Thursday 25 April 2013, 09.00–10.30

# BSR AND BHPR ORAL PRESENTATION OF ABSTRACTS

## ORAL ABSTRACTS 7: RA CLINICAL

### O37. LONG-TERM OUTCOMES OF EARLY RA PATIENTS INITIATED WITH ADALIMUMAB PLUS METHOTREXATE COMPARED WITH METHOTREXATE ALONE FOLLOWING A TARGETED TREATMENT APPROACH

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**Background:** This analysis assessed, on a group level, whether there is a long-term advantage for early RA patients treated with adalimumab (ADA) + MTX *vs* those initially treated with placebo (PBO) + MTX who either responded to therapy or added ADA following inadequate response (IR).
**Methods:** OPTIMA was a 78- week, randomized, controlled trial of ADA + MTX *vs* PBO + MTX in MTX-naïve early (<1 year) RA patients. Therapy was adjusted at week 26: ADA + MTX-responders (R) who achieved DAS28 (CRP) <3.2 at weeks 22 and 26 (Period 1, P1) were re-randomized to withdraw or continue ADA and PBO + MTX-R continued randomized therapy for 52 weeks (P2); IR-patients received open-label (OL) ADA + MTX during P2. This post hoc analysis evaluated the proportion of patients at week 78 with DAS28 (CRP) <3.2, HAQ-DI <0.5, and/or ΔmTSS ≤0.5 by initial treatment. To account for patients who withdrew ADA during P2, an equivalent proportion of R was imputed from ADA + MTX-R patients.
**Results:** At week 26, significantly more patients had low disease activity, normal function, and/or no radiographic progression with ADA + MTX *vs* PBO + MTX (Table 1). Differences in clinical and functional outcomes disappeared following additional treatment, when PBO + MTX-IR ($n = 348/460$) switched to OL ADA + MTX. Addition of OL ADA slowed radiographic progression, but more patients who received ADA + MTX from baseline had no radiographic progression at week 78 than patients who received initial PBO + MTX.
**Conclusions:** Early RA patients treated with PBO + MTX achieved comparable long-term clinical and functional outcomes on a group level as those who began ADA + MTX, but only when therapy was optimized by the addition of ADA in PBO + MTX-IR. Still, ADA + MTX therapy conferred a radiographic benefit although the difference did not appear to translate to an additional functional benefit.
**Disclosures:** P.E., AbbVie, Merck, Pfizer, UCB, Roche, BMS—Provided Expert Advice, Undertaken Trials, AbbVie—AbbVie sponsored the study, contributed to its design, and participated in the collection, analysis, and interpretation of the data, and in the writing, reviewing, and approval of the final version. R.F., AbbVie, Pfizer, Merck, Roche, UCB, Celgene, Amgen, AstraZeneca, BMS, Janssen, Lilly, Novartis—Research Grants, Consultation Fees. S.F., AbbVie—Employee, Stocks. A.K., AbbVie, Amgen, AstraZeneca, BMS, Celgene, Centocor-Janssen, Pfizer, Roche, UCB—Research Grants, Consultation Fees. H.K., AbbVie—Employee, Stocks. S.R., AbbVie—Employee, Stocks. J.S., AbbVie, Amgen, AstraZeneca, BMS, Celgene, Centocor-Janssen, GlaxoSmithKline, Lilly, Pfizer (Wyeth), MSD (Schering-Plough), Novo-Nordisk, Roche, Sandoz, UCB—Research Grants, Consultation Fees. R.V., AbbVie, BMS, GlaxoSmithKline, Human Genome Sciences, Merck, Pfizer, Roche, UCB Pharma—Consultation Fees, Research Support.

### O38. 24-WEEK RESULTS OF A BLINDED PHASE IIB DOSE-RANGING STUDY OF BARICITINIB, AN ORAL JAK1/JAK2 INHIBITOR, IN COMBINATION WITH TRADITIONAL DMARDS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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**Background:** BaBaricitinib (formerly LY3009104/INCB028050), a novel, oral inhibitor of JAK1 and JAK2 in the JAK-STAT signaling pathway, has been evaluated in a 24 week blinded phase IIb study in patients with moderate to severe RA with inadequate response to MTX.The primary endpoint after 12 weeks of treatment was met and previously reported. The 24 week safety and efficacy findings are reported here.
**Methods:** Patients with active RA (defined as at least 8 swollen and 8 tender joints based on the 66/68 joint assessment) on stable MTX were randomized 2:1:1:1:1 to receive placebo (PBO) or 1of 4 once-daily baricitinib doses (1, 2, 4, or 8 mg) for 12 weeks. Patients assigned to 2, 4 or 8 mg continued blinded treatment for an additional 12 weeks. Patients assigned to placebo or 1 mg were reassigned to an exploratory 4 or 2 mg BID group between weeks 12 and 24 and were excluded from the primary 24-week analysis.
**Results:** Three hundred one patients entered the study. After 12 weeks of treatment, significant differences *vs* placebo were observed in the proportion of patients achieving ACR20, ACR50 and ACR70, DAS28CRP < 2.6 (Table 1). At week 24, patients receiving 2 mg, 4 mg or 8 mg baricitinib maintained or improved in all measures. Over 12 weeks in the PBO and combined baricitinib groups, there were similar incidence rates of TEAEs (44% *vs* 41%), infections (12% *vs* 14%) and SAEs (2% *vs* 2%, respectively) over 12 weeks. Over 24 weeks in the 2 mg, 4 mg and 8 mg groups, the rate of TEAEs was 60%, 62% and 72%, the rate of infections was 27%, 25% and 28% and the rate of SAEs was 6%, 0 and 8%, respectively. There were no opportunistic infections and no deaths. Decreases in hemoglobin and small increases in serum creatinine were seen. Increases were seen in LDL and HDL.
**Conclusions:** Significant improvements in the signs and symptoms of RA *vs* placebo were observed over 12 weeks. These responses were maintained or improved for an additional 12 weeks of blinded

TABLE 1. Week 78 clinical, functional, and radiographic outcomes in patients who received continued ADA + MTX *vs* those who continued PBO + MTX or added open-label ADA following an inadequate response

| | ADA + MTX, *n/N* (%)[a] | | | PBO + MTX, *n/N* (%)[b] | | |
|---|---|---|---|---|---|---|
| Outcome | Week 26 | Week 52 | Week 78 | Week 26 | Week 52 | Week 78 |
| DAS28 (CRP) <3.2 | 246/466 (53) | 304/465 (65) | 303/465 (65) | 139/460 (30)*** | 284/460 (62) | 300/460 (65) |
| HAQ-DI <0.5 | 211/466 (45) | 220/466 (47) | 224/466 (48) | 150/460 (33)*** | 203/460 (44) | 208/460 (45) |
| ΔmTSS ≤0.5 | 402/462 (87) | 379/445 (86) | 382/443 (86) | 330/459 (72)*** | 318/440 (72)*** | 318/440 (72)*** |
| DAS28 (CRP) <3.2 + ΔmTSS ≤0.5 | 216/462 (47) | 260/443 (59) | 266/443 (60) | 112/459 (24)*** | 196/440 (45) | 211/440 (48)*** |
| DAS28 (CRP) <3.2 + HAQ-DI <0.5 + ΔmTSS ≤0.5 | 146/462 (32) | 168/443 (38) | 174/443 (39) | 82/459 (18)*** | 120/440 (27)*** | 135/440 (31)** |

[a]Includes patients from the ADA Continuation ($n = 105$) and OL ADA Carry On ($n = 259$) arms, as well as the proportional equivalent number of responders from the ADA Withdrawal arm ($n = 102$). [b]Includes patients from the MTX Continuation ($n = 112$) and Rescue ADA ($n = 348$) arms. Last observation carried forward: DAS28 (CRP) and HAQ-DI; Multiple imputations: ΔmTSS. ***$P < 0.001$ and **iP < 0.01, respectively, for differences between initial treatments from chi-square.

TABLE 1. Results

| | PBO ($n=98$) | 1 mg QD ($n=49$) | 2 mg QD ($n=52$) | 4 mg QD ($n=52$) | 8 mg QD ($n=50$) |
|---|---|---|---|---|---|
| % ACR20 at 12 weeks | 41 | 57* | 54* | 75* | 78* |
| % ACR50 at 12 weeks | 10 | 31* | 17 | 35* | 40* |
| % ACR70 at 12 weeks | 2 | 12* | 8 | 23* | 20* |
| %DAS28CRP < 2.6 at 12 weeks | 4 | 14* | 15* | 37* | 22* |
| %DAS28ESR < 2.6 at 12 weeks | 1 | 4 | 8* | 25* | 16* |
| % ACR20 at 24 weeks | – | – | 63 | 78 | 73 |
| % ACR50 at 24 weeks | – | – | 20 | 48 | 55 |
| % ACR50 at 24 weeks | – | – | 10 | 28 | 24 |
| %DAS28CRP < 2.6 at 24 weeks | – | – | 16 | 34 | 37 |
| %DAS28ESR < 2.6 at 24 weeks | – | – | 13 | 25 | 18 |

All values non-responder imputation and 1-sided *P*-value from Fisher's exact test; *$P < 0.05$ *vs* PBO.

treatment with 2 mg, 4 mg and 8 mg. In addition, safety signals observed over 12 and 24 weeks were consistent with previously conducted studies of baricitinib.

**Disclosures:** S.B., Eli Lilly and Company—Employee, Stock Holder. P.B., Eli Lilly and Company—Employee, Stock Holder. R.F., Incyte Corporation—Employee. M.G., Eli Lilly and Company—Research Grants, Consulting Fees. E.K., Abbot, Amgen, AstraZeneca, BMS, Centocor, F Hoffman-La Roche, Genzyme, Merck, Novartis, Pfizer, UCB—Research Grants, Abbot, AstraZeneca, Biotest, BMS, Centocor, F Hoffman-La Roche, Genentech, Merck, Nycomed, Pfizer, UCB, Amgen, Janssen—Consulting Fees. C.L., Eli Lillly and Company—Employee, Stock Holder. M.L., Incyte Corp—Employee. W.M., Eli Lilly and Company—Employee, Stock holder. D.S., Eli Lilly and Company—Employee, Stock holder. P.T., Merck, UCB, AstraZeneca, GlaxoSmithKline, Celgene, Abbot—Research Grants, Merck, Novartis, Pfizer, Bristol-Myers Squibb, Centocor, Eli Lilly, Roche, Genmab, AstraZeneca, Takeda, UCB—Consulting Fees. All other authors have declared no conflicts of interest.

## O39. TOCILIZUMAB MONOTHERAPY COMPARED WITH ADALIMUMAB MONOTHERAPY IN RA: RESULTS OF A 24-WEEK STUDY

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**Background:** Tocilizumab (TCZ) efficacy as monotherapy for RA has been assessed in 6 trials. ADACTA is the first trial to determine superiority of 1 approved biologic *vs* another [TCZ *vs* adalimumab (ADA)] as monotherapy.

**Methods:** ADACTA was a phase IV randomized, double-blind, 24-week study in patients with RA ≥6-mo duration, DAS28 >5.1, who were MTX intolerant or MTX was ineffective/inappropriate. Patients received TCZ 8 mg/kg i.v. every 4 weeks (+ PBO ADA) or ADA 40 mg SC every 2 weeks (+ PBO TCZ) for 24 weeks. Primary endpoint was mean change from BL in DAS28 at 24 weeks.

**Results:** ITT population was 325 patients (163 TCZ/162 ADA). Mean BL characteristics were similar in TCZ and ADA arms: age (54.4/53.3 y), RA duration (7.3/6.3 y), DAS28 (6.72/6.76). At week 24 (Table 1), mean change from BL in DAS28 was significantly greater with TCZ than ADA ($P < 0.0001$). Statistically significantly greater proportions of TCZ than ADA patients achieved DAS28 <2.6, DAS28 ≤3.2 and ACR20/50/70 responses ($P < 0.005$). A difference in favour of TCZ was observed in proportions of patients achieving CDAI and SDAI remission (≤2.8 and ≤3.3) at week 24 (post hoc analysis; $P < 0.05$). From week 16, the proportion of patients achieving ACR/EULAR remission was numerically greater with TCZ and by week 24 was 18% *vs* 11% for ADA. For exploratory endpoints HAQ-DI, SF-36 MCS, SF-36 PCS and FACIT Fatigue, differences in mean change from BL at week 24 were numerically higher for TCZ than ADA. Adverse events (AEs), serious AEs and serious infection were similar between arms (TCZ, 82.1%/11.7%/ 3.1%; ADA, 82.7%/9.9%/ 3.1%). Transaminase, LDL elevations and neutrophil count reductions were more common with TCZ. 2 deaths occurred in the TCZ arm (1 sudden death, 1 reported illicit drug overdose).

**Conclusions:** TCZ monotherapy was superior to ADA monotherapy in reducing RA signs/symptoms in MTX-intolerant patients/patients in whom MTX was ineffective/inappropriate. Agents had similar overall AE profiles. Lab changes were consistent with previous reports.

**Disclosures:** S.A., Roche—Employment, Stock Options. R.A., BMS, Novartis, Pfizer, Roche, UCB—Research Grants, Consulting Fees, Abbott—Consulting Fees. A.D., Genentech, UCB, Abbott, BMS—Speakers' Bureau. P.E., Merck, Abbott, Pfizer, UCB, Roche, BMS—Consulting Fees. C.G., Roche, Abbott, Merck, UCB, Pfizer, BMS, Merck Serono, Novartis, Amgen—Consulting Fees, Speaker Bureau. J.G., Roche—Employment, Stock Options. A.K., Roche, Amgen, Abbott, BMS, Janssen, UCB, Pfizer—Research Grants. M.K., Genentech—Employment. D.M., Genentech—Employment. R.V., Abbott, BMS, GSK, Merck Sharp and Dohme, Pfizer, Roche, UCB—Research Grants, Consulting Fees.

## O40. HEAD-TO-HEAD COMPARISON OF SUBCUTANEOUS ABATACEPT *VS* ADALIMUMAB IN THE TREATMENT OF RHEUMATOID ARTHRITIS: KEY EFFICACY AND SAFETY RESULTS FROM THE AMPLE TRIAL

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TABLE 1. Endpoints at week 24 (ITT population[a])

| | TCZ $n=163$ | ADA $n=162$ | $P^b$ |
|---|---|---|---|
| Primary: Δ from BL in DAS28 | –3.3[c] | –1.8 (diff: –1.5) | <0.0001 |
| Secondary | | | |
| DAS28 <2.6,% | 39.9 | 10.5 | <0.0001 |
| DAS28 ≤3.2,% | 51.5 | 19.8 | <0.0001 |
| ACR20, % | 65.0 | 49.4 | 0.0038 |
| ACR50, % | 47.2 | 27.8 | 0.0002 |
| ACR70, % | 32.5 | 17.9 | 0.0023 |
| Exploratory and post-hoc endpoints | | | |
| CDAI remission, % | 17.2 | 9.3 | 0.0389[d] |
| SDAI remission, % | 18.4 | 8.0 | 0.0067[d] |
| ACR/EULAR remission (Boolean), % | 18.0 | 11.0 | 0.0569[d] |
| Δ from BL in HAQ-DI | –0.7 | –0.5 (diff:–0.2) | 0.0653[d] |

Δ Change. [a]LOCF and non-responder imputation applied to primary and secondary continuous and categorical endpoints respectively. [b]*P*-values adjusted for region, duration of RA and for baseline. [c]2 TCZ patients (no post-baseline data) excluded. [d]*P*-value not adjusted for multiple testing/type 1 error therefore no significance claimed.

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**Background:** The availability of multiple biologic agents to treat RA has created a need for comparative assessment. AMPLE (Abatacept *Vs* Adalimumab Comparison in Biologic-Naïve RA Subjects with Background Methotrexate) is the first head-to-head study powered to compare subcutaneous (SC) abatacept (ABA) and adalimumab (ADA) on a background of MTX. Here, we report key 1-year data from AMPLE, including ACR core component data.
**Methods:** AMPLE is an ongoing, Phase IIIb, randomized, investigator-blinded study of 24 months' duration with a 12-month primary efficacy endpoint. Biologic-naïve RA patients with an inadequate response to MTX were randomized to 125 mg ABA weekly or 40 mg ADA bi-weekly, in combination with MTX. The primary endpoint was non-inferiority (NI) of ABA to ADA based on ACR 20 at 12 months; key secondary endpoints were rates of radiographic non-progression, safety, injection-site reactions and retention. ACR core component data were also analysed.
**Results:** A total of 646 patients were randomized and treated; 86.2% of ABA patients and 82.0% of ADA patients completed 12 months. Baseline characteristics were balanced across both arms (mean DAS28-CRP of 5.5 and disease duration ~1.8 years). At 1 year, 64.8% of ABA patients and 63.4% of ADA patients achieved an ACR20 response, with an estimated difference between the two arms (95% CI) of 1.8 (–5.6, 9.2) supporting NI of ABA to ADA. The kinetics of response across ACR scores were comparable overall, with an ACR50 of 46.2% and 46%, and ACR70 of 29.2%and 26.2% for ABA and ADA, respectively, at 1 year. Responses in some ACR core components were similar in ABA and ADA groups over time, although some differences were observed. At 1 year, the rates of radiographic non-progression were comparable, as were mean changes in van der Heijde–modified total Sharp scores (0.58 *vs* 0.38 for ABA *vs* ADA). The rates of adverse events (AEs), serious AEs, serious infections and malignancies were comparable. There were more patients with autoimmune AEs (3.1% *vs* 0.9%) in the ABA arm; however, none were serious. One patient in each arm discontinued due to an autoimmune event. There were fewer discontinuations with ABA due to AEs (3.5% *vs* 6.1%) and due to serious infections (0% *vs* 1.5%). Injection-site reactions occurred in significantly fewer ABA-treated patients (3.8% *vs* 9.1%, $P = 0.006$).
**Conclusions:** This first head-to-head study in RA patients comparing biologic agents on background MTX demonstrated that subcutaneous abatacept is comparable to adalimumab by most efficacy measures, including radiographic progression. Safety was generally similar, with fewer discontinuations and injection-site reactions observed with abatacept.
**Disclosures:** G.C., Pfizer Inc.—Research Support, Consultant Fees, BMS, AstraZeneca—Consultant Fees. R.F., Genentech Inc., MSD, BiogenIdec—Research Support, Roche, Abbott, Amgen, UCB, Pfizer, BMS, Lilly, Sanofi-Aventis, Lexicon, Novartis, Astellas, AstraZeneca, Janssen—Research Support, Consultant Fees, HGS—Consultant Fees. M.M., BMS—Shareholder, Employee. M.S., BMS—Consultant Fees, Abbott Laboratories—Speaker Bureau. R.V., UCB, Pfizer, Novartis, Eli Lilly, Takeda, Centocor—Research Support. D.V., Abbott, Amgen, AstraZeneca, BMS, Centocor, Chugai, Eli-Lilly, GSK, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Wyeth—Research Support, Imaging Rheumatology bv—Owner. M.W., BMS—Research Support, Consultant Fees. C.Z., BMS—Shareholder, Employee.

## O41. WHAT HAPPENS TO ACPA-POSITIVE PATIENTS WITHOUT CLINICAL SYNOVITIS?

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**Background:** Rheumatoid arthritis (RA) is associated with autoantibodies including anti-cyclic citrullinated peptide antibodies (ACPA) which may be present years before clinical presentation. The aim of the study was to investigate the pre-clinical phase of ACPA positive patients with non-specific musculoskeletal symptoms and factors associated with the development of inflammatory arthritis (IA).
**Methods:** Patients were recruited from rheumatology clinics and primary care under the UKCRN portfolio. Clinical assessment and investigations including ultrasound imaging of the hands and feet were undertaken at baseline and 3–6 month intervals or at change of symptoms. The end point was the development of clinical synovitis (CS), defined as the presence of at least one tender and swollen joint. A healthy control group was recruited and assessed using the same biomarkers including imaging and serology.
**Results:** A total of 122 patients without a diagnosis of IA were studied. At baseline 22 patients were found to have CS and hence were excluded from analysis. One hundred patients (74% females) with a median age of 51 years (24–77 years) had no CS at baseline. Median duration of follow up was 12 months (1–50 months). Thirty-eight (38%) patients developed CS after a median duration of 26.8 weeks (1–170 weeks); 33 patients met ACR EULAR 2010 criteria for RA and 5 patients were classified as undifferentiated IA. Nineteen of the 38 patients developed CS within 6 months of presentation; 12 patients between 6 and 12 months, and 7 patients after 12 months.

At baseline, the mean ultrasound PD score of the controls (n- = 26) was 0.39 (S.D. 0.2). In comparison with controls, the mean PD score was 1.00 (S.D. 1.87, *P* 0.011) in patients who did not progress to CS ($n = 53$), and 2.5 (S.D. 4.07, *P* 0.003) in patients who progressed ($n = 36$).
**Conclusions:** The results of this prospective cohort indicate that ACPA positive patients with non-specific musculoskeletal symptoms are at high risk of developing IA within 1 year of presentation. These patients represent a group with imminent RA who may be suitable for interventional studies.
**Disclosures:** The authors have declared no conflicts of interest.

## O42. INTERFERON GENE EXPRESSION SIGNATURE IN NEUTROPHILS FROM RA PATIENTS PRE- AND POST-ANTI-TNF THERAPY

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**Background:** There is a growing appreciation of the role of neutrophils in inflammatory diseases such as RA and JSLE. Neutrophils respond to inflammatory stimuli through the production of reactive oxygen metabolites and release of proteases, which can damage host tissue if released inappropriately. Neutrophils also drive chronic inflammation via the secretion of inflammatory molecules such as cytokines, chemokines and leukotrienes. The aim of this study was to investigate gene expression signatures which correlate with disease activity or which may predict response to therapy in RA patients.
**Methods:** Neutrophils were isolated from the venous blood of RA patients ($n = 14$) pre- and 12-weeks post-anti-TNF therapy, and from healthy controls ($n = 6$). RNA was poly-A selected and sequenced on the Illumina HiSeq 2000 platform using standard protocols. Reads (50 bp, single-ended) were mapped to the human genome (hg19, UCSC) using Tophat and differential expression analysis was carried out using edgeR applying a 5% false discovery rate (FDR). Signalling pathway analysis was carried out using Ingenuity Pathway Analysis software (IPA). Interferon (IFN) signalling was confirmed by Western blotting for phosphorylated STAT proteins in protein lysates.
**Results:** Pathway analysis of RNASeq data identified elevated activation of IFN signalling in RA neutrophils ($n = 14$) compared with healthy controls ($n = 6$). Specifically, IPA predicted that gene expression in RA neutrophils is regulated by IFN$\gamma$ ($P = 1.42E-35$), IFN$\alpha$ ($P = 2.96E-28$) and IFN$\beta$ (1.75E-12). IPA also predicted activation of STAT1 ($P = 3.75E-19$) and STAT3 ($P = 1.02E-22$) transcription factors in RA neutrophils, and this was confirmed by Western blotting of protein lysates. There was some heterogeneity in the level of expression of IFN target genes amongst the entire group of RA patients. However, patients who achieved a response to anti-TNF therapy ($\Delta DAS28 \geq 1.2$, $n = 11$) measured at 12-weeks had significantly higher expression of IFN target genes pre-therapy compared with non-responders. Anti-TNF therapy resulted in a significant up-regulation of IFN target genes in those patients who did not achieve a EULAR response ($\Delta DAS28 < 1.2$, $n = 3$) over 12 weeks of anti-TNF therapy.
**Conclusions:** RA neutrophils had a gene expression signature indicative of activation *in vivo* by IFNs. This IFN gene expression signature was more evident in patients who went on to achieve a response to anti-TNF therapy. Moreover, IFN gene expression was significantly up-regulated in anti-TNF non-responders by anti-TNF therapy. IFN gene expression signatures have been reported in RA patients in other cell types, but we believe this is the first account of an IFN signature in RA neutrophils. Expression of IFN genes may be a useful predictive marker of response to anti-TNF therapy in RA patients, and we are currently investigating this in a larger cohort of patients.
**Disclosures:** The authors have declared no conflicts of interest.

Thursday 25 April 2013, 11.30–13.00

# BSR AND BHPR ORAL PRESENTATION OF ABSTRACTS

## ORAL ABSTRACTS 8: GENETICS

### O43. A PILOT STUDY EVALUATING RNA TRANSCRIPTION PROFILES IN IDIOPATHIC INFLAMMATORY AND INCLUSION BODY MYOSITIS: A NEXT GENERATION SEQUENCING APPROACH

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**Background:** This pilot study investigates differences in RNA expression in idiopathic inflammatory (IIM; anti- Jo-1 antibody positive) and inclusion body myositis (IBM). Pathogenesis of IIM and IBM remains poorly understood. Features of IIM and IBM are readily identifiable clinically and histologically, and good evidence demonstrates clinical associations with autoantibodies in IIM. Previous work suggests several possible mechanisms in the development of IIM and IBM. However, the complexity and relative rarity of these conditions makes modeling and clinical validation of findings challenging.

The advent of high throughput next generation sequencing has enabled rapid sequencing of the entire human genome. Recent advances have seen this technology applied to RNA. Tissue RNA transcription profiles can now be quantified and mapped to their precise locations on the genome. This is a valuable new tool in exploratory studies to identify disease mechanisms, as it is possible to achieve a 'snapshot' of the RNA output of a specific tissue. By identifying and quantifying RNA production in muscle biopsies, it is possible to identify genes that are differentially expressed between samples, as well as identifying non-coding RNA, pseudo- and novel genes. This enables identification of altered cellular pathways between IIM, IBM and controls and highlights targets for future investigation.
**Methods:** RNA was extracted from muscle biopsies using commercially available kits (QIAshredder and Qiagen RNeasy columns) and pooled into 3 samples (IM, IBM and control) for next generation sequencing. RNA was extracted from 5 muscle biopsies for each of the IIM and control group, and 2 for the IBM group. The muscle transcriptome was determined using next generation sequencing (Illumina Hi-Seq 2000, Poly A + extraction). Data were mapped onto the human genome and changes in expression were analysed.
**Results:** Differences were noted between Jo-1, IBM and control pooled samples for a wide range of both coding and non-coding RNA. MHC 1 and 2 were upregulated in Jo-1 myositis and IBM. B2-microglobulin (a subunit of MHC class 1) was strongly expressed in RNA extracted from Jo-1 myositis (12.39 fold increase *vs* control) and IBM (5.25 fold change *vs* control) muscle biopsies. CD74 was upregulated in Jo-1 myositis and IBM (9.59 and 6.34 fold increase respectively).
**Conclusions:** Results suggest that MHC 1 and 2 play a role in the pathophysiology of both Jo-1 myositis and IBM. MHC 1 and 2 are most highly expressed in Jo-1 myositis, but also upregulated in IBM. This suggests possible defective antigen presentation and a muscle driven autoimmune process in these conditions. Sample size is limited, and sequencing data were obtained from pooled samples. However, this study demonstrates the feasibility of a next generation sequencing approach to evaluate RNA transcription in two complex and poorly understood conditions.
**Disclosures:** The authors have declared no conflicts of interest.

### O44. THE DEVELOPMENT OF PERIPHERAL JOINT EROSIONS AND RADIOGRAPHIC SACROILIITIS HAS STRIKING ASSOCIATION WITH CERTAIN HLA ALLELES AND HAPLOTYPES: GENOTYPE–PHENOTYPE CORRELATION OF 283 CONSECUTIVE PSORIATIC ARTHRITIS PATIENTS

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**Background:** We have previously shown in a rigorously ascertained PsA cohort the considerable genetic heterogeneity, which provided preliminary evidence that MHC genes determine quantitative traits within the PsA phenotype with different patterns of MHC effect. We now extend these findings by performing detailed clinical phenotyping of PsA cases to better characterize the clinical features associated with particular HLA class I alleles and their haplotypes.
**Methods:** A consecutive cohort of 283 PsA patients who were previously enrolled in a genetics study was included, and patients were invited to attend a dedicated research clinic. Following informed consent, patients underwent a detailed skin and rheumatologic assessment including disease activity measures (PASI, Body Surface Area (BSA) for Psoriasis (Ps); DAS28 CRP, HAQ for PsA) and radiographs were taken for involved joints along with hands, feet and sacroiliac joints. In addition, an extensive medical record review was performed to obtain information regarding their previous psoriatic disease features.
**Results:** A total of 283 PsA patients [mean age 54.6 ± 12 years; 52% female; mean PsA duration = 19 ± 9 years; 25% with sacroiliitis; 43.5% with radiographic peripheral joint erosions; median current PASI = 2.1] were studied. In univariate analysis, the inheritance of B*27:05 was associated with a more severe joint disease phenotype, and the presence of HLA-C*06, on any haplotype, conferred a reciprocal phenotype of significant negative associations with arthritis severity. B*08 and B*08–C*07 (EH8.1) were correlated with a more severe but delayed arthritic phenotype. The predictive value of these haplotypes was confirmed by logistic regression, which after adjustment for confounders showed, for example, the probability of developing sacroiliitis was almost completely determined by the inheritance of EH27.1, EH8.1 or C*05 (adjusted for age, PsA duration, uveitis, and maximal PASI score). Similarly, the probability of developing peripheral joint erosions was strongly associated with the presence of EH27.1, EH8.1 or C*03, figure B (adjusted for gender, PsA duration and lumbar axial disease).
**Conclusions:** Certain HLA alleles, and, most strikingly particular haplotypes, contribute importantly to the magnitude of traits comprising the diverse phenotypes of PsA, but this contribution does not completely parallel the role of these alleles or haplotypes in determining susceptibility.
**Disclosures:** The authors have declared no conflicts of interest.

### O45. ANKYLOSING SPONDYLITIS IS STRONGLY ASSOCIATED WITH VARIANTS IN THE *CMG2* GENE

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**Background:** AS is a polygenic inflammatory disease with well-established contributions from the genes *HLA-B*27, ERAP1* and *IL23R*. Whole genome association studies (GWAS) have identified more than 11 additional loci associated with AS, some of which have been independently confirmed, such as *KIF21B*, loci at 2p15 and 21q22. Other loci, such as *CARD9, TNFRSF1A* and *RUNX3* are strongly implicated, and are subject to confirmation and fine mapping in ongoing studies using the ImmunoChip. Single nucleotide polymorphisms (SNPs) in the *CMG2* gene, also known as *ANTXR2*, have shown suggestive association with AS in two previous GWAS. However, SNPs in *CMG2* were not included on the ImmunoChip. We have undertaken an independent replication of the TASC and WTCCC2 SNPs (either genotyped or imputed) in *CMG2* that showed suggestive association with AS previously ($P < 2 \times 10^{-5}$).

**Methods:** We studied 2978 new AS cases from the UK, and genotyped them for one coding SNP and eight non-coding SNPs in *CMG2* by KASPar technology (KBioscience, Hoddesdon Herts). We compared the allele frequencies in these cases to unrelated healthy individuals from the Avon Longitudinal Study of Parents and Children (ALSPAC) study ($n = 8365$) using contingency tables.
**Results:** Control data were available for eight of the nine SNPs, but not for the single coding SNP in the ALSPAC data set. A second ALSPAC SNP was not well imputed and was therefore excluded from the study. Of the non-coding SNPs, one showed genome-wide significant association (SNP1 $P = 1.2 \times 10^{-22}$, odds ratio = 0.72, 95% CI 0.68, 0.77). The next two most strongly associated markers were SNP2 ($P = 0.0001$) and SNP3 ($P = 0.0005$); one further SNP was associated ($P = 0.01$) and three were not.
**Conclusions:** We have replicated and extended the suggestive association of *CMG2* with AS. Its role in AS is not immediately obvious. *CMG2* encodes capillary morphogenic protein 2, which is dramatically up-regulated *in vitro* when cultured human umbilical venous endothelial cells are induced to undergo capillary morphogenesis. Its interactions with collagen IV and laminin are also consistent with this role. In mice, *CMG2* is expressed on the vasculature *in vivo* and is an angiogenic regulator. A hallmark of inflammation is increased vascular permeability, one potential consequence of which is angiogenesis. However, nothing is known about the role of CMG2 in the context of angiogenesis and inflammation. Subchondral vascularization in the femoral head has been described in AS at the time of hip joint replacement, and a significant increase in microvessels has been documented in bone marrow adjacent to the zygapophyseal joints in AS patients; both these processes may suggest a role for CMG2 in this disease.
**Disclosures:** The authors have declared no conflicts of interest.

## O46. ESTIMATING HERITABILITY OF RESPONSE TO TREATMENT WITH ANTI-TNF BIOLOGIC AGENTS USING LINEAR MIXED MODELS

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**Background:** The effectiveness of treatment with TNF inhibitors in RA is variable. A proportion of the variance may be underpinned by genetics; however studies, to date, have failed to identify robust genetic markers of response. Potential reasons include (i) there is little genetic basis to treatment response (ii) lack of statistical power of the studies undertaken or (iii) lack of an appropriate measure of response i.e. the 28-joint count DAS (DAS28). The aim of this study was to estimate heritability of treatment response using genome-wide genetic variation data in a large cohort of TNF-treated RA patients from the UK; and to investigate heritability of the individual components of the DAS28.
**Methods:** 1,168 RA patients, recruited into the BRAGGSS cohort were genotyped using Affymetrix or Illumina genome-wide single-nucleotide-polymorphism (SNP) arrays. Array datasets were merged following imputation and quality control (QC). Genome-wide Complex Trait Analysis (GCTA) software was used to estimate heritability. Related individuals were removed from the genetic relationship matrix (GRM). The DAS28 was calculated at treatment initiation and at 6 months following treatment. Outcome included change in: DAS28, swollen joint count, tender joint count (TJC), ESR, and patient VAS.
**Results:** Following QC, 3,140,396 SNPs were available for analysis in 1,140 patients. The cohort was 78% female, 78% were concurrently treated with DMARDs and the mean DAS28 at inclusion was 6.5. The GRM explained ~24% of the variance in treatment response when DAS28 was investigated. The variance explained by the GRM was lowest for TJC (5%) and highest for ESR (34%).
**Conclusions:** The amount of variability in treatment response explained by genetic variation was modest. The lack of consistent genetic signal for this phenotype is likely to be further compounded by the use of a composite measure i.e. DAS28. Future, well powered genetic association studies should prioritize objective components of DAS28 i.e. ESR.
**Disclosures:** The authors have declared no conflicts of interest.

## O47. MUSCULOSKELETAL PAIN IS ASSOCIATED WITH BMI THROUGH SHARED GENETIC FACTORS

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**Background:** Chronic musculoskeletal pain is a common condition in Western societies with prevalence of 5–15%. It is poorly understood and inadequately managed. It is known to be influenced by genetic factors but to date few genetic variants have been reliably confirmed. There is, however, a well documented positive association between chronic pain and elevated BMI, with people having raised BMI being more likely to manifest chronic pain. Longitudinal studies suggest that BMI does not arise as a result of pain limiting activity or exercise. Rather, it exists prior to the onset of pain, and thus can be considered a true risk factor for developing chronic pain. A number of studies have shown musculoskeletal pain to have genetic component [1,2] but to date few variants have been successfully and convincingly demonstrated identified. In contrast to our knowledge of the genetics of pain, however, BMI has been one of the success stories of the genome-wide association study (GWAS) era, with over 50 genetic regions identified as associated with BMI [3]. We asked the question: do pain and BMI share genetic factors, as a route to identifying genetic variants associated with CWP.
**Methods:** We used a classical twin design to determine the nature of the mechanism underlying this relationship. A large population-based sample of female twins was studied (TwinsUK), having information on subacute pain (SP). This was defined by having pain on both left and right sides of the body, above and below the diaphragm, lasting 7 days or longer and was ascertained by validated questionnaire (London Fibromyalgia Epidemiology Study Screening Questionnaire). BMI had been measured during a clinical visit. Bivariate modeling was performed to determine the relative contribution of genetic and environmental factors to the two phenotypes.
**Results:** The female twins ($n = 2588$) had a prevalence of SP of 23%, a mean age of 59.2 years and a mean BMI of 25.2 kg/m$^2$. Heritability estimates for SP = 49.9% (95% CI 42.8%, 57.4%) and BMI = 77.8% (95% CI 71.5%, 84.1%). Bivariate modeling showed that a major part (80%) of the phenotypic correlation between SP and BMI was accounted for by shared genetic factors ($P = 2.7 \times 10^{-7}$).
**Conclusions:** Our findings of shared genetic factors underlying the two phenotypes suggest that research into the aetio-pathology of SP might fruitfully be directed towards genetic variants associated with BMI.
**Disclosures:** The authors have declared no conflicts of interest.

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## O48. GENES CONTRIBUTING TO PAIN SENSITIVITY IN THE NORMAL POPULATION: AN EXOME SEQUENCING STUDY

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**Background:** Sensitivity to pain varies considerably between individuals and is known to be heritable. Increased sensitivity to experimental pain is a risk factor for developing chronic widespread pain—a common (prevalence = 9%) and debilitating symptom. To understand

better mechanisms underlying pain sensitivity and to search for rare gene variants (minor allele frequency $< 5\%$) influencing pain sensitivity we explored the genetic variation in individuals' response to experimental pain.
**Methods:** Quantitative sensory testing (QST) to heat pain was performed in 2500 volunteers from the TwinsUK register (TUK): exome sequencing to a depth of 70X was carried out on singletons selected from the high/low ends of the sensitivity distribution, in 2 subsamples ($n = 200$ each, 100 at each extreme, total $n = 400$). We compared 6 different classes of rare variant analysis method, and performed pathway analysis to understand better the links between genetic variants observed. We input 138 unique genes harbouring a rare variant (with $P < 0.01$) into causal reasoning which uses directed molecular interactions to work upstream from the genes to identify regulators that have a causally correct regulatory role. Correctness is determined by giving each input gene a direction of effect and here we assumed loss of function.
**Results:** The pattern of rare variation distribution was different in the pain insensitive and pain sensitive groups, with the insensitive individuals having greater numbers of rare variants. Rare variant analysis methods were highly correlated. GZMM was the gene most highly associated with pain sensitivity ($P = 6.86 \times 10^{-5}$ not statistically significant after correction for multiple testing). Network analysis of the 138 most associated genes revealed the angiotensin II regulatory network to be significantly associated with pain sensitivity (Bonferroni corrected $P = 3.8 \times 10^{-4}$). Angiotensin II had direct causal connections to 12 of the genes from our 138, which increased to 30 if one intermediary node was allowed in the network.
**Conclusions:** Data from animal and small clinical studies support a role for the angiotensin pathway in pain. A recent phase II study reported that a novel AT2 receptor antagonist successfully reduced post-herpetic neuralgia (http://www.spinifexpharma.com.au/DRUG-DISCOVERY.html). The present study did not, as we had hoped, identify novel variants having large effect on pain. However, we did observe a difference in rare variant distributions between the pain sensitive and insensitive groups. Furthermore, our work adds weight to evidence that the angiotensin II pathway plays an important role in pain sensation in humans and the components of the pathway may be targeted to create novel analgesics.
**Disclosures:** The authors have declared no conflicts of interest.

# ORAL ABSTRACTS 9: SCIENCE

### O49. THE ROLE OF PROTEIN KINASE D SIGNALLING IN THE INDUCTION OF MATRIX METALLOPROTEINASES IN HUMAN ARTICULAR CHONDROCYTES

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**Background:** The destruction of articular cartilage is a central feature of arthritis. The activity of collagenase enzymes, induced by pro-inflammatory cytokines, is a key step in this process and thus an important therapeutic target. The aim of the present study is to elucidate the signalling processes that regulate collagenase expression, focusing on the role of the small family of serine/threonine kinases termed protein kinase D (PKD). PKD consists of 3 distinct isoforms, all of which are expressed in articular chondrocytes.
**Methods:** Human primary articular chondrocytes were isolated by enzymatic digestion of OA cartilage and grown in monolayer culture. Chondrocytes were pre-incubated with the PKD inhibitor kb-NB142-70 and other agents, and then stimulated with the pro-inflammatory cytokine combination IL-1 and oncostatin M (OSM). Chondrocytes were also subject to siRNA-mediated gene silencing in some experiments. Lentiviral expressed shRNA mediated gene silencing was also used. Overexpression of PKD1 was performed in the human chondrosarcoma cell line SW1353. Western blotting was used to assess effects of gene silencing upon key signalling pathways. Alteration in gene expression was assessed using real time PCR.
**Results:** Stimulation of chondrocytes with either IL-1 or OSM lead to an increase in protein levels of each PKD isoform as well as increases in phosphorylation. PKD phosphorylation was dependent on Protein Kinase C (PKC) activity. Inhibition of PKD activity lead to a decrease in collagenase expression. Silencing of PKD3 in chondrocytes stimulated with IL-1 in combination with OSM lead to the inhibition of collagenase gene expression, whilst PKD2 silencing had no effect. Overexpression of PKD1 caused decreased collagenase gene expression in SW1353. PKD3 activity regulated the phosphorylation of STAT1 and STAT3, with a loss of serine and tyrosine phosphorylation upon PKD3 gene silencing.
**Conclusions:** Here we describe how closely related PKD isoforms regulate the expression of collagenase genes in a different manner. Silencing of PKD3 down regulated collagenase expression, with the same effect being observed upon overexpression of PKD1. This suggests the two isoforms may have opposing functions within chondrocytes. This regulation of collagenase expression is shown to be dependent on STAT serine and tyrosine phosphorylation.
**Disclosures:** The authors have declared no conflicts of interest.

### O50. EFFECTS OF PTPN22 R620W ON NEUTROPHIL FUNCTION IN HEALTH AND DISEASE

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**Background:** A single nucleotide polymorphism (SNP) variant of the PTPN22 gene, known as PTPN22 R620W, is a significant risk factor for the development of RA and other autoimmune inflammatory diseases such as vasculitis. PTPN22 encodes a protein tyrosine phosphatase Lyp, which is expressed in all leucocytes. Most studies of Lyp function have focused on lymphocytes and yet Lyp is expressed at the highest levels in neutrophils. These cells are thought to be important in the pathogenesis of RA, where they are found in abundance in the affected synovial joints and play an important role in organ damage in small vessel vasculitis. However, the role of Lyp and the effects of PTPN22 R620W expression have not been studied in neutrophils. Here we have investigated neutrophil function in healthy control subjects and vasculitis patients, control (GG), heterozygote (AG) and homozygote (AA) for the R620W allele.
**Methods:** 62 healthy individuals were genotyped for the PTPN22 R620W variant. Neutrophils were isolated from peripheral blood of age and sex matched control (GG) and variant (AG) expressing individuals. Cells were also isolated from GG and AA expressing vasculitis patients. Calcium signalling was assessed after stimulation of Indo-1 AM dye-loaded cells. Reactive oxygen species (ROS) production was measured using DHR oxidation as assessed by flow cytometry.
**Results:** The R620W allele (A) was highly expressed in healthy controls (AG = 28%, AA = 1%, GG = 71%), and 17 heterozygous/variant individuals were identified. An enhanced calcium flux in response to stimulation with fMLP was observed in AG neutrophils compared with GG neutrophils (GG = $0.21 \pm 0.027$ (indo FL ratio), AG = $0.24 \pm 0.035$, $n = 4$). This was also observed in neutrophils from vasculitis patients homozygous for the R620W allele (AA = $0.28 \pm 0.02$, $n = 2$). Baseline production of ROS was similar in unstimulated GG and AG neutrophils (GG = $93 \pm 8$ MFI, AG = $80 \pm 23$ MFI, $n = 3$). In cells stimulated with fMLP or primed with TNF$\alpha$, ROS production increased in neutrophils from GG individuals but the increase in AG neutrophils was much less. However, when neutrophils were first primed with TNF$\alpha$ then stimulated with fMLP, ROS production was greatly enhanced in AG neutrophils in comparison with control GG cells (GG = $215 \pm 66$ MFI, AG = $392 \pm 162$, MFI $n = 3$).
**Conclusions:** The function of Lyp in neutrophils has not previously been investigated, and our studies suggest that Lyp is an important regulator of neutrophil activation and function, particularly following priming with TNF$\alpha$. The allelic variant of PTPN22 may confer advantages in the individuals expressing it, by enhancing the ability of neutrophils to kill bacteria through increased ROS production. However, these hyperactive cells may have detrimental effects on chronic diseases such as RA and ANCA vasculitis, which are both associated with PTPN22 R620W expression and where neutrophils are important mediators of disease pathogenesis.
**Disclosures:** The authors have declared no conflicts of interest.

### O51. MACROPHAGE METABOTYPES IN THE HYPOXIC INFLAMMATORY ENVIRONMENT ASSESSED USING METABOLOMIC PROFILING

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**Background:** Macrophages are abundant in the synovium of RA and are the major source of many inflammatory cytokines, including TNF$\alpha$.

Disease severity correlates strongly with both synovial macrophage abundance and activation status but inversely with oxygen levels. Given the importance of oxygen to cell metabolism, differentiation and function, we hypothesized that the unique metabolic and oxygen environment of the joint may drive the differentiation of aggressive macrophages.

**Methods:** Human monocytes were differentiated into macrophage subsets (M1 and M2c) under GM-CSF and M-CSF polarizing conditions and under a variety of oxygen conditions, and stimulated with lipopolysaccharide (LPS). Cell metabolites were extracted for metabolomic analysis using NMR spectroscopy and secreted cytokines assessed. NMR spectra were analysed using partial least squares discriminant analysis (PLS-DA) to build models describing differences in metabolites, and partial least squares regression (PLS-R) to correlate these to cytokine production. Metabolites differentiating between experimental groups and pathways were identified and analysed using bespoke metabolic analysis tools.

**Results:** Macrophage subtypes exhibited unique metabolic patterns that, while shifting during differentiation, remained distinct throughout stimulation and subsequent activation with LPS. Differentiation of monocytes to both M1 and M2c macrophages increased production of myo-inositol, a marker of calcium signaling, and the proteinogenic amino acid serine. These correlated strongly with LPS-induced IL-6 production. M2c macrophages showed increased arginine production which correlated with IL-10 production, a key M2c anti-inflammatory cytokine. M1 macrophages exhibited higher glycolytic flux and a reduction in citric acid cycle metabolites.

Differentiation under hypoxia gave an altered metabolic phenotype, with a reduced citric acid cycle, and increased glycolytic flux. However, both M1 and M2c subsets remained metabolically distinct. Strikingly, differentiation of both M1 and M2c macrophages under reperfusion conditions resulted in an activated metabolic profile, indistinguishable from that induced by LPS, but interestingly up-regulation of IL-6 was not seen.

**Conclusions:** Classically-activated M1 macrophages and regulatory M2c macrophages each possess a unique metabotype that, while altered by environmental stressors, remains unique to the cell. This stability may depend on tight regulation at the gene and protein level, and we suggest that this is closely coupled to the macrophage differentiation programme. The increased arginine in M2c, for example, suggests a down-regulation of the arginase pathway in this resolution-associated subset. Therefore, while a capacity to adapt to the environment clearly remains, differentiation constrains this. We propose that this may impair subset survival or function in abnormal environments such as the rheumatoid synovium.

**Disclosures:** The authors have declared no conflicts of interest.

## O52. SYNOVIAL FIBROBLASTS SHAPE THE RECRUITMENT AND MIGRATION PATTERNS OF LYMPHOCYTES DURING RESOLVING AND PERSISTENT ARTHRITIS

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**Background:** Fibroblasts actively regulate the recruitment of leucocytes by endothelial cells, acting in a pro- or anti-inflammatory manner depending on their site of origin. The phenotype of the fibroblast may be a critical determinant of whether leucocyte recruitment, and therefore inflammation, resolves or persists. Here we examined how synovial fibroblasts from different stages of arthritis influenced the recruitment of peripheral blood lymphocytes (PBL) and their onward migration.

**Methods:** Fibroblasts were isolated from DMARD naive patients in the Birmingham Early Arthritis Cohort with resolving ($\leq$12week symptom duration) or persistent arthritis. Rheumatoid arthritis (RA) cohorts were categorized based on the stage of the disease at the time of sample collection: very early ($\leq$12week duration); newly presented established ($>$12week duration) or long established treated RA undergoing replacement surgery. Two forms of co-cultures were developed, appropriate to answer specific questions: (i) To assess the effects on recruitment, endothelial cells and fibroblasts were cultured on opposite sides of porous filters and incorporated into a novel flow chamber. PBL were perfused and observed as they bind to the endothelial surface. (ii) To examine effects on migration, endothelial monolayers were formed on a filter above a collagen gel in which fibroblasts were incorporated. PBL migration through the construct and their location within the gel were assessed. Conditioned media from co-cultures were collected and analysed by Luminex.

**Results:** In initial data, fibroblasts from patients with persistent inflammation increased the ability of endothelial cells to support PBL recruitment from flow in a disease duration-specific manner, with binding increasing from very early $<$established $<$replacement. Similar levels of binding were observed on co-cultures incorporating fibroblasts from patients with resolving inflammation and very early RA. In the multi-cellular gel model, all fibroblasts promoted PBL transendothelial migration but had no effect on the number of PBL entering into the gel. Interesting, a greater proportion of PBL migrated into the lower half of the gel when fibroblasts from patients with very early and established RA were incorporated. Elevated levels of IL-6, IL-1$\beta$, IL-8, Gro$\alpha$ and IP-10 were detected in the supernatants from RA co-cultures compared with resolving co-cultures. The presence of resolving fibroblasts dramatically reduced the secretion of these cytokines and chemokines by endothelial mono-cultures, suggesting they have a suppressive effect.

**Conclusions:** Collectively these preliminary data indicate that changes in the ability of fibroblasts to influence endothelial and lymphocyte behaviours may occur very early in the development of RA, possibly before clinical criteria are fulfilled. Moreover, some of these changes are distinct from the phenotype exhibited by fibroblasts taken from acutely resolving arthritis.

**Disclosures:** The authors have declared no conflicts of interest.

## O53. BIOLOGICAL ROLES OF C5ORF30 IN RHEUMATOID ARTHRITIS

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**Background:** A recent genome wide association study identified the variant rs26232 in the first exon of an uncharacterized gene C5orf30. In addition, this variant is also associated with severity of radiological joint damage suggesting a role in tissue breakdown. To date there is no function assigned for C5orf30 and neither the gene or protein coded show homology to any known functional sequences. However, C5orf30 is highly conserved in chimpanzee, dog, cow, mouse, chicken, and zebrafish (orthologs). The aim of this study is to determine the biological roles of C5orf30 in health and RA.

**Methods:** Real time PCR and western blotting was used to determine C5orf30 transcript and protein levels in fibroblast-like synovial cells (FLS-stimulated with TNF and hypoxia) and peripheral blood leucocytes isolated from RA patients and healthy individuals. Immunohistochemistry using synovial samples was used to determine cellular expression using anti-C5orf30 and antibodies to macrophages (CD68), fibroblasts (5B5), T (CD3) and B (CD19) cells. To investigate gene function siRNA was used to knockdown C5orf30 in synovial FLS *in vitro* and we have used morpholino antisense oligonucleotide (MO)-mediated knocked down of C5orf30 in zebrafish embryos (fms:mcherry) *in vivo*.

**Results:** Expression of C5orf30 was detected at lower levels in peripheral blood leucocytes of RA patients compared with healthy controls (117 patients *vs* 102 controls, $P = 0.00052$). C5orf30 was expressed in joint FLS and was found to be up regulated following treatment with hypoxia (8-fold) and down-regulated by TNF-a (0.5-fold). Confocal microscopy revealed C5orf30 was strongly expressed in both the nuclear and cytoplasmic compartment of synovial lining cells including macrophages and fibroblasts but not B and T cells. C5orf30 was undetectable in arthroscopy sections obtained from OA or control (knee replacement) patients. So far, 80% C5orf30 knockdown has been achieved in FLS and this led to increased invasion into matrigel. Interestingly, MO-mediated knock-down of C5orf30 impeded zebrafish development and increased total macrophage numbers by 40% following tail-fin injury compared with knockdown of a non-targeting control MO.

**Conclusions:** C5orf30 is expressed at both the transcript and protein level in synovial cells but not in circulating PBMC obtained from RA patients, suggesting that C5orf30 is expressed in a tissue-specific manner. C5orf30 knockdown increased FLS migration into matrigel suggesting C5orf30 is negatively regulating cellular invasion. In addition knockdown of C5orf30 in a zebrafish model of inflammation increased total macrophages numbers at the site of injury, indicative of a role for C5orf30 in macrophage development. We are currently performing proteomic studies including NMR and mass spectrometry to work out the biology of this important marker in the pathogenesis and severity of RA.

**Disclosures:** The authors have declared no conflicts of interest.

### O54. AUTOCITRULLINATED *PORPHYROMONAS GINGIVALIS* PEPTIDYLARGININE DEIMINASE: A NOVEL ANTIGEN WITH POTENTIAL FOR BREACHING IMMUNOLOGIC TOLERANCE IN RHEUMATOID ARTHRITIS

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**Background:** Rheumatoid arthritis (RA) is characterized by autoimmunity to citrullinated proteins. There is increasing molecular and epidemiological evidence linking periodontitis (PD) to RA. *Porphyromonas gingivalis* is unique amongst periodontal pathogens in possessing a citrullinating enzyme, peptidylarginine deiminase (PPAD) with the potential to generate citrullinated antigens driving the autoimmune response in RA. Because of the potential importance of PPAD in RA pathogenesis, we have examined the immune response to PPAD in a cohort of patients with RA compared with normal controls, in addition to individuals with periodontitis as a positive control for active *P. gingivalis* infection.

**Methods:** PPAD and an inactive PPAD mutant (C351A) were cloned and expressed and the enzyme activity of both was measured using a colorimetric PAD assay. Autocitrullination of PPAD was tested by immunoblotting with the anti-modified citrulline (AMC) antibody and by mass spectrometry using MASCOT. Enzyme-linked Immunosorbant assays (ELISAs) using PPAD and C351A were used to test serum from normal controls ($n = 80$), PD ($n = 44$) and RA ($n = 82$), calculated as units per ml (AU/ml) using a standard curve. Thirteen synthetic citrullinated peptides spanning the PPAD sequence were synthesized to test antibody reactivity with specific epitopes. The Mann–Whitney *U*-test was used to calculate p-values for differences between the sera groups for each antigen.

**Results:** Immunoblotting by AMC showed that PPAD was autocitrullinated with 7 out of a possible 18 citrulline residues demonstrated by mass spectrometry. Antibodies to PPAD were significantly higher in the RA sera (median 122 AU/ml), than the PD sera (median 60 AU/ml; $P < 0.01$) and the healthy control sera (median 70 AU/ml $P < 0.05$). There was no elevated antibody response in the RA sera to PPAD when the C351A PPAD mutant was used on ELISA. The specificity of the anti-citrullinated PPAD response was confirmed by the reaction of RA sera with multiple epitopes tested with synthetic citrullinated peptides spanning the PPAD molecule.

**Conclusions:** The heightened immune response of autocitrullinated PPAD in RA sera could be part of a cross-reactive anti-citrullinated protein antibodies (ACPA) response, but more importantly, it could also indicate that PPAD itself could be a mechanism for breaching immunological tolerance to citrullinated antigens.

Thursday 25 April 2013, 14.00–15.30

# BSR AND BHPR ORAL PRESENTATION OF ABSTRACTS

## ORAL ABSTRACTS 10: SPONDYLOARTHRITIS

### O55. APREMILAST, AN ORAL PHOSPHODIESTERASE 4 INHIBITOR, IN PATIENTS WITH PSORIATIC ARTHRITIS: RESULTS OF A PHASE III RANDOMIZED CONTROLLED TRIAL

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**Background:** Apremilast (APR), an oral phosphodiesterase 4 inhibitor, works intracellularly to modulate pro- and anti-inflammatory mediators. PALACE 1 compared APR efficacy and safety *vs* placebo (PBO) in patients with active PsA despite prior DMARDs and biologics.
**Methods:** Patients were randomized 1:1:1 to PBO, APR 20 mg BID, or APR 30 mg BID stratified by baseline (BL) DMARD use. At week 16, patients with $<20\%$ reduction in swollen and tender joint counts were re-randomized to APR 20 mg BID or 30 mg BID (PBO group) or remained on initial dose (APR groups). All patients continued treatment through week 24. Stable concurrent DMARD therapy was allowed (MTX, SSZ, LEF, or combination). Analysis done on per-protocol population used LOCF methodology for missing data.
**Results:** 504 patients were randomized and comparable across treatment arms for demographics, disease characteristics, and prior/concurrent therapy; 23.6% had prior biologic exposure; 9.3% were biologic failures. At BL, 64.9% were taking DMARDs (54.2% MTX). At week 16, more patients receiving APR 20 mg BID (31.3%; $P=.0140$) and 30 mg BID (41.0%; $P<.0001$) achieved an ACR20 *vs* PBO (19.4%). With APR 30 mg BID, higher ACR20 responses were seen in the APR monotherapy and biologic-naïve groups *vs* the overall population. At week 24, significant improvements in secondary endpoints were seen with APR *vs* PBO, including physical function and pain. APR was generally well tolerated. Adverse events (AEs) occurring in $\geq 5\%$ of any group were diarrhea (PBO 2.4%, 20 mg BID 11.3%, 30 mg BID 19.0%), nausea (6.5%, 9.5%, 18.5%), headache (4.8%, 10.1%, 10.7%), and URTI (3.6%, 6.0%, 4.2%). Most ($>95\%$) AEs were mild/moderate; discontinuations due to AEs were similar across all treatment arms (5–7%). Serious AEs occurred in 7 (PBO), 8 (20 mg BID), and 9 (30 mg BID) patients. There was no greater risk of opportunistic infections, lymphoma, or cardiovascular events. No TB reactivation was reported.
**Conclusions:** APR significantly improved signs and symptoms of PsA and resulted in statistically and clinically meaningful improvements in physical function. APR was generally well tolerated with no new safety/laboratory signals detected.

**Disclosures:** J.G., Roche, Schering-Plough—Research Grants, Lecture Fees, Advisory Boards, BMS—Lecture Fees, Advisory Boards, Wyeth—Lecture Fees, Pfizer, UCB SA—Advisory Boards. C.H., Celgene Corporation—Employee. A.K., Abbott, Amgen, AstraZeneca, BMS, Celgene, Centocor-Janssen, Pfizer, Roche, UCB—Research Grants. P.M., Abbott, Amgen, BiogenIdec, BMS, Genentech Janssen, Lilly, Pfizer, UCB—Research Grants, Consultant Fees, Speaker's Bureau, Celgene, Novartis, Roche—Research Grants, Consultant Fees. R.S., Celgene Corporation—Employee. J.W., Abbott Laboratories, BMS, MSD, Pfizer, UCB—Consulting Fees. All other authors have declared no conflicts of interest.

### O56. SUSTAINED EFFICACY OF ADALIMUMAB IN PATIENTS WITH NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS WITH POSITIVE MRI OF THE SACROILIAC JOINTS OR SPINE OR ELEVATED C-REACTIVE PROTEIN AT BASELINE

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**Background:** Adalimumab (ADA) is currently approved in the EU for the treatment of adults with severe axial SpA without radiographic evidence of AS, but with objective signs of inflammation by elevated CRP and/or MRI who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs.
**Methods:** ABILITY-1 is an ongoing double-blind (DB), randomized, controlled trial in non-radiographic axial SpA (nr-axSpA) patients fulfilling ASAS axial SpA criteria but not modified New York criteria who had an inadequate response, intolerance, or contraindication to NSAIDs. ADA 40 mg every other week or placebo (PBO) was given for a 12-week DB period followed by open-label ADA for up to 144 weeks. This post-hoc analysis describes the long-term efficacy and safety of ADA in patients with nr-axSpA who had a positive baseline (BL) MRI (defined as a SPARCC score $\geq 2$ for either the SI joints or spine) or an elevated CRP at BL. Clinical responses were summarized by observed case and non-responder imputation (NRI) analyses.
**Results:** 142 (69 ADA, 73 PBO) of the total efficacy study population ($N=185$) had a positive MRI at BL or elevated CRP (MRI+/CRP+). 139 patients completed the DB period; 111 patients had data available for week 68 analysis. BL demographics and disease characteristics of the MRI+/CRP+ subpopulation were comparable to the total population. At week 12, efficacy results were comparable between the total population and the MRI+/CRP+ subpopulation (Table 1). Efficacy was sustained with long-term ADA therapy up to week 68. At week 68, among the MRI+/CRP+ subpopulation ($N=111$), 69% of patients had an ASAS40 response and 48% were in a state of inactive disease as

TABLE 1. Results

| | PBO ($n=165$) | APR 20 mg BID ($n=163$) | APR 30 mg BID ($n=161$) |
|---|---|---|---|
| ACR20 at week 16, % (NRI %) | 19.4 (19.4) | 31.3* (31.3) | 41.0*** (40) |
| APR alone ($n=172$), % (NRI %) | 10.5 (10.5) | 31.5* (31.5) | 50.8*** (48) |
| APR + DMARDs ($n=317$) | 24.1 | 31.2[a] | 35.0[a] |
| ACR20 at week 16 | 23.7 | 31.2[a] | 43.3* |
| Biologic-naïve ($n=363$) | | | |
| APR alone ($n=89$), % (NRI %) | 11.5 (11.5) | 24.1[a] (24.1) | 58.8* (56) |
| APR + DMARDs ($n=274$) | 27.2 | 33.3[a] | 37.2[a] |
| Select secondary endpoints at week 24 | | | |
| ACR50, % | 4.2 | 15.3* | 19.9*** |
| ACR70, % | 0.6 | 5.5* | 11.2*** |
| HAQ-DI, LS mean Δ (S.E.) | –0.077 (0.037) | –0.212 (0.037)* | –0.260 (0.037)* |
| SF-36 PF, LS mean Δ (S.E.) | 1.46 (0.671) | 3.50 (0.675)* | 5.06 (0.674)*** |

Efficacy analyses conducted using per-protocol population ($N=489$); last observation carried forward (LOCF) used for missing data. NRI: nonresponder imputation. *$P<0.05$; ***$P\leq 0.0001$; [a]$P=$ NS *vs* PBO.

TABLE 1. Results

| | Total study population | | | MRI+/CRP+ subpopulation | | |
|---|---|---|---|---|---|---|
| | Week 12[a] ($n=185$), % | | Week 68[b] ($n=144$), % | Week 12[a] ($n=142$), % | | Week 68[b] ($n=111$), % |
| | PBO ($n=94$) | ADA ($n=91$) | | PBO ($n=73$) | ADA ($n=69$) | |
| ASAS40 | 15 | 36 | 67 | 14 | 41 | 69 |
| BASDAI50 | 15 | 35 | 65 | 14 | 39 | 67 |
| ASAS partial remission | 5 | 16 | 36 | 5 | 19 | 40 |
| ASDAS inactive disease | 4 | 24 | 47 | 4 | 29 | 48 |

[a]NRI. [b]Observed data.

measured by the ASDAS, with comparable results observed in the total study population (N = 144) (Table 1). As of week 68, in the total safety population (ADA exposure = 193.3 patient-years), there were 3 serious infections including 1 case of tuberculosis, 1 death due to suicide, but no malignancies, demyelinating diseases, or lupus-like syndromes.

**Conclusions:** Long-term data demonstrate sustained efficacy with ADA in nr-axSpA patients who have inadequate response, intolerance or contraindication to NSAIDs, in both the total efficacy study population and in a subpopulation with objective evidence of inflammation by MRI or elevated CRP. Almost half of the patients remaining in the study at week 68 is in ASDAS inactive disease. Long-term safety data were consistent with the known safety profile of ADA in AS and other immune-mediated diseases.

**Disclosures:** M.D., AbbVie, BMS, Merck, Pfizer, Sanofi-Aventis, UCB—Research Grants, Consulting Fees. P.G., AbbVie, BMS, Merck, Pfizer, UCB—Participated at Advisory Boards and Symposia. A.P., AbbVie—Employee, Stock and/or Stock Options, AbbVie sponsored the study, contributed to its design, and participated in the collection, analysis, and interpretation of the data, and in the writing, reviewing, and approval of the final version. S.R., AbbVie—Employee, Stocks/Stock Options. J.S., AbbVie, Merck, Pfizer, UCB—Research Grant, Consulting Fees. F.V., AbbVie, Merck, Pfizer, UCB—Consulting Fees, Speaker's Fees. D.V., AbbVie, Amgen, AstraZeneca, BMS, Centocor, Chugai, Eli Lilly, GSK, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Wyeth—Consulting fees, Imaging Rheumatology—Director.

## O57. SPINAL INFLAMMATION IN THE ABSENCE OF SI JOINT INFLAMMATION ON MRI IN PATIENTS WITH ACTIVE NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS

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**Background:** The imaging arm of the ASAS axial SpA criteria requires the presence of sacroiliitis on MRI or radiographs. In patients with non-radiographic axial SpA (nr-axSpA), there may be inflammation along the spine in the absence of sacroiliac joint (SIJ) inflammation on MRI. This analysis evaluated the existence of spinal inflammation on MRI at baseline (BL) in nr-axSpA patients with and without inflammation in the SIJs on MRI.

**Methods:** ABILITY-1 is an ongoing multicentre, randomized, controlled trial of adalimumab *vs* placebo in patients with nr-axSpA classified using the ASAS axial SpA criteria, who had an inadequate response, intolerance to, or contraindication for NSAIDs. MRI of the SIJ and spine performed at BL were centrally scored using the SPARCC method (6-DVU method for the spine) by 2 independent readers blinded to the treatment codes. Mean scores of the readers were used. SPARCC score $\geq$2 for either the SIJ or spine was used as the operational definition of positive MRI evidence of inflammation. For these analyses, all patients were combined, independent of randomization.

**Results:** Mean symptom duration of the study population (N = 185) was 10 years. At BL, 48% of patients were reported by the local investigator to have past or present MRI evidence of sacroiliitis as required by the ASAS axial SpA criteria. Of patients with available BL SPARCC scores, 40% had a BL SIJ score $\geq$2 and 52% had a BL spine score $\geq$2. Of the patients with BL SPARCC SIJ score <2, 49% had evidence of spinal inflammation (BL SPARCC spine score $\geq$2). Comparison of BL disease characteristics based on BL spine and SIJ scores <2 *vs* $\geq$2 were generally comparable except for a greater proportion of males among those with spine and SIJ scores $\geq$2, and younger age and shorter symptom duration among those with spine and SIJ scores <2. Similar distribution of SPARCC spine scores were observed regardless of presence or absence of SIJ inflammation on MRI. The most frequently involved DVUs with bone marrow edema were in the lower thoracic and lumbar spine.

**Conclusions:** Assessment by experienced readers shows that spinal inflammation on MRI may be observed in half of nr-axSpA patients without SIJ inflammation on MRI. MRI of both sites might be of value when evaluating patients with nr-axSpA. These data in patients with long-standing disease need to be confirmed in patients with shorter disease duration.

**Disclosures:** M.B., AbbVie, Eli-Lilly, Jansen-Cilag, Merck, Pfizer, Procter and Gamble, Schering-Plough and Wyeth—Research Grants, Speaker's Fees, Consulting Fees. W.M., AbbVie, BMS, Eli-Lilly, Janssen, Pfizer, and UCB—Research Grants, Speaker Fees, Consulting Fees. A.P., AbbVie—Employee, Stocks, AbbVie sponsored the study, contributed to its design, and participated in the collection, analysis, and interpretation of the data, and in the writing, reviewing, and approval of the final version. S.R., AbbVie—Employee, Stocks. J.S., AbbVie, Merck, Pfizer, and UCB—Research Grant, Speaker Fees, Consultations Fees. D.V., AbbVie, Amgen, AstraZeneca, BMS, Centocor, Chugai, Eli-Lilly, GSK, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, and Wyeth—Consultation Fees, Imaging Rheumatology bv—Owner.

## O58. DISEASE BURDEN IS COMPARABLE IN PATIENTS WITH NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS AND ANKYLOSING SPONDYLITIS

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**Background:** Chronic back pain and functional impairment are disease characteristics common to all patients with axial SpA, regardless of the presence of radiographic sacroiliitis in AS or its absence in non-radiographic axial SpA (nr-axSpA). This analysis compares baseline disease characteristics of patients with nr-axSpA and AS in registries and randomized clinical trials (RCT) with adalimumab (ADA).

**Methods:** Registry data in this analysis include the German SpA Inception Cohort (GESPIC) that compared patients with AS by modified New York criteria (divided into >5 years and $\leq$5 years) and nr-axSpA ($\leq$5 years) meeting modified ESSG criteria and a prospective cohort of TNF-naïve SpA patients meeting ASAS criteria for axial SpA (Kiltz). ADA RCT data were derived from the ATLAS study in AS patients, and the ABILITY-1 and Haibel studies in nr-axSpA patients. Patients in RCTs were selected based on a pre-specified level of disease activity and inadequate response to non-steroidal anti-inflammatory drugs.

**Results:** Mean age was similar in nr-axSpA and AS patients, ranging from 36 to 42 years (Table 1). A higher proportion of AS patients had elevated CRP as compared with nr-axSpA patients and gender differences were observed, with nr-axSpA patients being predominantly female and AS patients primarily male. Symptomatic patients with nr-axSpA and AS often went undiagnosed for years. Similar levels of disease activity as measured by the BASDAI, pain scores, and pt and physician global assessments of disease activity were seen between nr-axSpA and AS patients in registries and RCTs, with levels

TABLE 1. Nr-axSpA and AS baseline disease characteristics

| | Registries | | | | | RCTs | | |
|---|---|---|---|---|---|---|---|---|
| | GESPIC | | | Kiltz | | ATLAS | ABILITY-1 | Haibel |
| | All AS $n=236$ | AS ≤5 years $n=119$ | nr-axSpA ≤5 years $n=226$ | AS $n=56$ | nr-axSpA $n=44$ | AS $n=315$ | nr-axSpA $n=185$ | nr-axSpA $n=46$ |
| Age, years | 35.6 | 36.1 | 36.1 | 41.2 | 39.1 | 42.2 | 38.0 | 37.5 |
| Female, % | 36.0 | 34.5 | 57.1 | 23.2 | 68.2 | 25.1 | 54.6 | 54.3 |
| HLA-B27+, % | 88.2 | 73.1 | 74.7 | 89.1 | 86.4 | 78.7 | 75.1 | 67.4 |
| Symptom duration, years | 5.2 | 3.0 | 2.6 | 12.8 | 9.4 | – | 10.1 | 7.5 |
| Duration since diagnosis, years | 2.8 | 1.7 | 1.7 | 7.5 | 5.0 | 10.6 | 2.9 | – |
| BASDAI 0–10 | 4.0 | 4.0 | 3.9 | 4.2 | 3.6 | 6.3 | 6.5 | 6.3 |
| Abnormal CRP, % | 51.9 | 49.6 | 29.8 | 69.1 | 29.5 | 67.6 | 35.7 | 37.8 |
| Total back pain, VAS 0–10 | – | – | – | – | – | 6.5 | 6.9 | – |
| Total pain, VAS 0–10 | 5.0 | 4.8 | 4.8 | 4.7 | 4.0 | _– | 6.8 | 7.2 |
| Patient Global Assessment of disease activity, VAS 0–10 | 5.0 | 5.0 | 4.9 | 4.6 | 4.0 | 6.3 | 6.8 | 6.6 |
| Physician Global Assessment of disease activity, VAS 0–10 | 4.5 | 4.4 | 3.6 | 3.5 | 2.7 | 5.7 | 5.7 | 5.9 |

Values are the mean unless otherwise indicated. nr-axSpA: non-radiographic axial SpA.

of disease activity generally higher in RCT patients due to minimum levels of baseline disease activity required for study eligibility.

**Conclusions:** Registry and clinical trial data demonstrate that both nr-axSpA and AS patients have comparable burden of disease. These findings suggest that all patients with axial SpA can present with similar debilitating signs and symptoms requiring treatment regardless of the extent of radiographic damage.

**Disclosures:** J.A., AbbVie—Employee, Stock and/or Stock Options. D.E., AbbVie—Research Grants, Speaker's Fees. A.P., AbbVie—Employee, Stock and/or Stock Options. J.S., AbbVie, Merck, Pfizer, UCB—Research Grants, Consulting Fees, Speaker's Fees. D.V., AbbVie, Amgen, AstraZeneca, BMS, Centocor, Chugai, Eli Lilly, GSK, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Wyeth—Research Grants, Consulting Fees, Imaging Rheumatology—Director.

## O59. A PROPOSED ALGORITHM AND ITS PERFORMANCE EVALUATION FOR THE BEST REFERRAL BY OPHTHALMOLOGISTS OF ACUTE ANTERIOR UVEITIS PATIENTS WITH POSSIBLE UNDERLYING SPONDYLOARTHROPATHY

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**Background:** Recent reports claim that the prevalence figures of mostly undiagnosed underlying SpA is more than 60% of patients presenting with acute anterior uveitis (AAU). Unfortunately, there are no formal guidelines or referral pathways for AAU patients developed or endorsed by any international or even national societies. Therefore, in a condition where significantly delayed diagnosis is common and where AAU may frequently be the first interaction with medical care, an opportunity to identify SpA early is often missed leading to less than ideal care for SpA patients.

**Methods:** The objectives of our study were: (i) to develop an assessment algorithm for referral from Ophthalmologists of appropriate AAU patients to rheumatology that will aid the early diagnosis of the SpA; and. (ii) to investigate the prevalence of undiagnosed SpA in patients presenting with AAU in a primary care ophthalmology setting.

All consecutive patients attending emergency department of local ophthalmology hospital (RVEEH) with AAU, but who did not have a known diagnosis of SpA, were eligible to partake in this study. Patients with any other known cause of AAU were excluded. The HLA-B27 status was checked in all patients, and assessment and onward referral was made as per a test algorithm which combined clinical features and HLA-B27. Patients without risk factors for SpA and who were HLA-B27 negative remained part of the study as a control group.

**Results:** 104 consecutive patients attending from September 2011 through to June 2012 were recruited. Mean age of the cohort was $42 \pm 15$ years, 56.4% were male, HLA- B27 was positive in 52.5%. After rheumatologic evaluation, 41.5% of patients were noted to have undiagnosed SpA as per ASAS classification criteria; 64% of them had radiographic axial SpA, and only 2 patients had peripheral SpA. The mean age of these newly diagnosed SpA patients was $41 \pm 13$ years; average duration of backache was $11.65 \pm 11$ years; and HLA-B27 was negative in only 4 patients. Our algorithm version 1 was noted to have: sensitivity 100%, specificity 53.5%, PPV 61% and NPV 100%. Further simple step wise re-analysis of the data revealed that algorithm version-2 can make following improvements: sensitivity 95%, specificity 98%, PPV 97.5%, NPV 96.6%, which is undergoing further testing at present in an additional cohort.

**Conclusions:** 41.5% of patients presenting with idiopathic AAU have undiagnosed SpA. Recognition of undiagnosed SpA is an achievable goal, but requires an integrated multidisciplinary approach. A simple to apply algorithm is described with excellent sensitivity and specificity that is currently being validated in an additional cohort.

**Disclosures:** The authors have declared no conflicts of interest.

## O60. EFFECTIVENESS OF SEQUENTIAL BIOLOGIC USE IN PSORIATIC ARTHRITIS: RESULTS OF A LARGE RETROSPECTIVE SURVEY

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**Background:** Treatment of PsA has been revolutionized by the use of anti-tumour necrosis factor inhibitors (TNF). By August 2007, 3 anti-TNFs were approved by The National Institute of Clinical Excellence (NICE) for the treatment of moderate-severe PsA and later combined to form TA199. NICE permits the use of sequential biologics in RA, however switching between anti-TNFs in PsA is not endorsed at present. Increasingly PsA patients who fail on 1st line anti-TNF therapy due to inefficacy/adverse effects are left with no further therapeutic options. Limited data from open label studies and registries have confirmed the potential benefits of switching between anti-TNFs. Our aim was to assess compliance with current NICE guidance regionally and the outcome of patients who fail their 1st anti-TNF drug.

**Methods:** A retrospective audit was conducted up to June 2012, to include all PsA patients on a current anti-TNF in the north-west. Each rheumatology department in the region was invited to participate. Data were collected locally by a designated site coordinator, then analysed centrally using Microsoft Excel 2011.

**Results:** Data on 548 patients were collected across 18 sites. Mean age was 48 years (range 20–80 years), with 51% of patients being female. Mean time from diagnosis to starting anti-TNF was 7.5 years. 80% commenced anti-TNFs after NICE guidance was introduced. 28% were on biologic monotherapy and 72% were on a concomitant DMARD- of which 84% on MTX. Majority of patients were started on adalimumab 1st line (64%), followed by etanercept (34%), infliximab (2%) and golimumab (1%). At 12 weeks 74% of patients had an adequate response however 24% of patients were not on their initial anti-TNF at the time of the audit (reasons included: 41% secondary inefficacy, 19% primary inefficacy, 26% intolerance, 4% pregnancy). 17% of all patients switched between anti-TNFs against NICE guidance, with 3% switching between 3 and 4 biologics. Subsequent lines of biologics included anti-TNFs but also rituximab ($n=2$), ustekinumab ($n=1$) and tocilizumab ($n=1$). 74% switched due to inefficacy, 26% due to intolerance. Only 24% of switchers obtained permission from their PCT; 4 patients regionally had an individual

funding request rejected. Of the switchers, 52% of patients responded to 2nd line biologic and a further 8% to 3rd line biologic; 19% were non-responders, 2% intolerant and 19% were awaiting follow up to assess response to switching at the time of the audit.
**Conclusions:** Every centre in the north-west participated, most sites auditing all eligible patients representing an accurate reflection of current practice. PCTs across the region varied significantly regarding their policy on switching anti-TNFs in PsA. The results support the effectiveness of switching and signify a need for updating current national guidance to allow more therapeutic alternatives for the most severely affected patients.
**Disclosures:** The authors have declared no conflicts of interest.