Methods: Patients recruited to both the British Society for Rheumatology Biologics Register-RA (safety data) and the Biologics in RA Genetics and Genomics Syndicate (serological samples) were included. Both are large national prospective RA cohorts. Biologic drug levels were measured at 3/6/12 months after biologic initiation and stratified as low/normal or high drug levels (HL) as per thresholds defined using concentration-effect curves for each drug. The risk of first and total infections within the first year was analysed. Events occurring on drug or within 90 days of last dose were included. The risk of an event was compared between low/normal vs HL groups using Cox proportional-hazard models. Factors affecting both drug levels and infection risk were adjusted for in the models.

Results: 703 patients (286 etanercept, 179 adalimumab, 120 certolizumab, 104 tocilizumab and 14 infliximab) had clinical data and serological samples. 74% were women, mean (SD) age 58¹² years, on a first biologic (89%). The crude rate/1000 pyrs was 314 and 464 for AI; 54 and 76 for SI in the low/normal and HL groups respectively. The adjusted hazard ratio for AI within the first year differed significantly between the two groups with the HL group having 50 percent higher risk of AI (HR: 1.51; 95% CI: 1.14, 2.01) (table 1). The most common types of AI in the HL group were lower (34%) and upper (16%) respiratory tract infections, urinary tract infections (15%), skin infections including shingles (8%).

Abstract OP0229 – Table 1

	Low/normal drug level (n=241)	High drug levels (n=462)
All events with follow up censored at 1 year (95% CI)		
All infections (n)	63	232
Crude rate (/1000 pyrs)	314 (245–401)	464 (408, 528)
Unadjusted HR	Ref	1.44 (1.09, 1.91)*
Adjusted HR †	Ref	1.51 (1.14, 2.01)*
Serious infections (n)	11	38
Crude rate (/1000 pyrs)	54 (30–98)	76 (55–104)
Unadjusted HR	Ref	1.36 (0.70–2.67)
Adjusted HR†	Ref	1.17 (0.58–2.30)
First event within 1 st year (95% CI)		
All infections (n)	46	150
Crude rate (1000 pyrs)	229 (172–256)	300 (256–352)
Unadjusted HR	Ref	1.24 (0.89–1.73)
Adjusted HR †	Ref	1.26 (0.91–1.78)
Serious infections (n)	6	22
Crude rate (/1000 pyrs)	29 (13–67)	44 (28–67)
Unadjusted HR	Ref	1.39 (0.56–3.44)
Adjusted HR†	Ref	1.26 (0.50–3.16)

*p<0.05 † Adjusted for age, gender, DAS score, methotrexate use

Abstract OP0229 – Figure 1 All infection Nelson-Aalen cumulative hazard estimates

Conclusions: RA patients with high biologic drug levels have a higher risk of infection. Monitoring drug levels may be helpful in prediction of infection. In disease remission patients with HL, biologic dose tapering may lower infection risk.

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OP0230

PREDICTORS OF HYPOGAMMAGLOBULINEMIA DURING RITUXIMAB MAINTENANCE THERAPY IN RHEUMATOID ARTHRITIS: A 12-YEAR LONGITUDINAL MULTI-CENTRE STUDY

G Boletto^{1,2}, J. Avouac¹, J. Wipff¹, M. Forien³, M. Dougados⁴, C. Roux⁴, A. Kahan¹, P. Dieudé³, Y. Allanore¹. ¹Department of Rheumatology A, Cochin Hospital, Paris Descartes University, Paris; ²Department of Rheumatology, Maison Blanche Hospital, Reims University Hospitals, Reims; ³Department of Rheumatology Bichat Hospital, Paris Diderot University; ⁴Department of Rheumatology B, Cochin Hospital, Paris Descartes University, Paris, France

Background: Rituximab (RTX) is an anti-CD20 monoclonal antibody that selectively depletes B-cell population. One of the drawbacks of a prolonged peripheral B-cell depletion is the suppression of protective antibodies and an increased risk for infectious events. However, few long-term data are available on predictors for the development of low levels of serum immunoglobulins in patients receiving repeated courses of RTX.

Objectives: We aimed at the identification of predictors for hypogammaglobulinemia occurrence in RA patients long-term treated with RTX in a 'real-life' setting.

Methods: Multicenter longitudinal observational usual care study including RA patients according to ACR 1987 and/or ACR/EULAR 2010 classification criteria followed and treated with RTX. A previous study assessing the safety profile of RTX in patients with RA reported a median follow-up of 30 months.¹ Therefore, we decided to include RA patients on RTX maintenance therapy, after a minimal exposition of 30 months. Serum protein electrophoresis was performed before each RTX infusion. Hypogammaglobulinemia and severe hypogammaglobulinemia were defined as total gammaglobulin <6 g/L and <4 g/L, respectively. Safety monitoring included the collection of all adverse events (AE) in particular severe infections.

Results: 134 patients met inclusion criteria: 113 female subjects (84.3%); mean age 52.1±11.4 years. Mean follow-up was 79.5±24.6 months and analysis was based on 854.9 patient-years (pt-yrs). Mean RTX cumulative dose was 12.0 ±4.9 g. Hypogammaglobulinemia (<6 g/L) occurred during the follow-up period in 23 patients (2.7 events per 100 pt-yrs), leading to an incidence of 17.1%. The mean time to development of hypogammaglobulinemia was 64±23 months. A total of 9.7% of patients had severe infections (1.5 events per 100 pt-yrs). Patients who developed hypogammaglobulinemia were more likely to experience severe infections (26.1% vs 6.3%, p=0.033). Univariate Cox analysis identified age over 65 years (HR 4.28 [95% CI: 0.92 to 19.97], p<0.001), low gammaglobulin levels prior the first RTX infusion (<8 g/L) (HR 7.35 [95% CI: 1.82 to 29.68], p<0.001) as predictors of protective factor (HR 0.26 [95% CI: 0.08 to 0.87], p=0.03).

Conclusions: Our results show that gammaglobulin levels of less than 8 g/L at baseline is a strong independent risk factor for developing subsequent hypogammaglobulinemia, whereas concomitant MTX therapy seems to be a protective factor in RA patients treated long-term with RTX. Identifying such predictors will raise clinicians' awareness and allow more tailored monitoring of RA patients long-term treated with RTX.

REFERENCE:

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Disclosure of Interest: None declared

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OP0231

GASTRO-INTESTINAL PERFORATIONS AMONG RHEUMATOID ARTHRITIS PATIENTS TREATED WITH BIOLOGIC DMARDS: A NATIONWIDE SWEDISH COHORT STUDY

A. Barbulescu, J. Askling, T. Frisell, on behalf of ARTIS. Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden

Background: Use of glucocorticosteroids and NSAIDs for the treatment of RA has been associated with an increased risk of gastrointestinal (GI) perforations. The introduction of disease modifying agents, such as methotrexate or tumour necrosis factor inhibitors (TNFi) provided a seemingly safer treatment option, but the safety of other types of biologics relative to TNFi remains unclear.

Objectives: To estimate the incidence of gastro-intestinal perforations among Swedish RA patients treated with TNFi and non-TNFi biologics, and compare it with the incidence among bionative patients with RA and a matched general population comparator group.

Methods: We performed a register-based cohort study, including all Swedish RA patients, with follow-up between 2010 and 2015. For these, all treatment initiations with biologic disease modifying anti-rheumatic drugs were identified through the Swedish Rheumatology register (SRQ), and grouped by class into TNFi and non-TNFi drugs (10 857 and 5823 treatment starts). Biologics naïve patients with RA were identified by recorded diagnosis in the Swedish National Patient Register (NPR), since 2001 (n=54,732). Five general population controls were matched to

each biologic-treated patient with RA (n=53,214) by sex, age, and geographical region. A patient could participate to several of these exposure cohorts. For each patient, follow-up under a cohort ended either with an outcome event (GI perforation identified in the NPR as an ICD10 code from a predefined list) or with the first of any of the following censoring events: emigration from Sweden, death, transition to another cohort, discontinuation of treatment (+90/+180 days lag time) or end of study period. Crude incidence rates were tabulated for each cohort and adjusted hazard ratios (HR) and 95% confidence intervals were estimated in multivariable Cox regressions, controlling for baseline differences. The final adjusted model included the following covariates: sex, age, line of biologic treatment, disease characteristics, co-medication at treatment start, co-morbidities and a history of GI perforation.

Results: We found 31 GI perforations among 18 604 person-years (pyr) exposed to TNFi, and 31 GI perforations among 10 947 pyr exposed to non-TNFi, corresponding to crude incidence rates of 1.67 and 2.83 per 1000 pyr, respectively. The crude incidence rate among the biologics-naïve was 2.54 while among the general population comparators it was 0.94. The rate of GI perforations remained higher in patients with RA compared to the general population after adjustment for patient characteristics, HR of 1.78 (95% CI: 1.44 to 2.17), whereas the seemingly increased rate among bionative and non-TNFi users vs TNFi was largely explained by differences in age and disease history at start of follow-up, with adjusted HRs of 1.10 (0.68–1.78) for TNFi vs bionative and 1.10 (0.63–1.91) for TNFi vs non-TNFi, respectively.

Conclusions: Although patients with RA had a higher rate of GI perforations than matched general population comparators, no significant differences in risk remained between bionative, TNFi or non-TNFi treated RA patients after adjusting for baseline patient characteristics.

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OP0232

FEMALE GENDER AND POSITIVE RHEUMATOID FACTOR PREDICT LOW SERUM INFlixIMAB LEVELS AND POSITIVE ANTI-DRUG ANTIBODIES, WHICH ASSOCIATE WITH TREATMENT FAILURE ON INFlixIMAB IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS. REPORT FROM THE SWEFOT TRIAL POPULATION

K. Hambardzumyan¹, C. Hermanrud¹, P. Marits¹, N. Vivar¹, S. Ernestam¹, J. K. Wallman², R.F. van Vollenhoven^{1,3}, A. Fogdell-Hahn¹, S. Saevarsdottir¹, on behalf of SWEFOT trial group. ¹Karolinska Institutet, Stockholm; ²Lund University, Lund, Sweden; ³Amsterdam Rheumatology and Immunology Center, Amsterdam, Netherlands

Background: Tumour necrosis factor (TNF) inhibitors, with infliximab (IFX) first on the market, have revolutionised treatment of patients with rheumatoid arthritis (RA). However, in a substantial proportion of patients, they lose efficiency, and up to 44% of patients have been found to develop anti-drug antibodies (ADA), leading to low serum IFX (sIFX) levels. Despite this, sIFX measurement is still rarely used for clinical decision making, and standardised clinical threshold titre levels have not been clearly defined.

Objectives: In an early RA trial adding IFX to methotrexate (MTX) in patients not achieving low disease activity (LDA=DAS28≤3.2) after 3 months monotherapy, we studied whether sIFX or ADA were associated with treatment outcome, and whether easily available baseline parameters predicted ADA development.

Methods: Of IFX-treated SWEFOT patients (n=128), 101 had available serum samples at follow-up, which were analysed for sIFX levels at 3, 9 and 21 months (routine ELISA). Samples with undetectable sIFX (<0.2 µg/ml) were analysed further for ADA using direct ELISA with plate-bound TNF. Primary and secondary outcome measures were LDA and remission (DAS28 <2.6) at 21 months. Clinical and demographic characteristics of patients at start of IFX therapy (baseline) were tested as potential predictors of ADA development, using uni- and multivariate logistic regression.

Results: At 3, 9 and 21 months from IFX add-on to MTX, 15%, 23% and 28% of patients, respectively, had undetectable sIFX, and 34% were ever ADA-positive. Significantly higher proportion of patients achieved LDA among those with detectable sIFX, versus undetectable sIFX and positive ADA (67% vs 26%, p=0.002, figure 1A), with similar difference for remission (47% vs 11%, p=0.004, figure 1B). When sIFX levels were further stratified into <0.2, 0.2–5.0, 5.0–10.0 and >10 µg/ml, there was a significant trend across the groups in achievement of LDA (30%, 65%, 70% and 83% respectively, p=0.008, figure 1C) or remission (10%, 41%, 52% and 67%, respectively, p=0.004, figure 1D). Women had undetectable sIFX at 21 months more often than men (35% vs 7%, p=0.006). In multivariate logistic regression analysis, the following baseline characteristics were significant

predictors of ever ADA-positivity: female gender, RF-positivity, higher tender joint count, erythrocyte sedimentation rate and lower health assessment questionnaire score (data not shown).

Abstract OP0232 – Figure 1 Clinical outcome of patients at 3, 9 and 21 months stratified by sIFX and ADA status at the same time points. Proportion of patients in LDA (A) and remission (B) among patient with detectable sIFX level (blue dots) and ADA positive patients with undetectable sIFX levels (red dots). Proportion of patients in LDA (C) and remission (D) among four strata of patients according to sIFX levels undetectable (<0.2 µg/ml) – blue bars, low (0.2–5.0 µg/ml) – red bars, moderate (>5.0–10.0 µg/ml) – green bars, and high (>10.0 µg/ml) – orange bars.

Conclusions: In early RA patients receiving add-on IFX therapy, ADA-positivity or lower serum IFX levels were associated with a higher risk of not reaching treatment targets, that is LDA or remission. RF positivity and female gender, factors known to be associated with worse clinical outcomes, predicted development of ADA.

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OP0233

LONG-TERM SAFETY OF ADALIMUMAB IN ADULT PATIENTS FROM GLOBAL CLINICAL TRIALS ACROSS MULTIPLE INDICATIONS: AN UPDATED ANALYSIS IN 29,987 PATIENTS REPRESENTING 56,951 PATIENT-YEARS

G. Burmester¹, R. Panacchione², K. Gordon³, J. Rosenbaum⁴, D. Arian⁵, W. Lau⁵, R. Tarzynski-Potempa⁵. ¹Charité – University Medicine Berlin, Berlin, Germany; ²University of Calgary, Calgary, Canada; ³Medical College of Wisconsin, Milwaukee; ⁴Oregon Health and Science University and Legacy Devers Eye Institute, Portland; ⁵AbbVie Inc., North Chicago, USA

Background: Adalimumab is an anti-tumour necrosis factor- α (TNF- α) agent indicated for the treatment of immune-mediated diseases. The long-term safety of adalimumab was previously reported in 23 458 patients representing up to 12 years of clinical trial exposure in rheumatoid arthritis (RA), juvenile idiopathic arthritis, ankylosing spondylitis (AS), psoriatic arthritis (PsA), plaque psoriasis (Ps), and Crohn's disease (CD).

Objectives: Here we report an updated analysis examining the long-term safety of adalimumab in adult patients with RA, AS, non-radiographic axial spondyloarthritis (nr-axSpA), peripheral SpA (pSpA), PsA, Ps, hidradenitis suppurativa (HS), CD, ulcerative colitis (UC), and non-infectious uveitis (UV).

Methods: Here we report an updated analysis examining the long-term safety of adalimumab in adult patients with RA, AS, non-radiographic axial spondyloarthritis (nr-axSpA), peripheral SpA (pSpA), PsA, Ps, hidradenitis suppurativa (HS), CD, ulcerative colitis (UC), and non-infectious uveitis (UV).