Conclusions: ACPA +at risk individuals have features on imaging which assists prediction of development to IA. MRI TSV provides additional predictive ability over and above the clinical and US variables.

REFERENCES:

- [1] Rakieh C. 2014.
- [2] Mangnus L. 2016.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.2397

OP0043

PREDICTORS OF DRUG-FREE REMISSION IN RHEUMATOID ARTHRITIS: RESULTS FROM THE PROSPECTIVE BIOMARKERS OF REMISSION IN RHEUMATOID ARTHRITIS(BIORRA) STUDY

K.E. Baker, A. Skelton, D. Lendrem, B. Thompson, A.G. Pratt, J.D. Isaacs. *Musculoskeletal Research Group, Newcastle NIHR Biomedical Research Centre, Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK*

Background: Remission is now a realistic and achievable target for many patients with rheumatoid arthritis (RA) using disease-modifying anti-rheumatic drugs (DMARDs) prescribed in modern treat-to-target regimens. However, DMARDs carry risks of potentially serious adverse effects, and require regular and expensive blood monitoring. Recent studies suggest that half of patients with RA in remission can discontinue DMARDs without a flare of arthritis activity, though this cannot currently be reliably predicted.

Abstract OP0043 – Table 1

Demographic	Value
Satisfied 2010 ACR/EULAR classification criteria: n (%)	44 (100%)
Age: median (IQR) [range]	66.5 (54.5–71.3) [35 – 82]
Female: n (%)	23 (52%)
Years since RA diagnosis: median (IQR) [range]	5.5 (3–11) [1–40]
Seropositive (rheumatoid factor and/or anti-citrullinated peptide antibody): n (%)	32 (73%)
Current methotrexate use: n (%)	38 (86%)
Baseline DAS28-CRP: median (IQR) [range]	1.07 (0.99–1.63) [0.96–2.34]
ACR/EULAR Boolean remission: n (%)	29 (66%)
Presence of joint erosion on baseline 7-joint ultrasound scan: n (%)	29 (70%)

Objectives: To identify baseline biomarkers that can predict sustained drug-free remission (DFR) versus arthritis flare following DMARD cessation.

Methods: Patients with established RA satisfying clinical (disease activity in 28 joints with CRP [DAS28-CRP] < 2.4) and ultrasound (absence of power Doppler synovitis on a blinded 7-joint scan) remission criteria discontinued conventional synthetic DMARDs (methotrexate, sulfasalazine, and/or hydroxychloroquine) and

were monitored for 6 months. The primary outcome was time-to-flare, defined as DAS28-CRP ≥ 2.4 . Baseline clinical and ultrasound parameters (synovial/tenosynovial greyscale and joint erosions), circulating levels of 26 cytokines/chemokines, and gene expression by peripheral CD4 + T cells (RNA sequencing) were assessed for their ability to predict time-to-flare and flare/DFR status by multivariate Cox regression and receiver-operating characteristic (ROC) analysis.

Results: 44 patients were eligible for DMARD cessation (table 1); 23 (52%) experienced an arthritis flare at a median (IQR) of 48 (31.5–86.5) days. A composite score incorporating five variables (three genes [currently subject to patent application], one cytokine [IL-27], and one clinical [ACR/EULAR Boolean remission]) differentiated future flare and DFR with an area under the ROC curve of 0.96 (95% CI: 0.92 to 1.00), sensitivity 0.91 (0.78–1.00) and specificity 0.95 (0.84–1.00) (figure 1).

Conclusions: Our study provides proof-of-concept evidence for the existence of biomarkers of DFR in RA. If validated in an external cohort, these biomarkers may hold promise in guiding DMARD withdrawal, with consequent minimisation of medication adverse events and healthcare costs.

Acknowledgements: KB was supported by the Wellcome Trust [102595/Z/13/A] and the NIHR Newcastle Biomedical Research Centre [BH136167/PD0045]. A patent application is currently in process regarding the gene expression biomarkers, the identity of which will subsequently be disclosed.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.2775

OP0044

AFTER HOW LONG OF DISEASE DURATION DOES THE INCREASED MORTALITY RISK APPEAR IN RECENT ONSET RHEUMATOID ARTHRITIS?

J. Widdifield¹, S. Bernatsky², A. Huang³, E.C. Sayre⁴, M. Paterson³, D. Lacaille⁴.

¹Sunnybrook Research Institute, Toronto; ²McGill University, Montreal; ³Institute for Clinical Evaluative Sciences, Toronto; ⁴Arthritis Research Canada, Vancouver, Canada

Background: For decades studies showed that rheumatoid arthritis (RA) patients died earlier than their general population counterparts. Some inception cohorts have failed to detect an increased mortality risk, possibly due to limited followup or to improvement in mortality risk in cohorts of more recent onset.

Objectives: To evaluate the risk of all-cause mortality in incident RA patients and to estimate when the increased risk appears amongst two Canadian inception cohorts with RA onset after 2000

Methods: Using a common protocol, we conducted 2 independent population-based cohort studies, using administrative health data, of incident RA patients in British Columbia (BC) and Ontario (ON), Canada over 2000 to 2015. In each province, we identified all RA patients (using validated criteria) diagnosed between 2000 and 2005 (to allow a minimum of 10 years of follow-up), and identified non-RA general population comparators for each RA patient, matched 1:2 on age, sex and index years. All patients were followed from index date until death (ascertained from vital statistics), out-migration, or end of study period (2015). Adjusted hazard ratios (HRs) and 95% CIs were estimated using multivariable Cox regression, controlling for baseline comorbidities, healthcare use, and socio-demographic factors. To estimate when the increased mortality risk appeared in incident RA patients, and to assess the proportional hazards assumption, we included an interaction between RA diagnosis and follow-up time in the multivariable model, to detect if and how the HR varied according to RA duration. Quadratic and logyear interactions were tested in the multivariable Cox models to assess linearity of the interaction.

Results: Among 13 834 incident RA patients in BC (27 668 matched comparators), 66% were female with a mean (SD) age of 58¹⁶ years at cohort entry. Among 27 405 incident RA patients in ON (54 810 matched comparators), 70% were female with a mean (SD) age of 56¹⁶ years. The prevalence of individual comorbidities at baseline was comparable across RA cohorts. During follow-up, 3139 (23%) of BC RA patients and 6270 (23%) ON RA patients died, with corresponding crude mortality rates of 2.3 deaths per 100 person-years in both provinces. Crude mortality rate ratios for BC and ON were 1.11 (95% CI: 1.07 to 1.16) and 1.27 (95% CI: 1.23 to 1.31), respectively. Multivariable analyses detected an increased risk of all-cause mortality in incident RA (relative to non-RA) patients by 6 years of follow-up, with a linear relationship suggesting further increase over time (figure 1). By 10 years of followup, the adjusted HR for RA was 1.14 (95% CI: 1.07 to 1.22) in BC and 1.13 (95% CI: 1.08 to 1.18) in ON.

Abstract OP0044 – Figure 1 Adjusted HR (solid black line) and 95% CIs (grey line) for all-cause mortality, over time since cohort entry

Conclusions: In 2 large Canadian RA population-based inception cohorts, a small increased mortality risk appeared after 6 years of RA duration and increased to a 14% (in BC) and 13% (in ON) increased risk after 10 years. While these findings represent an improvement in the mortality risk associated with RA compared to previous reports in older historical cohorts, the increasing mortality risk associated throughout the disease course suggests increased efforts to prevent disease progression and optimise comorbidity management are needed.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.4863

OP0045 ADVERSE EVENT REPORTING RATES AND PLACEBO/STANDARD-OF-CARE-ARM ACR RESPONSES VARY BY REGION IN RHEUMATOID ARTHRITIS TRIALS

D. Keebler, E. Teng, J. Chia, D. Lee, J. Galanter, J. Peake, K. Tuckwell.
Genentech, South San Francisco, USA

Background: Clinical trials are increasingly globalised, with more trials conducted in Asia, Latin America, and the Russian Federation and Eastern Europe (RFEE).¹ Adverse event (AE) reporting rates and placebo (or standard-of-care-arm) response may differ by geographic region and level of economic development²⁻⁴; efficacy and safety may not be generalizable across regions. This potential heterogeneity and its implications for rheumatoid arthritis (RA) trials have not been studied in detail.

Objectives: To assess potential regional differences in rates of ACR responses and AE reporting using patient-level data (PLD) from RA trials in the TransCelerate initiative.⁵

Methods: We obtained PLD for all 17 RA trials available through TransCelerate as of August 2017 and analysed data from 7 trials with geographic information available (NCT01198002, NCT01202760, NCT01202773, NCT01404585, NCT00605735, NCT00048581, NCT00647270). We grouped patients by region and evaluated differences in demographics, AE reporting rates, and ACR response. Pairwise comparisons were made between regions using Fisher's exact test, with false discovery rate (FDR) correction for multiple comparisons. All patients were included in analyses of AE reporting. Only patients with data sufficient to calculate ACR scores were included in analyses of ACR response. Demographics for patients in each region are shown in table 1.

Results: The lowest rates of AE reporting and ACR50 response were seen in RFEE. The highest rate of ACR20 response was seen in Asia. After FDR

correction, significantly lower 12 week and 52 week AE reporting rates were seen in RFEE than in Asia, Latin America, or the United States. Only the ACR50 response difference between RFEE and Latin America survived FDR correction; however, ACR20 rates in Asia remained significantly higher than in RFEE and the United States (table 2).

Abstract OP0045 – Table 1 Patient demographics by region

Region	AE Analysis, n	ACR Response Analysis, n	Female, %	Median Age, y (SD; range)
US	369	268	81	55 (11; 21-78)
RFEE	213	160	81	51 (12; 25-79)
Latin America	167	132	89	51 (12; 22-76)
Asia	164	107	88	52 (12; 18-83)

Abstract OP0045 – Table 2 Proportions of patients attaining ACR50/20 response at 12 week and/or reporting ≥ 1 AE at 12 and 52 weeks across regions

Attaining ACR50	6	9 ^a	7	1
Attaining ACR20	17	24	29 ^{a,b}	15
With AE at 12 weeks	53 ^a	49 ^a	51 ^a	22
With AE at 52 weeks	68 ^a	58 ^{a,b}	65 ^a	39

^ap < 0.05 vs RFEE. ^bp < 0.05 vs US. All p values corrected for multiple comparisons.

Conclusions: Patient-level data from placebo arms in the TransCelerate initiative revealed significant regional differences in AE reporting rates and ACR50/ACR20 response rates. Differences in Latin America, RFEE, and Asia were especially notable; future patient populations from these regions may show distinct efficacy/safety profiles regardless of treatment. Given ongoing globalisation of clinical trials, country- and region-specific treatment patterns, patient populations, and safety issues should be explored to avoid misguided inferences across regions. Capping recruitment by region to balance these factors may be warranted.

REFERENCES:

- [1] Drain PK, et al. *Nat Rev Drug Discov* 2014;13:166–7.
- [2] Contopoulos-Ioannidis D, et al. *J Clin Epidemiol* 2016;78(suppl C):10–21.
- [3] Yusuf S, Wittes J. *N Engl J Med* 2016;375:2263–71.
- [4] Xu X, et al. *Arthritis Rheumatol* 2016;68(suppl 10).
- [5] Gill D. *Nat Rev Drug Discov* 2014;13:nrd4437.

Acknowledgements: This study was sponsored by F. Hoffmann-La Roche Ltd

Disclosure of Interest: D. Keebler Shareholder of: Roche, Employee of: Genentech, E. Teng Employee of: Genentech, J. Chia Employee of: Genentech, D. Lee Employee of: Genentech, J. Galanter Employee of: Genentech, J. Peake Employee of: Genentech, K. Tuckwell Shareholder of: Roche, Employee of: Genentech

DOI: 10.1136/annrheumdis-2018-eular.2724

WEDNESDAY, 13 JUNE 2018: Immunobiology of vasculitis

OP0046 EFFECT OF A SELECTIVE C5aR ANTAGONIST, AVACOPAN (CCX168), ON PLASMA COMPLEMENT LEVELS IN ANCA ASSOCIATED VASCULITIS (AAV)

D.O. Bunch¹, J. Deng², E.A. McInnis¹, P. Bekker², J.L. Hillson², T.J. Schall², C. J. Jennette³, P. Nachman¹, J. Deng⁴, on behalf of the CLEAR Study Group.
¹Kidney Center, University of North Carolina, Chapel Hill; ²Chemocentryx, Chemocentryx, Mountain View; ³Department of Pathology, University of North Carolina, Chapel Hill; ⁴850 Maude Ave, Chemocentryx, Mountain View, USA

Background: The interaction between primed neutrophils and anti-neutrophil cytoplasmic autoantibodies (ANCA) releases factors that activate the alternative complement pathway, initiating an amplification loop that is thought to sustain necrotizing inflammation during flares of AAV.¹ Avacopan (CCX168), a selective, orally available, small molecule C5aR1 antagonist, was associated with rapid clinical benefit in the Phase 2 CLEAR trial in patients with AAV,² indicating that therapeutic intervention in this pathogenic process can be accomplished by inhibiting the C5aR1-dependent cellular response to C5a, without broad inhibition of upstream complement functions important to host defense.

Objectives: The present study was designed to confirm the reported elevated levels of complement activation products in AAV,² demonstrate that inhibiting cellular (e.g. neutrophil) activation by C5a with avacopan is effective in AAV while preserving upstream functions of complement, and compare effects of avacopan to those of high dose prednisone.

Methods: The CLEAR trial compared 3 regimens in 67 patients with AAV:¹ full dose prednisone (60 mg daily, tapered);² avacopan 30 mg twice daily plus low dose prednisone (20 mg, tapered);³ avacopan 30 mg twice daily plus no