hague, Netherlands; ¹³University College London, London, United Kingdom; ¹⁴Leeds General Infirmary, Leeds, United Kingdom; ¹⁵University Hospital La Paz, IdiPaz, Madrid, Spain; ¹⁶ZHAW Zurich University, Zurich, Switzerland; ¹⁷University Sao Paulo, Sao Paulo, Brazil; ¹⁸Bnai-Zion Medical Center, Haifa, Israel; ¹⁹Ghent University Hospital, Ghent, Belgium; ²⁰Leiden University Medical Centre, Leiden, Netherlands; ²¹Cedars-Sinai Medical Center, Los Angeles, United States of America; ²²Rheuma-Liga, Cologne, Germany

Background: There is wide variation in the management of patients with axial spondyloarthritis (axSpA) worldwide with significant unmet needs such as delayed diagnosis. A major goal of the international organization Assessment of SpondyloArthritis international Society (ASAS) is to improve quality of care and health outcomes in axSpA. One way to achieve this is to define quality standards (QS) in order to identify resources and processes which may need to be optimized. Such

standards must be specific, measurable, aspirational and achievable in daily care.

Objectives: To develop ASAS QS to ultimately improve the quality of care for adults with axSpA.

Methods: The ASAS QS group, established in 2015, developed a step-wise approach starting with (I) an overview and open discussions resulting in a proposal for possible key areas for quality improvement. Thereafter, (II) ASAS members and invited patients discussed and commented on a provisional list via a web-based survey with the possibility to propose additional key areas for quality improvement. (III) The complete list was then evaluated by ASAS members and invited patients. (IV) Then, the ASAS QS group prioritized key areas for which quality statements and measures are to be developed, and (V) phrased QS for the most important key areas. Finally (VI), a draft version was commented on, discussed and finally agreed by the ASAS members at the Annual ASAS Meeting 2019.

Results: The ASAS QS group, consisting of 20 rheumatologists, 2 physiotherapists and 2 patients, provided 34 potentially key areas for quality improvement which were commented by 140 participants (86 physicians, 42 patients). Within that process 3 new key areas were proposed and all 37 key areas for improvement were again evaluated by 120 participants (86 physicians, 29 patients). Five key areas were identified to be most important to phrase QS: referral, rheumatologic assessment, treatment, education/self-management and comorbidities. Altogether, 9 QS, each accompanied by a rationale and a measure (figure), were endorsed by ASAS.

Conclusion: ASAS successfully developed the first QS set for improvement of health care provided for adults with axSpA. All QS are achievable in daily care in an optimized situation and intend to minimize variation in quality of care. It is emphasized that ASAS is well aware that all QS are ideal visions of an optimal care which may currently not be realistic in many countries.

No	Domain	Quality statement
1	Referral	People with suspicion of axial SpA are referred to a rheumatologist for diagnostic assessment within 3 working days.
2	Time to specialist	People with suspicion of axial SpA are assessed by a rheumatologist within 3 weeks after referral.
3	Assessment	People with suspected axial SpA have their diagnostic work-up completed within 2 months.
4	Monitoring	Disease activity of people with axial SpA is monitored under the supervision of a rheumatologist with validated composite scores at least twice a year.
5	Disease control	In people with axial SpA and active disease despite conventional therapy, treatment escalation with biologics is discussed.
6	Non-pharmacological treatment	People with axial SpA are informed about the benefits of regular exercise.
7	Education and self-management	People with axial SpA are offered education on the disease including self-management within two months of diagnosis.
8	Rapid access	Patients with axial SpA and disease flare or possibly drug-related side effects receive advice within 2 working days of contacting the rheumatologist.
9	Annual review	People with axial SpA have a comprehensive annual review by the rheumatologist.

Abstract THU0358 – Figure 1. ASAS quality standards for patients with axial spondyloarthritis

Discloser of Interest: Uta Kiltz Grant/research support from: AbbVie, Chugai, Eli Lilly, Grünenthal, Janssen, MSD, Novartis, Pfizer, Roche, and UCB., Consultant for: AbbVie, Chugai, Eli Lilly, Grünenthal, Janssen, MSD, Novartis, Pfizer, Roche, and UCB., Robert B.M. Landewé: None declared, Désirée van der Heijde Consultant for: AbbVie, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, Union Chimique Belge, Martin Rudwaleit Consultant for: AbbVie, BMS, Celgene, Janssen, Eli Lilly, MSD, Novartis, Pfizer, Roche, UCB Pharma, Consultant for: AbbVie, BMS, Celgene, Janssen, Eli Lilly, MSD, Novartis, Pfizer, Roche, UCB Pharma, maxime dougados Grant/research support from: Eli Lilly and Company, Pfizer, AbbVie, and UCB Pharma, Consultant for: Eli Lilly and Company, Pfizer, AbbVie, and UCB Pharma, Nurullah Akkoc: None declared, Annelies Boonen: None declared, Jan Brandt-Juergens: None declared, Philippe Caroon: None declared, Laure Gossec Grant/research support from: AbbVie, BMS, Celgene, Janssen, Lilly, MSD, Novartis-Sandoz, Pfizer, Sanofi, and UCB, Consultant for: AbbVie, Biogen, BMS, Celgene, Janssen, Lilly, MSD, Nordic Pharma, Novartis-Sandoz, Pfizer, Roche, Sanofi, and UCB, Consultant for: L Gossec has received honoraria from Celgene as investigator for this study, Meryn Jongkees: None declared, Pedro Machado Consultant for: Abbvie, BMS, Celgene, Janssen, MSD, Novartis, Pfizer, Roche and UCB, Speakers bureau: Abbvie, BMS, Celgene, Janssen, MSD, Novartis, Pfizer, Roche and UCB, Helena Marzo-Ortega Grant/research support from: Janssen, Novartis and Pfizer, Consultant for: AbbVie, Celgene, Janssen, Eli-Lilly, Novartis and UCB,