Conclusions: The CANTOS trial confirms that serum urate is a risk marker for both gout and cardiovascular events and demonstrates that IL-1 β inhibition is effective in preventing both of these inter-related conditions. However, canakinumab had no effects on serum urate itself.

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OP0015 MORTALITY OF THE COBRA EARLY RHEUMATOID ARTHRITIS TRIAL COHORT AFTER 23 YEARS FOLLOW UP

P.B.M. Poppelaars¹, L.H.D. van Tuyl¹, M. Boers^{1,2}. ¹Amsterdam Rheumatology and Immunology Center | VU University Medical Center; ²Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, Netherlands

Background: Mortality in patients with rheumatoid arthritis (RA) is higher than the general population. Most cohorts show that the adverse effect of RA becomes apparent only after more than a decade of follow up. Whether early, intensive treatment can improve this is still unknown. COBRA combination therapy (COmbinatietherapie Bij Rheumatoïde Artritis) showed long-term effectiveness for treatment of early RA without undue harm.¹ In 2010, after 11 years of follow up, the COBRA follow up study showed lower mortality in patients with COBRA treatment compared to patients with sulphasalazine monotherapy.²

Objectives: Our aim was to investigate mortality in the COBRA-trial cohort after 23 years and compare this mortality to a reference sample of the general population in the Netherlands.

Methods: In the COBRA trial, patients with early RA (median disease duration, 4 months) were treated with sulphasalazine monotherapy (SSZ, n=79) or a combination of SSZ, low-dose methotrexate and initially high, step-down prednisolone (COBRA, n=76). In the current study, we investigated mortality in the COBRA trial with the help of the Dutch state registry for mortality (Centrum van familiegeschiedenis, CBG). We compared the mortality in this cohort to a reference sample of the general population in the Netherlands matched for age and gender (data from Statistics Netherlands). The Standardised Mortality Ratio (SMR) compared the trial groups and the general population.

Results: With data of 154 out of the 155 patients, follow up was nearly complete. Duration of follow up was mean 23 (in patients alive, range 22–24) years. In total 44 patients died (28%, SMR=0.80 [95% CI: 0.59 to 1.06]); 20 of 75 COBRA patients (27%, SMR 0.75; [0.47–1.14]) and 24 of 79 SSZ patients (30%, SMR 0.85 [0.56–1.25]); the difference in mortality was not significant (p=0.61). In the reference sample of the general population (n=154) 55 people (36%) died. The positive trend for COBRA over SSZ decreased over time (figure 1).

Conclusions: This prospective cohort study of early RA is one of the first to show a normalisation of RA mortality compared to the general population after 23 years of follow up. In fact, this trial population had a numerically lower mortality than expected. This confirms that early, intensive treatment of RA (that can include glucocorticoids) has long-term benefits, and strongly suggests these benefits include normalisation of mortality.

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OP0016 A MULTICENTRE RANDOMISED CONTROLLED TRIAL OF ZOLEDRONIC ACID FOR OSTEOARTHRITIS OF THE KNEE WITH BONE MARROW LESIONS

G. Cai¹, D. Aitken¹, L. Laslett¹, C. Hill², L. March³, A.E. Wluka⁴, Y. Wang⁴, L. Blizzard¹, F. Cicuttini⁴, T. Winzenberg¹, G. Jones¹. ¹Menzies Institute for Medical Research, University of Tasmania, Hobart; ²The Queen Elizabeth Hospital, Woodville; ³Royal North Shore Hospital, University of Sydney, Sydney; ⁴Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

Background: No disease-modifying drugs are currently available for the treatment of osteoarthritis (OA). Bone marrow lesions (BMLs) visualised on magnetic resonance imaging (MRI) have been identified as a promising therapeutic target. Our pilot study showed that a single infusion of zoledronic acid (ZA) reduced knee pain and BML size in knee OA patients over 6 months.¹ A longer, larger study was required to assess whether these improvements can be reproduced in a larger multicentre design.

Objectives: To compare the effect of once-yearly intravenous infusion of ZA to placebo on knee pain and BML size over 24 months in knee OA patients with significant knee pain and BMLs.

Methods: The Zoledronic Acid for Osteoarthritis Knee Pain (ZAP2) study is a multicentre, randomised, double-blinded, placebo-controlled trial over 24 months. Patients ≥ 50 years who had significant knee pain (defined as a visual analogue scale (VAS) ≥ 40 mm) and MRI-detected knee BML were randomised to receive either ZA (5 mg in 100 ml saline) or placebo (100 ml saline) once-yearly. Those with severe knee OA (joint space narrowing (JSN) on X-ray of Grade 3 using the Osteoarthritis Research Society International (OARSI) atlas) were excluded. Outcomes included knee pain and function by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), knee pain by VAS and change in knee total BML size (sum of medial femoral, lateral femoral, medial tibial, lateral tibial and patellar sites) by proton density weighted MRI from baseline to 24 months. Effect modification of the absence or presence of radiographic OA (JSN grade 0 or grade 1–2) was pre-specified. Mixed effect modelling using an intent-to-treat design was performed for data analyses. Adjustment for baseline values were performed for knee pain and function outcomes due to baseline imbalances.

Results: 223 patients (mean $\pm$ SD age 62.0 $\pm$ 8.0 years, 117 females) were enrolled. At baseline, mean $\pm$ SD knee WOMAC pain (0–500), WOMAC function (0–1700) and VAS pain scores (0–100) were 200.0 $\pm$ 105.0, 656.9 $\pm$ 352.9 and 51.0

± 20.5 , and median BML size was 489.6 mm^2 . After 24 months, there was no significant difference in changes in knee pain (WOMAC pain: -37.5 vs -58.0 , $p=0.205$; VAS pain: -11.5 vs -16.8 , $p=0.17$) or function scores (-134.9 vs -159.2 , $p=0.65$), or knee BML size (-33.5 mm^2 vs -11.7 mm^2 , $p=0.68$) between the ZA group and the placebo group. Pre-specified analyses consistently showed that ZA was more effective than placebo in patients without radiographic OA (JSN Grade 0) on changes in WOMAC pain (-88.3 vs -42.6 , $p=0.21$), VAS pain (-21.8 to -8.3 , $p=0.11$), WOMAC function (-296.9 vs -78.5 , $p=0.06$) and BML size (-67.4 vs 98.2 , $p=0.14$). Adverse events were more frequent in the ZA group, primarily flu-like symptoms and musculoskeletal pain and stiffness.

Conclusions: Once-yearly infusion of ZA did not significantly reduce knee pain or BML size overall in knee OA patients over 24 months but may have symptomatic benefit in milder disease.

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OP0017 THE IMPACT OF THE DURATION OF BISPHOSPHONATE DRUG HOLIDAYS ON HIP FRACTURE RATES

J.R. Curtis¹, R. Chen¹, Z. Li¹, T. Arora¹, K.G. Saag¹, N.C. Wright¹, S. Daigle¹, M. Kilgore¹, E. Delzell². ¹University of Alabama at Birmingham; ²University of Alabama at Birmingham – Retired, Birmingham, USA

Background: Given FDA warnings, drug holidays (temporary or permanent discontinuation) of bisphosphonates (BPs) after long-term (3–5 years) continuous therapy is becoming increasingly common in the United States (US). However, the benefits and risks of stopping BPs, and the optimal timing to restart, remain unclear.

Objectives: We conducted a population-based cohort study of women on long term BP therapy to evaluate the rate of hip fracture following a drug holiday.

Methods: We used Medicare data (2006–2014) to identify all women with medical and pharmacy coverage who initiated a BP and were at least 80% adherent for ≥ 3 years ('baseline'), at which follow-up time began. Patients using other bone therapies (e.g. denosumab, oestrogen, teriparatide, calcitonin) were excluded or censored if they started after follow-up began. We calculated crude rates of hip fracture for continuing BP therapy and among those who discontinued, for categories of time since discontinuing (i.e., length of drug holiday), extending up to 3 years. We used Cox proportional hazards models to evaluate the risk of discontinuing per the length of the drug holiday, using age as the time axis and controlling for potentially confounding factors, with and without adjusting for death as a competing risk.

Results: We identified 1 56 236 women who were highly adherent, long-term BP users. The mean (SD) age was 78.5 (7.5) years. The most commonly used BPs were alendronate (71.7% ever use, 52% exclusive use) and zoledronic acid (16.2% ever use, 8.9% exclusive use). During a median (IQR) followup of 2.1 (1.0, 3.3) years, 62 676 (40.1%) of women stopped BP therapy for at least 6 months or more. Among these women, 7947 (12.7%) subsequently restarted any BP. Overall, 16 904 (10.8%) died.

A total of 3745 hip fractures occurred during follow-up. Hip fracture rates were lowest among women who were current users, and gradually increased as the length of the drug holiday increased, achieving their maximum with a drug holiday >2 years (table 1).

Abstract OP0017 – Table 1. Hip fracture rate by duration of BP drug holiday, adjusting for competing risk of death

Time since Bisphosphonate Discontinuation (yrs)	Number of hip fractures, n	Crude Incidence Rate per 1000 person-years	Adjusted* Hazard Ratio (95% CI)
0 (i.e. current use)	1958	9.6 (9.2–10.1)	1.0 (reference)
>0 to ≤ 3 months	530	13.1 (12.0–14.3)	1.29 (1.17–1.42)
>3 months to ≤ 1 year	539	12.0 (11.0–13.1)	1.12 (1.02–1.24)
>1 to ≤ 2 years	422	13.3 (12.0–14.6)	1.21 (1.09–1.35)
>2 to ≤ 3 years	235	15.7 (13.7–17.8)	1.39 (1.21–1.59)

*adjusted for age, region, race, rural or urban, median income, calendar year, comorbidity (fragility fracture, charlson comorbidity index score), DXA, number of physician visits, care by a rheumatologist or endocrinologist, long term care residence, vitamin D deficiency, glucocorticoids, and proton pump inhibitors

Conclusions: In a large cohort of U.S. women, a BP drug holiday greater than 2 years was associated with a significantly increased risk for hip fracture of up to 39% compared to continued BP use.

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OP0018 THE VALUE OF ADDING MRI TO A CLINICAL TREAT-TO-TARGET STRATEGY IN RHEUMATOID ARTHRITIS PATIENTS IN CLINICAL REMISSION: CLINICAL AND RADIOGRAPHIC OUTCOMES FROM THE IMAGINE-RA RANDOMISED CONTROLLED TRIAL

S. Møller-Bisgaard, K. Hørslev-Pedersen, B. Ejbjerg, M. Hetland, L. Ørnbjerg, D. Glinatsi, J. Møller, M. Boesen, R. Christensen, K. Stengaard-Pedersen, O. R. Madsen, B. Jensen, J. Villadsen, E.-M. Hauge, P. Bennett, O. Hendricks, K. Asmussen, M. Kowalski, H. Lindegaard, S.M. Nielsen, H. Bliddal, N. Krogh, T. Ellingsen, A.H. Nielsen, L. Balding, A.G. Jurik, H. Thomsen, M. Østergaard. *Depts of Rheumatology and Radiology, Musculoskeletal Statistics Unit, Hospitals at Slagelse, Graasten, Gentofte, Aarhus, Frederiksberg, Silkeborg, Hjørring, Odense, Herlev, the Parker Institute and Rigshospitalet, Zealand, Funen and Jutland, Denmark*

Background: Targeting MRI remission in rheumatoid arthritis (RA) patients in clinical remission may improve clinical outcome and halt joint damage progression.

Objectives: To determine whether a treat-to-target (T2T) strategy based on structured MRI assessments targeting absence of osteitis/bone marrow oedema (BME) would lead to improved clinical and radiographic outcomes, compared with a conventional T2T strategy in RA patients in clinical remission.

Methods: The IMAGINE-RA study was a 2 year investigator-initiated, randomised, open-label multicentre study. Two hundred RA patients in clinical remission (defined as: DAS28-CRP < 3.2 and no swollen joints) receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) were randomly assigned 1:1 to a conventional DAS28-CRP guided T2T strategy, targeting

Abstract OP0018 – Table 1. Primary and secondary outcomes at 24 months

	MRI T2T	Conventional T2T	Difference between groups	P value*
Primary endpoints				
Radiographic:				
No radiographic progression, n (%)	49 (66.2%)	58 (62.4%)	OR, 1.19 (0.04 to 39.47)	0.922
Clinical:				
DAS28-CRP remission (DAS28 < 2.6), n (%)	64 (85.3%)	83 (88.3%)	OR, 1.03 (0.31 to 3.43)	0.958
Secondary endpoints				
Clinical				
ACR-EULAR Boolean remission, n (%)	37 (49.3%)	30 (31.9%)	OR, 4.19 (1.30 to 13.57)	0.017
SDAI remission (SDAI ≤ 3.3), n (%)	48 (64.0%)	56 (62.2%)	OR, 1.67 (0.59 to 4.71)	0.336
CDAI remission (CDAI ≤ 2.8), n (%)	53 (69.7%)	59 (64.8%)	OR, 2.75 (0.90 to 8.36)	0.075
DAS28-CRP	1.9 (3.1)	2.1 (3.1)	-0.2 (-0.3 to 0.0)	0.093
Morning stiffness, min	13.1 (3.2)	10.1 (2.9)	3.0 (-5.4 to 11.4)	0.486
Tender joint count (0-28)	0.2 (0.1)	0.5 (0.1)	-0.2 (-0.6 to 0.1)	0.171
Swollen joint count (0-28)	0.0 (0.1)	0.3 (0.1)	-0.3 (-0.5 to -0.0)	0.038
Patient VAS global (0-100)	15.5 (1.8)	21.2 (1.6)	-5.7 (-10.4 to -0.9)	0.019
Patient VAS pain (0-100)	14.2 (1.7)	18.7 (1.6)	-4.5 (-9.0 to 0.0)	0.052
Patient VAS fatigue (0-100)	21.8 (1.9)	24.4 (1.7)	-2.6 (-7.7 to 2.4)	0.311
Physician VAS global (0-100)	4.7 (0.8)	6.9 (0.8)	-2.3 (-4.4 to -0.1)	0.041
Radiographic				
Change in TSS	1.0 (0.3)	1.3 (0.3)	-0.3 (-1.1 to 0.6)	0.559
Function and quality of life				
Change in HAQ	-0.052 (0.024)	0.091 (0.023)	-0.143 (-0.209 to -0.078)	< 0.001
Patient with normal function (HAQ ≤ 0.5), n (%)	61 (80.3%)	75 (79.8%)	OR, 0.73 (0.08 to 7.14)	0.790
Change in SF-36 PCS	1.1 (1.0)	-0.2 (0.9)	1.3 (-1.3 to 4.0)	0.330
Change in SF-36 MCS	-0.5 (1.0)	-0.9 (0.9)	0.5 (-2.1 to 3.0)	0.727
Change in EQ-5D	0.040 (0.015)	0.019 (0.013)	0.021 (-0.017 to 0.060)	0.279

95% CI, 95% confidence interval; ACR=American College of Rheumatology; CDAI=Clinical Disease Activity Index; CRP=C-reactive protein; DAS28-CRP=Disease activity score in 28 joints based on four variables, including CRP; EQ-5D=EuroQol-5 dimensions; EULAR=European League Against Rheumatism; HAQ=Health Assessment Questionnaire; MCS=Mental Component Summary score; MRI=Magnetic Resonance Imaging; PCS=Physical Component Summary score; RAMRIS=RA magnetic resonance imaging scoring system; SDAI=Simplified Disease Activity Index; SF-36=Short Form 36 item questionnaire; T2T=treat-to-target; TSS=Total Sharp/van der Heijde score; VAS=Visual Analogue Scale. Data are presented as least square means (SE) unless otherwise stated. Analyses are based on full analysis set (patients having a baseline visit and at least one follow-up visit) with no data imputation to replace missing data.*P values are based on repeated-measures logistic regression models. For some of the variables, fewer patients were included in the analyses due to missing data, with the minimum being 86 patients in the MRI T2T arm (range 86-98) and 91 (range 91-99) in the conventional T2T arm.