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SHORT REPORT

Identification of patient endotypes and adalimumab treatment responders in axial spondyloarthritis using blood-derived extracellular matrix biomarkers

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ABSTRACT

Objective To explore the potential of a panel of ECM remodelling markers as endotyping tools for axial spondyloarthritis (axSpA) by separating patients into subtypes and investigate how they differ among each other in disease activity scores and response to treatment with adalimumab.

Methods In three axSpA studies, a panel of 14 blood-based ECM biomarkers related to formation of collagen (PRO-C2, PRO-C3, PRO-C6), degradation of collagen by metalloproteinases (C1M, C2M, T2CM, C3M, C4M, C6M, C10C), matrix metalloproteinase (MMP)-degraded prolargin (PROM), MMP-degraded and citrullinated vimentin (VICM), basement membrane turnover (PRO-C4) and neutrophil activity (CPa9-HNE) were assessed to enable patient clustering (endotyping). MASH (n=41) was a cross-sectional study, while Adalimumab in Axial Spondyloarthritis study (ASIM,n=45) and Danish Multicenter Study of Adalimumab in Spondyloarthritis (DANISH, n=49) were randomised, double-blind placebo-controlled trials of adalimumab versus placebo every other week for 6 or 12 weeks, respectively, followed by active treatment. Biomarker data were log-transformed, standardised by mean centering and scaled by the SD prior to principal component analysis and K-means clustering.

Results Based on all three studies, we identified two orthogonal dimensions reflecting: (1) inflammation and neutrophil activity (driven by C1M and CPa9-HNE) and (2) collagen turnover (driven by PRO-C2). Three endotypes were identified: high inflammation endotype (Endotype1), low inflammation endotype (Endotype 2) and high collagen turnover endotype (Endotype3). Endotype1 showed higher disease activity (Ankylosing Spondylitis Disease Activity Score (ASDAS)) at baseline compared with Endotype2 and Endotype3 and higher percentage of patients responding to adalimumab based on ASDAS clinical improvement at week 24. Endotype3 showed higher percentage of patients with 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index response at week 24 compared with Endotype2.

Conclusion These endotypes differ in their tissue remodelling profile and may in the future have utility for patient stratification and treatment tailoring.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Axial spondyloarthritis (axSpA) is a heterogeneous disease associated with extracellular matrix remodelling and inflammation.
⇒ Chondrocyte activity is increased in axSpA.

WHAT THIS STUDY ADDS

⇒ By principal component analysis, we identified two orthogonal dimensions: (1) inflammation and neutrophil activity (driven by C1M and CPa9-HNE) and (2) collagen turnover (driven by PRO-C2).
⇒ Three clusters (endotypes) were identified and had statistically significant differences in disease activity scores and treatment response.

HOW THIS STUDY MIGHT AFFECT RESEARCH PRACTICE OR POLICY

⇒ The biomarker-based endotypes of axSpA encourage further investigation to classify patients based on underlying molecular profiles rather than clinical phenotypes. Further research is needed to validate the found endotypes.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease of the spine and sacroiliac joints.[1] The main pathological feature is inflammation which may cause structural damage and is associated with extracellular matrix (ECM) remodelling of the cartilage, bone and connective tissues.[2 3] Due to ECM remodelling, metabolites from ECM proteins, such as collagens, are generated and can be quantified. Other proteins such as vimentin and calprotectin are also degraded due to the activation of enzymes derived from tissue inflammation.[4 5] Even though the diagnosis of axSpA has majorly improved during the last years, there are still some unmet needs

in axSpA.[6] Like other chronic inflammatory diseases, there is heterogeneity not only in the clinical presentation of the disease, but also in treatment response and progression, that is, reflecting different phenotypes of the disease. However, within these clusters of phenotypes, there may be several subtypes based on different types and degree of inflammation as well as different extent of tissue involvement and degradation,[7] thus reflecting different biological mechanisms of the disease, that is, endotypes.[8 9] Several studies have shown that in axSpA inflammation reflected by ECM remodeling biomarkers, such as matrix metalloproteinase(MMP)-derived type I collagen degradation (C1M), citrullinated and MMP-degraded vimentin (VICM), calprotectin degradation (CpA9-HNE) and C-reactive metabolite (CRPM), is altered.[2 3 10 11] Chondrocyte activity, leading to enhanced cartilage collagen metabolism, has also been associated with axSpA.[12] Thus, quantifying ECM fragments and understanding their patterns may potentially help in the comprehension of the molecular drivers behind axSpA pathogenesis and provide a basis for endotyping.[8 9] Few studies have used cluster analysis to define clinical endotypes of axSpA, and they primarily found two groups based on axial or peripheral involvement of the disease, which were associated to different long-term disease outcomes.[7 13] However, no studies have investigated endotypes based on ECM remodelling.

We aimed to (1) identify endotypes of patients with axSpA using a panel of blood-based ECM biomarkers and (2) based on these endotypes to investigate differences in response to treatment with adalimumab, a tumour necrosis factor (TNF) inhibitor, by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) criteria.

MATERIALS AND METHODS

Patients

Patients with AxSpA from three studies were used. MASH[14] was a cross-sectional study that included 41 patients with axSpA. Danish Multicenter Study of Adalimumab in Spondyloarthritis (DANISH)[15] and Adalimumab in Axial Spondyloarthritis study (ASIM)[16] were randomised double-blind placebo-controlled trials including 49 and 45 patients, respectively, where patients were randomised to receive treatment with adalimumab 40 mg or placebo every other week (e.o.w.) for 6 or 12 weeks (ASIM and DANISH, respectively) followed by adalimumab 40 mg e.o.w. for an additional 18 or 12 weeks. BASDAI and ASDAS response criteria were calculated at baseline and 24 weeks for both studies. BASDAI response was defined as ≥50% reduction in the BASDAI index from baseline. For ASDAS, we applied the cut-offs for treatment response: no improvement (ΔASDAS<1.1), clinically important improvement (1.1≤ ΔASDAS<2.0) and major improvement (ΔASDAS≥2.0). MRI sacroiliac joint scores were assessed by the Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint inflammation score and structural scores (SSS)) of fat, erosion, backfill and ankylosis.

Biomarker measurements

A panel of 14 ECM biomarkers was measured in baseline serum samples from the three studies using either manual solid-phase competitive ELISA or the Immunodiagnostic Systems robotic platform (IDS-i10; Immunodiagnostic Systems, Bolden, Tyne & Wear, UK). The panel included: MMP-degraded type I (C1M), II (C2M and T2CM), III (C3M), IV (C4M), and IV(C6M) collagen, HNE-mediated degradation of calprotectin (CPa9-HNE), CRPM, MMP-cleaved prolargin (PROM), citrullinated and MMP-degraded vimentin (VICM), type II (PRO-C2), III (PRO-C3) and IV (PRO-C6) collagen formation and basement membrane turnover (PRO-C4). See online supplemental table 1 for detailed biomarker descriptions.[2 11]

Statistical analysis

For each individual study, baseline biomarker data were log-transformed and only those of the 14 biomarkers presenting a SD>0.3 were selected, to ensure that the variability among patients was explained by biological variance and not by the technical variation of the biomarker assays, which is a SD of 0.15.

Subsequently, biomarker data from the three studies were pooled, standardised by mean centering and scaled by the SD. Next, principal component analysis (PCA) was performed, where the first axis (principal component) captured the most variance, followed by subsequent components with less variance (online supplemental figure 1). Afterwards, we applied an iterative portioning K-means on the PCA coordinates using the Hartigan and Wong algorithm based on Euclidean distances[17] and three clusters (endotypes) were identified.

Demographic, clinical and MRI parameters, and treatment response were compared between clusters using Kruskal-Wallis and χ^2 test. To identify individual differences between clusters, post-hoc analysis was performed by Dunn's tests.

Data managing and statistical analysis was performed using R software V.4.3.1, with use of FactoMineR (V.1.34) and pheatmap (V.1.0.12). Statistics were run using the stats package (V.4.3.1).

RESULTS

The variability of baseline ECM biomarker data among patients with axSpA was mainly explained by the first two principal components. C1M and CPa9-HNE, reflecting tissue inflammation and neutrophil activity, respectively, were the primary contributors to dimension 1, whereas PRO-C2, reflecting cartilage turnover, contributed the most to dimension 2 (figure 1).

Three distinct clusters (endotypes), representing different subgroups of patients, were identified (figure 1). Endotype1 (41 subjects) was characterised by high levels of tissue inflammation markers, Endotype2

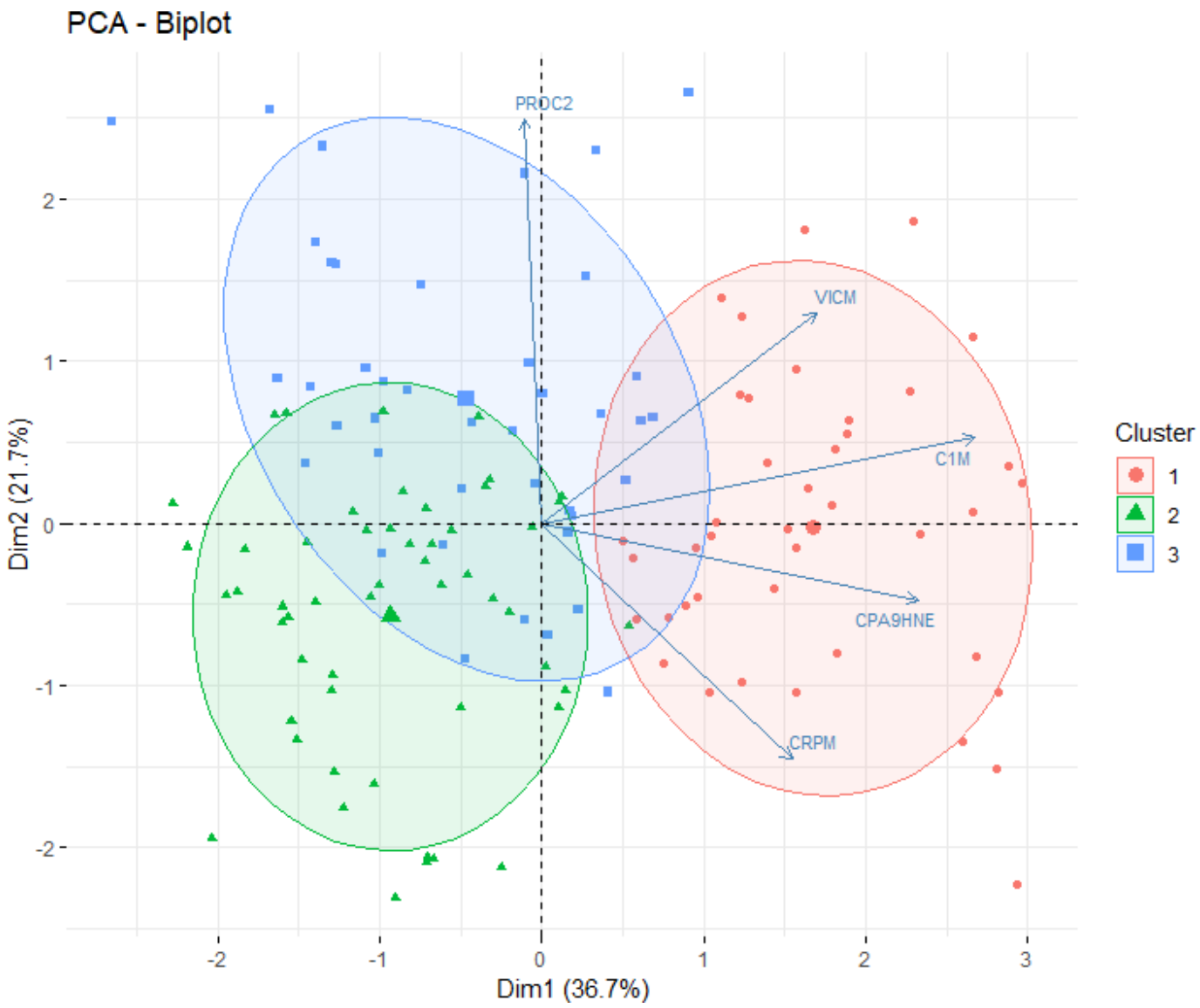

Figure 1 Principal component analysis biplot of individuals and principal component dimensions. Ellipses represent 80% of the patients within the cluster, which are differentiated by colour. Cluster 1, 2 and 3 correspond to Endotype1, 2 and 3, respectively.

(53 subjects) by low level of tissue inflammation markers and Endotype3 (41 subjects) by high levels of cartilage turnover marker. As a post-hoc analysis, we investigated the differences in demographic and clinical scores between endotypes (table 1). No differences were found in the demographic characteristics among endotypes (age, gender, symptom duration, HLA-B27, table 1). Regarding the MRI SPARCC scores, only the SSS ankylosis score differed significantly at baseline between the endotypes (table 1). Regarding the disease activity scores, CRP and ASDAS were significantly different among endotypes, as did the functional assessment through BASFI (p<0.001, p<0.001 and p=0.02, respectively). From the response to adalimumab (based on DANISH and ASIM data), we observed significant differences among endotypes in ASDAS clinical improvement after 24 weeks of treatment (p=0.02). Post-hoc analysis indicated that CRP, BASFI, SPARCC ankylosis and ASDAS scores were significantly higher in Endotype1 than Endotype2 (p<0.001, p<0.001, p=0.01 and p=0.04, respectively). ASDAS, CRP, BASFI and BASDAI were also significantly higher in Endotype1 than Endotype3 (p<0.001, p<0.001, p=0.01 and p=0.02, respectively). Endotype1 had a significantly higher percentage of patients with ASDAS major improvement and a lower percentage of no improvement than Endotype2 (p=0.003 and p=0.02), whereas Endotype3 had a significantly higher percentage of patients with BASDAI50 response after 24 weeks of treatment than Endotype2 (p=0.03). There were no other statistically significant between-group differences for ASDAS or BASDAI50 response.

DISCUSSION

This study was a post-hoc analysis of three clinical studies, aiming to identify endotypes of patients with axSpA based

Table 1 Baseline demographic, clinical, MRI and treatment response characteristics of the cluster-analyses based ECM endotypes

	All (n=135)	Endotype1 (n=41)	Endotype2 (n=53)	Endotype3 (n=41)	P value
Demographic feature					
Age, years	36.3 (10.1)	34.6 (8.7)	38.4 (11.7)	35.2 (9.0)	0.338
Male sex, no. (%)	78 (57.8%)	20 (48.8%)	34 (64.2%)	24 (58.5%)	0.324
HLA-B27, positive, no. (%)	110 (81.5%)	33 (80.5%)	42 (79.2%)	35 (85.4%)	0.736
Symptom duration, years	10.7 (8.8)	10.3 (7.4)	10.4 (9.9)	11.4 (9.0)	0.693
CRP, mg/L	13.3 (18.3)	26.4 (17.4)	5.6 (15.2)	10.3 (16.0)	< 0.001*†
CRP≥3 mg/L	85 (63.0%)	40 (97.6%)	19 (35.8%)	26 (63.4%)	< 0.001*†‡
Clinical examination					
BASDAI (0–10)	5.5 (2.0)	6.0 (2.0)	5.6 (2.1)	5.0 (1.8)	0.074*‡
ASDAS	3.4 (0.8)	4.2 (0.6)	3.0 (0.6)	3.1 (0.5)	< 0.001*‡
BASFI (0–10)	4.2 (2.3)	5.0 (2.2)	4.0 (2.2)	3.5 (2.1)	0.017‡
BASMI (0–10)	2.3 (2.1)	2.6 (2.3)	2.2 (2.0)	2.0 (1.9)	0.481
Tender joint count 0–28, no. (%) ≥1	29 (21.5%)	9 (22.0%)	11 (20.8%)	9 (22.0%)	0.986
Swollen joint count 0–28, no. (%) ≥1	11 (8.1%)	6 (14.6%)	4 (7.5%)	1 (2.4%)	0.128
MRI inflammation and structural damage					
SPARCC SIJ inflammation score (0–48)	8.7 (10.0)	10.2 (11.5)	7.9 (8.5)	8.3 (10.1)	0.759
SPARCC SSS fat lesion score (0–40)	11.5 (12.6)	12.6 (14.9)	11.4 (12.2)	10.4 (10.5)	0.986
SPARCC SSS erosion score (0–20)	3.5 (4.2)	3.1 (4.3)	3.4 (4.0)	4.0 (4.4)	0.435
SPARCC SSS backfill score (0–20)	3.8 (5.1)	4.3 (5.7)	4.0 (5.1)	3.1 (4.5)	0.747
SPARCC SSS ankylosis score (0–20)	4.6 (7.0)	6.5 (8.0)	2.8 (5.5)	5.2 (7.3)	0.03 *
SPARCC SIJ inflammation score≥2, no (%)	89 (66.4%)	29 (70.7%)	35 (67.3%)	25 (61.0%)	0.636
SPARCC SSS fat lesion score≥2, no (%)	98 (73.1%)	28 (68.3%)	40 (76.9%)	30 (73.2%)	0.648
SPARCC SSS erosion score≥2, no (%)	72 (53.7%)	20 (48.8%)	28 (53.8%)	24 (58.5%)	0.675
SPARCC SSS backfill score≥2, no (%)	65 (48.5%)	20 (48.8%)	27 (51.9%)	18 (43.9%)	0.744
SPARCC SSS ankylosis score≥2, no (%)	51 (38.1%)	20 (48.8%)	14 (26.9%)	17 (41.5%)	0.085
Treatment response§	n=94	n=27	n=39	n=28	
BASDAI50 responders, no (%)	65 (70.7%)	21 (77.8%)	21 (56.8%)	23 (82.1%)	0.053†
ASDAS no improvement	19 (22.4%)	2 (8.0%)	11 (33.3%)	6 (22.2%)	0.072*
ASDAS clinical important improvement	28 (32.9%)	5 (20.0%)	13 (39.4%)	10 (37.0%)	0.256
ASDAS major improvement	38 (44.7%)	18 (72.0%)	9 (27.3%)	11 (40.7%)	0.003*
Biomarker levels					
C1M (ng/mL)	92.3 (89.3)	159.3 (84.)	49.6 (56.9)	80.3 (90.2)	
CPa9-HNE (ng/mL)	100.2 (53.6)	143.8 (57.)	78.7 (34.6)	84.5 (44.1)	
VICM (ng/mL)	5.3 (4.4)	8.2 (5.8)	3.9 (3.0)	4.0 (2.5)	
CRPM (ng/mL)	12.6 (9.2)	16.1 (15.3)	10.3 (3.0)	12.2 (4.1)	
PRO-C2 (ng/mL)	20.9 (10.4)	18.8 (6.5)	14.9 (5.2)	30.9 (11.5)	

Except where indicated otherwise, mean±SD is presented. Mann-Whitney and χ^2 test was used to compare differences between the clusters. Inter-group comparisons were conducted among endotypes, and statistical significance is indicated as follows:
*p<0.05 for comparisons between Endotype1 and Endotype2.
†p<0.05 for Endotype2 versus Endotype3.
‡p<0.05 for Endotype1 versus Endotype3.
§Analyses of treatment response were based on patients from ASIM and DANISH only.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C reactive protein; HLA, human leucocyte antigen; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of Canada; SSS, SI joint structural lesion score.

on their biomarker tissue profile. The main findings of this exploratory study were as follows: (1) two orthogonal dimensions were identified, one related to inflammation (driven by C1M and CPa9-HNE) and one related to cartilage turnover (PRO-C2); (2) three clusters (endotypes) were determined: high inflammation endotype (Endotype1), low inflammation endotype (Endotype2) and high cartilage turnover endotype (Endotype3); (3) when treated with a TNF-inhibitor patients from Endotype1 (high inflammation profile) had higher percentage of ASDAS major clinical improvement than those from Endotype2 (low inflammation profile), whereas patients from Endotype3 (high cartilage turnover profile) had higher frequency of BASDAI50 response than those from Endotype2.

Few clinical studies have investigated clusters in axSpA.[7 13] These studies have identified two clinical endotypes based on analyses of clinical characteristics only (ie, clinical phenotypes) and identified to patient subsets: pure axSpA and a combination of axial and peripheral SpA. The latter group showed higher disease activity and despite faster initiation of biologics, worse functional outcome.[7] However, from our knowledge, our study is the first exploratory study using a panel of ECM remodelling biomarkers to identify endotypes of axSpA. We observed that inflammation and cartilage turnover were two clear differentiated patterns, the former associated with higher ASDAS response as previously found by Pedersen *et al*.[18] Previous endotyping-based analysis have been performed in other rheumatic diseases, such as rheumatoid arthritis (RA) and osteoarthritis (OA), using ECM biomarkers. Blair *et al*[19] identified putative endotypes of patients with RA and OA characterised by different patterns based on biomarkers reflecting joint tissue metabolism. Angelini *et al*[20] found three clusters among patients with OA reflecting low turnover of bone and cartilage, high structural damage and systemic inflammation, which were linked to non-progression, structural progression and sustained progression and pain, respectively.

The biomarker clustering analysis performed herein supports that axSpA is a heterogeneous disease with underlying molecular mechanisms that are not only driven by inflammation, but also by cartilage turnover leading to structural damage.[12 21] Our findings encourage further investigation into developing tools to improve patient stratification.

The limitations of this exploratory study include the small sample size of the clinical studies and the reduced number of used biomarkers due to the technical variability of the biomarker assays. The endotypes identified in this study should be validated with an external cohort to evaluate their stability.

In conclusion, this exploratory study shows how clustering of patients with axSpA using ECM remodelling biomarkers allows identification of three endotypes, which may help elucidating axSpA pathogenesis and treatment response in patients with axSpA.

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Contributors HP performed the biomarker measurements, analysed and interpreted the data, and was the major contributor in writing the manuscript. SHN design the biomarker measurements, interpreted the data, and revised the manuscript. FC and PF analysed and interpreted the data. A-CB-J and MAK interpreted the data and revised the manuscript. SS, IJS, AGL and ORM collected the serum samples and performed the physical examinations of the patients. MØ and SJP designed and directed the clinical studies, interpreted the data and provided meticulous revisions to the manuscript.

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Competing interests MØ: research grants from AbbVie, BMS, Merck, Novartis and UCB, and speaker and/or consultancy fees from AbbVie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Galapagos, Gilead, Hospira, Janssen, MEDAC, Merck, Novartis, Novo Nordisk, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi and UCB. SJP: speaker's bureau MSD, Pfizer, AbbVie, UCB, Novartis. Consulting fees and/or honoraria: AbbVie, UCB, Novartis. Grant/research support: AbbVie, MSD and Novartis. HP: none. Frederik Christiansen: Employed at Nordic Bioscience A/S. SHN: employed and shareholder of Nordic Bioscience A/S. PF: none. A-CB-J: employed and shareholder of Nordic Bioscience A/S. MK Shareholder of: employed and shareholder of Nordic Bioscience A/S. SS: None. IJS: none. AGL: speaking and/or consulting fees from AbbVie, Janssen, Lilly, MSD, Novartis, Pfizer, and UCB. Research grant from Novartis. ORM: none.

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