affected by early RA, while Etanercept and Abatacept are the biologics with the highest probability of inducing ACR70.

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FRI0146

CORRELATION BETWEEN THE RHEUMATOID FACTOR POSITIVITY AND THE HIGHER DISCONTINUATION RATE OF BIOLOGICAL THERAPY IN RHEUMATOID ARTHRITIS: A FINE-GREY PROPORTIONAL HAZARD REGRESSION ANALYSIS

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Background: As quantifying the occurrence of outcome over time holds vital importance in clinical medicine, the presence of competing risks must be considered when assessing the impact of prognostic factors on the incidence of an outcome over time. A competing risk is defined as an event that precludes the occurrence of an event of interest. For example, event arising from adverse effect causes is a competing risk when evaluating the effect of risk factors on the incidence of discontinuation of biological therapy because of inadequate response. The presence of biased estimates of the effect of covariates on the incidence in the presence of competing risks is attributed to the naïve use of the conventional Cox proportional hazards model that censors the competing event. Fine and Grey developed the subdistribution hazard model that facilitates modelling the effects of covariates on the cumulative incidence function in the presence of competing risks.

Objectives: The discontinuation of biological therapy in rheumatoid arthritis (RA) is attributed to several reasons, including inadequate response, adverse effect, remission, and changing hospital. In particular, inadequate response constitutes a principal and compelling reason. This study aims to investigate the correlation between covariates, including the rheumatoid factor (RF) positivity and the discontinuation of biological therapy due to inadequate response in bio-naïve patients with RA using the Fine–Grey proportional hazard regression for competing events.

Methods: In this study, we enrolled patients in the Tsurumi Biologic Communication Registry that comprises Nagoya University and 15 affiliated institutions in Japan. We assessed the correlation between individual characteristic components and patient outcomes using the Fine–Grey proportional hazard regression for competing events. Apparently, time-based models estimate the effects of various characteristics (e.g., RF positivity, sex, and age) on time to develop events of interest, including the discontinuation owing to inadequate response. The Fine–Grey proportional hazard regression considered competing events, implying that this model generated separate hazard ratios for each competing event. All analyses were conducted in EZR version 1.36.

Results: A higher crude discontinuation rate was observed due to inadequate response in RF-positive patients than that in RF-negative patients using the cumulative incidence function of competing events and Grey test (figure 1). After adjusting for the baseline characteristics, including age, sex, stage, disease at the baseline, methotrexate use, prednisolone use, and tumour necrosis factor inhibitor (TNFi) or non-TNFi (HR, 1.57; 95% CI: 1.01–2.43; $p < 0.05$; table 1), the difference was significant in the Fine–Grey proportional hazard regression analysis.

	Hazard ratio	Lower 95% CI	Upper 95% CI	p.value
RF positivity	1.57	1.01	2.43	<0.05
Sex	0.91	0.61	1.36	0.67
Age	0.99	0.98	1.01	0.12
Das28esr at baseline	1.31	1.15	1.48	<0.05
non-TNFi	0.53	0.31	0.91	<0.05
MTX use	1.64	1.01	2.67	<0.05
PSL use	1.16	0.82	1.64	0.38
Stage	0.99	0.98	1.01	0.57

Conclusions: Using the Fine–Grey proportional hazard regression for competing events, this study demonstrated a correlation between the RF positivity and inadequate response to biological therapy on bio-naïve patients with RA.

Disclosure of Interest: None declared

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FRI0147

ANALYSIS OF RADIOGRAPHIC JOINT DESTRUCTION IN THE PATIENTS WITH RHEUMATOID ARTHRITIS WHO HAVE WITHDRAWN, SPACED AND CONTINUED BIOLOGICS AFTER ACHIEVING SUSTAINED REMISSION FROM LOCAL BIOLOGICS REGISTRY

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Background: Increasing of remission reached by biologics agents in early and established RA patients^{1, 2}. Data on withdrawn, spacing or reducing of biologics (BIO) medication after sustained remission are limited^{3, 4}. After withdrawn, spacing or reducing, it is less known to be influenced the radiographic destruction of the joints.

Objectives: To retrospectively analyse the joint destruction using modified Total Sharp Score (mTSS) in RA patients in sustained remission, either withdrawing, spacing and continuing BIO.

Methods: Local prefectural (ZAO) registry which is open-labelled BIO cohort study has registered 356 RA patients. RA Patients were enrolled into this study if they maintained in DAS remission (DAS28-ESR<2.6) more than one year after starting BIO. Δ mTSS1 was estimated between starting BIO and withdrawn or spacing or reaching remission in each group, Δ mTSS2 between the beginning of withdrawn or spacing, or reaching remission in continuing group and latest follow-up or flare-up.

Results: 40 RA patients (32 female) using BIO was fulfilled in the criteria of this study in ZAO registry. Of 40 RA Patients, 10 has withdrawn BIO, 15 has spaced and 15 has continued it after maintain DAS remission more than one year. Mean age was 43, 55, 54 year-old, mean RA affiliation 4.6, 15.3, 9.1 years before BIO and mean duration of remission 6.2, 7.6, 7 years, mean dosage of MTX and PSL was 7.7, 6, 5 mg/week and 1.1, 3, 4 mg/day, respectively. Δ mTSS1 and Δ mTSS2 was +2.4 and +4.5 in withdrawn group, +3.6 and +0.9 in spacing group, +0.2 and -1.4 in continuing group, respectively (figure 1, $p < 0.05$). Five cases in withdrawing group had resumed BIO because of flare-up of their disease activity.

Abstract FRI0147 – Figure 1. Radiographic destruction of joint in each withdrawn, spacing, continuing groups

Conclusions: Several studies reported the potential of BIO withdrawing, spacing or reducing in the patients with RA who reached remission^{3, 5}. All cases in spacing and withdrawing group have shown DAS28-4ESR<2.6 in this study, however, 50% (5/10 cases) in withdrawing group have re-flare and shown the radiological joint destruction. Spacing or reducing of BIO may have potential to maintain the remission of RA and prevent the joint destruction. Withdrawing of BIO after even sustained deeper remission may be difficult to keep real remission.

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Spondyloarthritis – etiology, pathogenesis and animal models

FRI0148 A STUDY OF MICROBIAL TRANSLOCATION IN AN ANIMAL MODEL OF SPONDYLOARTHRITIS

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Background: The intestinal microbiota is believed to have a central role in SpA pathogenesis. However, the mechanism through which enteric microbes contribute to peripheral inflammation remains enigmatic.

Objectives: The primary objective of this study was to determine whether microbial translocation can be observed to extra-intestinal tissues in the HLA-B27/β2m transgenic rat – a foremost translational model of spondyloarthropathy. Moreover, since an arthritis phenotype only presents in less than half of HLA-B27/β2m transgenic animals, we could examine whether microbiota composition between transgenic animals with and without arthritic disease.

Methods: Intestinal tissue (cecal contents), mesenteric lymph nodes (MLN), spleen, serum, liver, lung, ankle joint and eye were collected from age matched (20–24wk old) HLA-B27/β2m transgenic rats with or without arthritis and WT controls (n=20–45 per group). DNA was extracted and the 16 s rRNA V4 region amplified according to the standard Earth Microbiome Project protocol. Extraction blanks were run with each tissue to control for environmental contamination. Sequencing data (generated by Illumina MiSeq) was first processed using the SourceTracker algorithm to identify and remove contaminant sequences. Remaining reads were run through the DADA2 pipeline implemented in QIIME2.

Results: Our study of microbial translocation revealed a number of striking observations.

Firstly 16 s rRNA was detected at all tissue sites examined. Second, rather than observing a limited number of species, a highly polymicrobial and intestinal DNA signature was observed in all tissue sites examined. This observation was independent of genotype or disease state. The number of total reads in each tissue was highest in cecum as anticipated (approx. 1 00 000 reads) with the yield from other tissues roughly an order of magnitude lower.

The most abundant species in joint tissue included *Prevotella* spp. *Prevotella shahii* and *Prevotella stercorea*, *Roseburia faecis* and *Muribaculum intestinale*. The microbe *Blautia obeum*, a close relative of [*Ruminococcus*] gnavus within the same genus was also found in joint tissue. This of interest since this microbe has recently been associated with disease activity in SpA patients.

Interestingly an arthritis phenotype was strongly associated with a loss of intestinal bacterium *Eubacterium Oxidoreducens*. This is a flavone metabolising bacterium and supports previous metabolomic studies in which we have shown flavone compounds are greatly over-represented in the HLA-B27/β2m transgenic rats vs WT controls.

Conclusions: We propose translocation of microbes/microbial products from the gut to extra-intestinal tissues may be a contributory mechanism to SpA pathogenesis, although alone is not sufficient to elicit inflammatory disease. Specific changes in microbial community DNA profile in the gut or elsewhere may serve as useful biomarkers of disease state in either patient populations or disease models. This approach may yield useful candidates for further study such as *Eubacterium Oxidoreducens*. Future studies will verify our findings using PCR-independent methods.

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FRI0149 INFLAMMATION INTENSITY-DEPENDENT EXPRESSION OF OSTEOINDUCTIVE WNT PROTEINS IS CRITICAL FOR ECTOPIC NEW BONE FORMATION IN ANKYLOSING SPONDYLITIS

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Objectives: To investigate the molecular mechanism underlying the inflammation-related ectopic new bone formation in ankylosing spondylitis (AS).

Methods: Spinal tissues and sera were collected from patients or normal volunteers to detect the expression of Wnt proteins. An *in vitro* cell culture system mimicking the local inflammatory microenvironment of bone-forming sites was established to study the relationship between inflammation and Wnt expression, the regulatory mechanism of inflammation-induced Wnt expression and the role of Wnt signalling in new bone formation. A modified collagen-induced arthritis (mCIA) and a proteoglycan-induced spondylitis (PGIS) animal model were used to confirm the key findings *in vivo*.

Results: The levels of osteoinductive Wnt proteins were obviously increased in the sera and spinal ligament tissues of patients with AS. Only constitutive low-intensity TNF-α stimulation, but not short-term or high-intensity TNF-α stimulation, induced persistent expression of osteoinductive Wnt proteins and subsequent bone formation through NF-κB (p65) and JNK/AP-1 (c-Jun) signalling pathways. Furthermore, inhibition of either Wnt/β-catenin or Wnt/PKCδ pathway significantly suppressed new bone formation. The increased expression of Wnt proteins was confirmed in both mCIA and PGIS models. A kyphotic and ankylosing phenotype of the spine was observed during long-term observation in mCIA model. Inhibition of either Wnt/β-catenin or Wnt/PKCδ signalling pathway significantly reduced the incidence and severity of this phenotype.

Conclusions: Inflammation intensity-dependent expression of osteoinductive Wnt proteins is a key link between inflammation and ectopic new bone formation in AS. Activation of both canonical Wnt/β-catenin and noncanonical Wnt/PKCδ pathways is required for inflammation-induced new bone formation.

Abstract FRI0149 – Figure 1. (A) IHC staining of Wnt proteins in spinal tissues from patients with AS and DS. (B) ELISA analysis of Wnts expression in RAW cells subject to different pattern of TNF-α stimulation. (C) Alizarin red staining of MC3T3 cells stimulated with CM produced from Raw cells transfected with Wnt siRNAs. (D) Site-directed mutagenesis analysis of the Wnt3a promoter. (E) MicroCT images of the spines and hind paws of the mCIA mice. (F) Immunohistological staining of Wnt3a, Wnt5a and Wnt7b in