4. REGIONAL VARIATIONS IN JOINT REPLACEMENT: DISEASE OR SERVICE PROVISION?

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Background: The objective of this study is to describe regional variations in joint replacement rates for hip (THR) and knee (TKR) in the UK and to describe their variation over time. The General Practice Research Database (GPRD) comprises all computerized medical records of a sample of patients visiting GPs in the UK. It covers a population of more than 6.25 million men and women from 683 contributing practices. Data was collected for all THRs and TKRs from inception of the database in 1987 up to the end of 2006. This amounts to approximately 28000 THRs and 24000 TKRs.

Methods: GPRD data was used to calculate age-standardized sex-specific incidence rates of THR and TKR for each health region. The scope of the study was confined to first incidences of THR and TKR from 1987 to the end of 2006. Assessment of temporal changes in incidence were achieved by comparing the sex-specific distribution of incidence rates by health service region for the six-year period 1991 to 1996 with rates for the period 2001 to 2006. Direct age-standardised rates with 95% confidence intervals were calculated using 2003 mid-year population estimates from the ONS as a reference.

Results: The rate of joint replacement has increased significantly across all regions over the study period. Major regional variations in the age-standardised incidence of joint replacement were observed in the period 2001 to 2006 (table) for both THR and TKR. For THR the variation in rates was less apparent in the period 1991 to 1996. The rate for THR increased significantly across all regions for the period 1991 to 1996: Scotland 67.4/100000 person years (95% CI 64.6 to 70.3) compared with the South West 59.2 (57.3 to 61.0). For the period 2001 to 2006, the rate had risen to 102.2 (99.5, 104.8) for Scotland and 160.5 (158.4, 162.7) for the South West.

Conclusions: This study has demonstrated that there are major geographical differences in the incidence of THR and TKR across each Health Region of the United Kingdom and that for THR the regional variation is a relatively recent phenomenon.

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5. A LONGITUDINAL STUDY EXAMINING THE ROLE OF EXPECTATIONS IN EXERCISE BEHAVIOUR IN OSTEOARTHRITIS (OA) OF THE KNEE

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Background: Previous work has indicated a positive relationship between patient expectations and health-related outcomes. However, many studies focus on self-efficacy and outcome expectations, disregarding expectations about the condition. Most work also examines expectations cross-sectionally, so it is unclear whether expectations predict outcomes, including behaviour. This study longitudinally examined the role of expectations on self-reported exercise behaviour in knee OA. It was hypothesised that: i) baseline (T1) outcome, self-efficacy and illness expectations would significantly predict self-reported exercising levels 2 months (T2) and 8 months later (T3); ii) illness expectations would predict behaviour when outcome and self-efficacy expectations were controlled for.

Methods: 57 people with knee OA (recruited from a rehabilitation trial) completed questionnaire, pain, WOMAC function, and exercise exercise delivered by physiotherapists provided no additional improvement in WOMAC pain scores. Small benefits in pain intensity and unpleasantness were observed in both acupuncture groups, making it unlikely that this was due to specific acupuncture needling effects. (Clinical Trials number ISRCTN88597683).

Disclosure: The authors have declared no conflicts of interest.

Concurrent Oral 2 – Paediatrics

7. LONG-TERM SAFETY AND EFFICACY OF ADA LUMAB THERAPY IN PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS (JRA) – RESULTS FROM OVER 2 YEARS OF TREATMENT

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Background: JRA is the most common rheumatic disease of childhood & is an important cause of disability among children. This study evaluated the long-term efficacy and safety of adalimumab (ADA) in patients (pts) with JRA. The 26-week double-blind (DB) placebo (PBO)-controlled withdrawal study of 171 pts (4-17 years) with polyarticular JRA (n = 116); A&E plus true acupuncture (n = 117) or A&E plus non-penetrating acupuncture (n = 119).

Disclosure: The authors have declared no conflicts of interest.
Rheumatologic Pediatric (ACR Pedi) 30 response were stratified by methotrexate (MTX) use and randomised to receive either ADA or PBO for 32 wks or until disease flare (end point). Pts could then choose to enter the OL extension (OLE) study, with initial dosing by BSA and a subsequent change to weight-based fixed dosing (pts <30 kg received 20 mg ADA and pts ≥30 kg received 40 mg). Efficacy/safety were assessed at routine intervals. ITT analyses using non-response imputation (RT) were performed and calculated ACR Pedi responses during the OL and DB periods. Pts with a disease flare were declared non-responders for ACR Pedi responses at Wk 32, regardless of actual ACR Pedi response. Because pts in the OLE had varying lengths of ADA exposure, an ITT, last-observation-carry-forward analysis was used to calculate ACR Pedi responses.

Results: At Wk 16, ACR Pedi 30/50/70/90 responses were achieved by 84/77/59/40% of pts, respectively. Despite use of stringent flare criteria, which could determine ACR Pedi <30% of pts of a minimal increase in disease activity, and ACR Pedi >30% more pts in the PBO group flared compared with the ABA group. At Wk 48 (end of the DB period), pts receiving ADA maintained significantly higher ACR Pedi 30/50/70/90 responses compared with PBO pts (36/37/27/24 vs 34/36/30/22). Responses for pts after 2 yrs of participation in the OLE (regardless of dose regimen) for ACR Pedi 30/50/70/90/100 were 89/86/77/59/40%. These results were similar in both MTX and non-MTX strata. The safety profile during the OLE was similar to that during previous study periods; the benefit/risk profile of ADA during long-term treatment of pts with JRA is favourable.

Conclusions: Throughout over two years of treatment with adalimumab, patients with JRA experienced substantial and sustained improvement. Discordant results between intrinsic factors and non-linear non-remunerative immune position with Abbott, Bristol Myers Squibb, Centocor, Novartis, Regeneron and Roche. M.M. is a full-time employee of and has stock options in Abbott. A.M. has received research grants from Abbott, Bristol-Myers Squibb, Roche, Novartis and Regeneron (non-linear remunerative). E.G. is a part-time employee of and has financial interests with JRA experienced substantial and sustained improvement. Discordant results between intrinsic factors and non-linear non-remunerative immune position with Abbott, Bristol, Myers Squibb, Centocor, Novartis, Regeneron and Roche. Roche, Novartis, Regeneron and Centocor. E.G. has received research grants from Amgen, and consulting fees from Abbott, Genzyme Regeneron, Bristol-Myers Squibb, Hoffman-La Roche and Centocor. All other authors have declared no conflicts of interest.

8. ABATANCE IS WELL TOLERATED IN A DOUBLE-BLIND, RANDOMISED WITHDRAWAL STUDY, WITH AN OPEN-LABEL EXTENSION, IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

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Background: Report of safety experience in a double-blind (DB), randomised withdrawal study, with an open-label (OL) extension in patients with juvenile idiopathic arthritis (JIA) treated with abatacept (ABA).

Methods: Patients meeting the ACR Pediatric (Pedi) 30 definition of improvement following a 4-month OL lead-in period were randomised 1:1 to DB therapy with ABA or placebo (PBO) every 28 days for up to 6 months. Safety is presented for the OL lead-in and DB periods.

Results: 190 patients enrol, and 170 completed the OL lead-in period; 123 patients achieved an ACR Pedi 30 response and 122 elected to receive the DB withdrawal period. During the OL lead-in, 6 patients reported serious adverse events (SAEs): 3 related to underlying disease (flare [2 cases]; joint replacement [1 case]) and 1 case each of varicella, ovarian cyst and acute lymphocytic leukaemia. The disease was diagnosed at age 89 in a patient who was anemic and in remission - with progressive decreasing haemoglobin from Day 1 (relationship to study medication was unlikely). 70% of patients had AEs; most common were headache (13.2%), nausea (10.0%), cough (8.9%), diarrhoea (8.9%), upper respiratory tract infection (URTI; 7.4%) and pyrexia (6.3%). Other than URTI, there were few infectious AEs (all had typical course and resolved with treatment) and no opportunistic infections. Eight (4.2%) patients experienced acute infusional AEs; all but 1 were mild in intensity; none were severe; most were single events in 1 patient each; headache and dizziness occurred in 4 and 2 patients, respectively, with no recurrences. In the DB period, no SAEs were reported in the ABA group; 3 SAEs were reported for 2 PBO-treated patients (haematuria in 1; varicella and encephalitis in the other); all resolved and none resulted in discontinuation. AEs were reported by 61.7% vs 58.4% in the ABA vs PBO groups; the most common events were influenza (5 [8.3%] vs 4 [6.5%]), bacteriuria (4 [6.7%] vs 0 [0%]), nasopharyngitis (4 [6.7%] vs 3 [4.8%]), URTI (4 [6.7%] vs 5 [8.1%]) and pyrexia (4 [6.7%] vs 5 [8.1%]). Other AEs occurred with similar frequencies in both groups. Acute infusional AEs were reported in 1.7 vs 3.2% of ABA vs PBO groups; all were mild/moderate (none serious) in intensity. No serious infections, auto-immune disorders or anaphylaxis episodes were reported. No consistent patterns of treatment-emergent flares were noted. No patients receiving data were used to calculate ACR Pedi responses during the OL and DB periods.

Conclusions: Abatacept appeared to be well tolerated in patients with JIA through the DB lead-in and DB periods of this study.

Disclosure: N.R.’s institution has received research support from Bristol-Myers Squibb, Novartis, Pfizer, Genzyme Regeneron and Xoma. A.C. and L.S. are employees of Bristol-Myers Squibb. E.G. has received research grants from Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

9. GENOME WIDE ASSOCIATION ANALYSIS OF JUVENILE IDIOPATHIC ARTHRITIS (JIA) IDENTIFIES A NOVEL JIA SUSCEPTIBILITY LOCUS

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Background: Juvenile idiopathic arthritis (JIA) is a chronic rheumatic disease of childhood involving the synovium. There have been no published genome-wide association studies (GWAS) to identify JIA susceptibility loci. Here we report the results of a GWAS that employed a genome-wide association (GWA) study approach. We therefore aimed to perform a systematic search of the genome to identify novel susceptibility loci for JIA.

Methods: A GWA study using the Affymetrix GeneChip® 100K array was performed in a discovery cohort of 279 JIA cases and 184 healthy controls. SNP SNPs showing the most significant differences between JIA cases and controls were genotyped (using Sequenom genotyping technology) in a validation sample of 311 JIA cases and 544 healthy controls. The control data was combined with published data from the 1958 birth cohort.

Results: SNPs which failed to genotype in ≥95% of DNA samples, had a MAF <5% or failed HWE (p < 0.0001) were excluded, leaving 88,682 SNPs that were analysed for association with JIA. 112 SNPs which showed association at p < 0.001 were selected for follow up in an independent validation cohort. Six SNPs were associated with JIA (p < 0.05) at the validation stage. The second strongest association, after a SNP in the HLA region, was with a SNP within the VTCN1 gene. Fine-mapping of the gene was performed using 25 SNPs, capturing 96% of known variation across the gene. The 367 healthy controls and the data combined with control data from the 1958 birth cohort. Ten SNPs were associated with JIA, p < 0.05.

Conclusions: This GWA study shows that there is a novel gene that has been associated with disease association of UK JIA cases (OR 0.84 95% CI 0.62-0.88, p = 4.9 × 10-4).
Conclusions: We have found significant evidence of association of the IL2RA gene with JIA in a UK study and replicated this association in North American JIA cases using the PTPN22 variant. Using a new SNP, the IL2RA gene also showed a well-described role in immune regulation, may be associated with a predisposition to autoimmune in general. Further investigation of the gene using both genetic and functional approaches is now required.

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Disclosure: The authors have declared no conflicts of interest.

11. THE ROLE OF GROWTH FACTORS AND OSTEOCLAST MEDIATORS IN THE PATHOGENESIS OF EARLY UNTREATED JUVENILE IDIOPATHIC ARTHRITIS (JIA)

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Background: This study forms part of a larger five year prospective study into the progression and outcome of JIA. The aim was to evaluate the function of growth factors and osteoclast mediators in the pathogenesis of early untreated disease.

Methods: Sputival biopsies were obtained from 41 JIA patients defined according to ILAR criteria. They had to be sterile naive and never treated with disease modifying drugs. We report the immunopathology of the oligo and poly populations. The density and distribution of IGF-1, IGF-2, IGF-BP2 and IGF-BP3, OPG, VEGF and markers of the RANK/RANK-L axis were assessed. RT-PCR was also performed on the synovial membrane to assess the expression of growth factors and osteoclast mediators.

Results: Twenty five patients were diagnosed with oligoarticular, and 16 with a polyarticular JIA. The mean age at biopsy was 5.5 years (range 1-14.5yrs). The mean disease duration was 5.3 months (range 1-11 months).

By definition of the study inclusion criteria, all had at least one knee involved.

Preliminary assessment of all patients highlighted marked expression of RANK and its ligand highly in the lining layer and modestly in the sub-lining layer, but OPG was not detected. However, modest OPG m-RNA expression within the synovial membrane was detected.

IGF-2 and IGF-BP2 were localised to regions where new vessels were established, and where the angiogenic factors OPG and VEGF were co-locally expressed.

Conclusions: Our novel study highlighted the expression of growth factors and osteoclast mediators in early untreated JIA. Our analysis of the distinguishing profiles of potential joint destruction Vs joint repair will be compared to identify differences in the expression of these markers within the clinical subgroups.

Disclosure: The authors have declared no conflicts of interest.

12. ANKLE DISEASE IN JUVENILE IDIOPATHIC ARTHRITIS: CORRELATION BETWEEN CLINICAL AND ULTRASONOGRAPHIC FINDINGS

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Background: The ankle joint is frequently involved in juvenile idiopathic arthritis (JIA). Intra-articular steroids are an effective treatment of arthritis in JIA however ankles had tibialis posterior tenosynovitis but only 19% had tibiotalar effusion of swollen ankles had a tibiotalar effusion alone. 33% had both tenosynovitis and ankle joint injection following clinical assessment only.

Results: Using ultrasound (US) during our clinics we have found that clinically swollen ankles had tibiotalar effusion; MRI scans are costly, stressful for young children and may require ankle with intra-articular steroid injection. The relative rarity of main ankle joint synovitis explains the poor results with ankle joint injection following clinical assessment only.

Conclusions: In 39% of cases the main ankle joint was not involved. This has major implications for therapeutic intervention and more importantly for the clinical assessment of children with JIA. Using a new SNP, the IL2RA gene also showed a with ankle joint injection following clinical assessment only.

Conclusion: The authors have declared no conflicts of interest.

Disclosure: The authors have declared no conflicts of interest.

13. BIOMECHANICAL UNCOUPLING OF BONE EROSION AND NEW BONE FORMATION IN SPONDYLOARTHROPATHY

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Background: The spondyloarthopathies (SpA) are characterized by inflammation at the enthesis, the adjacent bone and the synovium. However the relationship between enthesitis, new bone formation and bone erosion remains poorly understood.

This study tests the hypothesis that the anatomy and biomechanics of the normal enthesis could directly influence bone erosion formation and bone spur formation. We combined ultrasound of Achilles entheses in SpA at different stages of disease and microanatomical studies of normal enthesis to study erosion and spur formation.

Methods: Ultrasound was performed in 20 early SpA patients with Achilles entheses (mean age 43 years; 12 males, 8 females; 1 ankylosing spondylitis (AS), 13 psoriatic arthritis (PsA), and 6 reactive arthritis (ReA); mean disease duration 11 months) and in 10 normal controls (mean age 44 years; 6 males, 4 females).

To ascertain whether the changes in late SpA were similar, we also scanned 17 SpA patients with well-established Achilles enthesitis (mean age 52.8 years; 9 males, 8 females; 13 AS, 3 PsA and 1 ReA; mean disease duration 272.6 months). Bone erosion and spur formation was recorded at 3 sites - proximal and distal halves of the enthesis, and the superior tuberosity. Parallel histology was performed on 10 normal cadaveric Achilles enthesis material (ages 62-91 years) to determine whether the pattern of disease in SpA could be related to regional variations in bone density and trabecular architecture in relation to fibrocartilage distribution in the enthesis organ.

Results: Bone erosion in SpA occurred exclusively at the proximal part of the insertion or the superior tuberosity (11/20 cases, p < 0.001), whereas spurs were exclusively formed distally (6/20 cases, p = 0.0001). The same pattern of disease was observed in chronic SpA. Erosion formation was absent but spur formation detectable in the control patients. Histologically, the distal part of the enthesis was the site of highest bone density and was also associated with spur formation. In marked contrast, sites prone to erosion had a significantly lower bone density and were associated with fibrocartilage damage.

Conclusions: This study shows that erosion and bone formation at the Achilles tendon occur at different anatomical sites in SpA. This likely reflects differing variations in bone density and trabecular architecture in relation to fibrocartilage distribution in the enthesis organ.

Disclosure: The authors have declared no conflicts of interest.

14. A PROINFLAMMATION RESPONSE IS MEDIATED BY SYNOVIAL FIBROBLAST AND NATURAL KILLER CELL INTERACTION IN RHEUMATOID ARTHRITIS AND SPONDYLOARTHRITIS

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Background: Fibroblast-like synoviocytes (FLS) are potentially directly involved in propagation of inflammation. Recent evidence shows that FLS are not passive players in the immune response and may regulate the switch from acute resolving to chronic persistent inflammation. Little is known of the role of FLS in SpA. We have previously shown evidence of an expanded activated population of NK