POSTER VIEWING III

Rheumatoid arthritis - treatment

180. UTILITY OF BODY WEIGHT CLASSIFIED LOW-DOSE LEFLUNOMIDE IN JAPANESE RHEUMATOID ARTHRITIS

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Background: In Japan, more than 20 rheumatoid arthritis (RA) patients died of interstitial pneumonia (IP) caused by leflunomide (LEF) were reported, but many of them were considered as the victims of opportunistic infection currently. In this paper, efficacy and safety of low-dose LEF classified by body weight (BW) were studied.
Methods: Fifty-nine RA patients were started to administrate LEF from July 2007 to July 2009. Among them, 25 patients were excluded because of the combination with tacrolimus, and medication modification within 3 months before LEF. Remaining 34 RA patients administered 20 to 50 mg/week of LEF were followed up for 1 year and enrolled in this study. Dose of LEF was classified by BW (50 mg/week for over 50 kg, 40 mg/week for 40 to 50 kg and 20 to 30 mg/week for under 40 kg). The average age and RA duration of enrolled patients were 55.5 years old and 10.2 years. Prednisolone (PSL), methotrexate (MTX) and etanercept were used in 23, 28 and 2 patients, respectively. In case of insufficient response or adverse effect, dosage change or discontinuance of LEF were considered. Failure was defined as dosages up of PSL and MTX, or dosages down or discontinuance of LEF. Last observation carried forward method was used for the evaluation of failed patients at 1 year.
Results: At 1 year after LEF start, good/ moderate/ no response assessed by the European League Against Rheumatism (EULAR) response criteria using Disease Activity Score, including a 28-joint count (DAS28)-C reactive protein (CRP) were showed in 14/ 10/ 10 patients, respectively. The dosage changes of LEF at 1 year were dosage up: 10, same dosage: 5, dosage down: 8 and discontinuance: 11 patients. The survival rate of patients in this study was 23.5% (24 patients failed) but actual LEF continuous rate was 67.6% (11 patients discontinued) at 1 year. The major reason of failure was liver dysfunction, and pneumocystis pneumonia was occurred in 1 patient resulted in full recovery. One patient died of sepsis caused by decubitus ulcer infection. DAS28-CRP score was decreased from 3.9 to 2.7 significantly. Although CRP was decreased from 1.50 to 0.93 mg/dl, it wasn't significant. Matrix metalloproteinase (MMP)-3 was decreased from 220.0 to 174.2 ng/ml significantly. Glutamate pyruvate transaminase (GPT) was increased from 19 to 35 U/l and number of leukocyte was decreased from 7832 to 6271 significantly. DAS28-CRP, CRP, and MMP-3 were improved significantly with MTX, although they weren't without MTX. Increase of GPT and leukopenia were seen significantly with MTX, although they weren't without MTX.
Conclusions: It was reported that the risks of IP caused by LEF in Japanese RA patients were past IP history, loading dose administration and low BW. Addition of low-dose LEF is a potent safe alternative for the patients showing unsatisfactory response to current medicines, but need to pay attention for liver function and infection caused by leukopenia, especially with MTX.
Disclosure statement: The authors have declared no conflicts of interest.

181. PREDICTORS OF RESPONSE TO RITUXIMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS: RESULTS FROM THE BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS REGISTER (BSRBR)

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Background: Rituximab (RTX) has proven efficacy in the management of rheumatoid arthritis (RA) in both clinical trials and observational studies. Identifying the factors that are associated with better response to RTX is important to optimise its use in clinical practice. This analysis aimed to identify predictors of six month response to RTX and disease remission, in routine clinical practice, in RA patients who had failed traditional non-biologic Disease Modifying Anti-Rheumatic Drugs (nbDMARDs) and at least one anti-Tumor Necrosis Factor (anti-TNF) therapies.
Methods: The analysis involved 463 patients with RA prospectively registered with the BSRBR; an observational cohort study. Univariate and multivariate linear regression models were used to identify factors associated with the change in Disease Activity Score (DAS28) after 6 months from starting RTX. Stepwise selection was used to select the covariates to be included in the multivariate models based on a significance level of 0.05. Univariate and multivariate logistic regression models were used to identify factors associated with achieving disease remission (DAS28$<$2.6). The models examined (i) baseline demographics [age, gender, current smoking, presence of co-morbidities], (ii) baseline disease characteristics [disease duration, rheumatoid factor (RF), DAS28], (iii) baseline quality of life [Health assessment Questionnaire (HAQ), European Quality of life 5 Dimensions (EQ5D) utility score], (iv) baseline concurrent therapy [concurrent steroid, concurrent nbDMARDs (no nbDMARD, methotrexate, or other nbDMARDs)], and (v) previous drug history [previous steroid, number of previous nbDMARDs, the type of the most recently stopped anti-TNF therapy (etanercept or monoclonal antibody), number of failed anti-TNF therapies, the reason for stopping the last anti-TNF therapy (inefficacy, adverse event or other reasons)].
Results: In the multivariate analysis, subjects with higher baseline DAS28 were more likely to respond to the therapy ($p < 0.001$), as measured by the change in DAS28, while patients with higher physical disability were less likely to respond ($p = 0.001$). RF positive patients were more likely to achieve disease remission while patients with higher baseline physical disability or higher baseline DAS28 were less likely to achieve remission (Table 1). Current smokers showed tendency towards not achieving disease remission ($p = 0.06$).
Conclusions: In routine clinical practice, response to RTX was influenced by baseline disease activity and baseline physical function.
Disclosure statement: The authors have declared no conflicts of interest.

TABLE 1.

Significant predictors of change in DAS28		Significant predictors of achieving remission	
Variables	Coefficient (95% confidence intervals)	Variables	Odds ratio (95% confidence intervals)
Baseline DAS28	−0.56 (-0.68, -0.44)	Baseline DAS28	0.69 (0.47, 0.99)
Baseline HAQ	0.38 (0.15, 0.61)	Baseline HAQ	0.31 (0.15, 0.65)
–	–	RF positive patient	3.69 (1.01, 13.64)

182. ARE GUIDELINES FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS BEING MET?

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Background: NICE currently recommends aggressive therapy with combination DMARDs in rheumatoid arthritis (RA) as opposed to step up treatment starting with monotherapy. The British Society of Rheumatology (BSR) has advised that a DAS28 $>$3.2 warrants escalation or change of treatment using a 'treat to target' approach. We were interested in assessing the mean DAS in our patients on different clusters of therapy to see whether disease control related to the therapeutic regime. We also wished to assess the value of performing real time DAS scores in clinic to aid treating to target.
Methods: Data was collected from 170 patients with RA attending consecutive outpatient review clinics. Information was collected on DAS28 scores, prognostic factors (rheumatoid factor, anti-CCP, nodules, smoking, erosions on x-ray), duration of RA, current treatment, and all changes to treatment. Patients were divided into clusters based on treatment and mean DAS scores calculated for each

treatment group. Prognostic factors were also ranked against DAS scores and treatment group. Changes in treatment were noted in relation to DAS score in clinic.
Results: The group comprised 71% females with a mean age of 63 (range 32 to 90 years) and mean RA duration of 10 years. Monotherapy was used in 57 (34%) patients and the mean DAS score was 2.8 in this cluster. Combination DMARDs were used in 56 (33%) patients, with a group mean DAS of 3.4. Biologic agents were used in 35 (21%) with a mean DAS of 3.8., while parenteral methotrexate was used in 22 (12%) with a mean DAS of 4.5. There was no correlation between the number of adverse prognostic factors and DAS score. There was a strong relationship between DAS score and the percentage of patients in whom treatment was escalated at that clinic visit (Table 1)
Conclusions: Patients can enter remission on monotherapy. Our results demonstrate that not all RA patients need aggressive first line combination therapy as presently recommended. Prognostic factors do not readily allow prediction of the level of treatment required to achieve DAS remission in an individual. Treating to target does lead to appropriate escalation in most patients and the use of DAS scores in clinic to guide treatment change is valuable and practical.
Disclosure statement: The authors have declared no conflicts of interest.

TABLE 1. Percentage of patients in each DAS category who had treatment escalated

DAS <2.6	DAS 2.6-3.2	DAS 3.2-5.1	DAS >5.1
6	16	42	88

183. LOW DISEASE ACTIVITY DURING FOUR YEARS OF ADALIMUMAB TREATMENT FOR PATIENTS WITH RHEUMATOID ARTHRITIS WITH AND WITHOUT HISTORY OF OTHER TUMOUR NECROSIS FACTOR-ANTAGONIST THERAPIES

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Background: Switching to a subsequent tumor necrosis factor (TNF) antagonist is an effective treatment for patients with rheumatoid arthritis (RA) after failure or intolerance of a prior anti-TNF therapy. However, long-term data on disease activity after switching to adalimumab are sparse. The objective was to investigate the achievement of low disease activity (LDA) during 4 years of treatment with adalimumab in patients with and without a history of anti-TNF therapy, stratified by reason for discontinuation of the prior TNF antagonist.
Methods: Data were analyzed from patients with and without a history of infliximab and/or etanercept therapy who continued adalimumab in an ongoing, 5-year observational study (ReAlise) after completion of a multinational, uncontrolled, Phase 3b study (Research in Active Rheumatoid Arthritis Trial [ReAct]), during which patients received adalimumab therapy for $\geq$12 weeks. Treatment effectiveness was measured by 28-joint Disease Activity Score (DAS28) LDA (DAS28 $\leq$3.2) with last observation carried forward (LOCF) because of decreasing numbers of patients with available data in this ongoing study.
Results: Data were available for 408 patients with and 3,025 patients without prior anti-TNF therapy. At ReAct baseline, mean (SD) DAS28 values in patients with and without prior anti-TNF therapy were 6.3 (1.1) and 5.9 (1.1), respectively. The mean (SD) changes in DAS28 from baseline to month 48 were -2.7 (1.5) and -2.5 (1.6) ($P < 0.001$ for patients with and without prior anti-TNF treatment). In addition, 165 (40%) patients with and 1,652 (55%) patients without prior anti-TNF therapy achieved LDA at month 48. Relative to patients without prior anti-TNF therapy, those with prior anti-TNF therapy achieved LDA somewhat later, mainly because the percentage of patients in LDA was still relevantly increasing beyond month 12 for patients who discontinued a prior TNF antagonist because of lack of response. After 2 years of adalimumab therapy, the percentages of patients in LDA were similar irrespective of the reason for discontinuation of prior anti-TNF therapy (Table 1).
Conclusions: Although the therapeutic responses to adalimumab were greatest in patients without prior anti-TNF therapy, many patients who switched to adalimumab after discontinuing prior anti-TNF therapy achieved LDA during 4 years of adalimumab therapy, albeit at a somewhat slower rate.
Disclosure statement: G.B. has received research grants and consultancy fees and is/has been a member of a speakers' bureau for Abbott. B.G., H.K. and K.U. are employees of Abbott and own Abbott stock or stock options. S.K. and U.O. are contract employees of Abbott.

TABLE 1. Percentages of patients achieving LDA (LOCF) during 4 years of adalimumab treatment in subgroups of patients with and without prior anti-TNF Therapy

	Month 3	Month 6	Month 12	Month 24	Month 36	Month 48
No prior anti-TNF therapy (N = 3,025)	41.9	48.3	51.0	54.5	55.1	55.0
Prior anti-TNF therapy (N = 408)	28.0	30.9	34.1	39.7	42.2	40.4
Lack of Response (N = 76)	17.8	22.4	27.6	36.8	40.8	40.8
Loss of Response (N = 142)	19.4	26.8	33.8	38.7	37.3	36.6
Intolerance (N = 87)	39.8	36.8	40.2	40.2	48.3	43.7

184. WHAT ROLE DOES GENDER PLAY IN ACCESS TO BIOLOGIC AGENTS AND DOES IT INFLUENCE CHOICE OF INDIVIDUAL AGENT?

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Background: While severe clinical disease activity, structural damage, and deformities have been reported equally in both genders in rheumatoid arthritis (RA), women typically report more severe symptoms and greater disability, and often have higher work disability rates compared with men. We utilised the British Society of Rheumatology Biologics Register (BSRBR) to assess whether these observations are translated into any difference in uptake in biologic agents between the 2 sexes; we also assessed gender differences in choice of individual agent.
Methods: The analysis included 10,749 subjects [2,545 (23.7%) men and 8204 (76.3%) women] commenced on their first biologic agent between 1999 and 2010 and registered with the BSRBR, a UK national observational cohort study set up to monitor the long term safety of biologic agents in patients with rheumatoid arthritis receiving antiTNF therapy. We also studied 753 (27.3%) men and 2004 (72.7%) women with active RA treated with traditional disease-modifying antirheumatic drugs (DMARDs), and 48 (23.5%) men and 156 (76.5%) women who switched from DMARDs to biologic agents.
Results: Both male and female cases who received biologic therapy were younger and had higher DAS28 scores compared with patients treated with traditional DMARDs recruited to the control arm. Women who received biologic therapy were younger at treatment initiation than their male counterparts [55.9 years (SD 12.4) versus 57.5 years (SD 11.3) years, $p < 0.001$]; they typically had also received more traditional DMARDs prior to initiation of therapy and also had a longer duration of illness (median 12 years versus 11 years, $p < 0.001$). However, this was not reflected in any difference in erosive disease between the 2 sexes (69%, $p = 0.85$). Very similar patterns were seen in the control group. Fourty eight (23.5%) men and 156 (76.5%) women switched to biologic agents from DMARDs. The mean age at switching was 58 years in both sexes; women had a longer duration of disease (median 11 years vs. 7.5 years), but there was no difference in the number of previous DMARDs used in men and women previously (median 3). We found little difference in choice of individual biologic agent used in either group.
Conclusions: In both sexes, patients with more severe disease appeared to receive biologic agents. While women recorded higher DAS28 scores, this was not reflected in a difference in recorded erosive disease. There was little gender difference in choice of individual biologic agent.
Disclosure statement: B.C., K.H., D.S. and K.W. have received support for the BSRBR from Schering-Plough, Wyeth, Abbott and Amgen. All other authors have declared no conflicts of interest.

185. DISCONNECT BETWEEN DISEASE ACTIVITY AND JOINT SPACE NARROWING FOR PATIENTS WITH EARLY RA TREATED WITH ADALIMUMAB PLUS METHOTREXATE BUT NOT METHOTREXATE ALONE: CASE FOR ANTI-TNF CARTILAGE PROTECTION

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Background: Joint space narrowing (JSN) is inhibited by treatment with the combination of adalimumab (ADA) and methotrexate (MTX). Importantly, it is not known whether ADA + MTX treatment exerts these protective effects solely by controlling inflammation or also by a specific effect on cartilage as has been shown for joint erosions. The objective of this analysis was to compare the relationship between disease activity (DAS28) and progression of JSN in patients with early rheumatoid arthritis (RA) treated with ADA + MTX vs. MTX.
Methods: Two-year data from the PREMIER study (a randomized controlled trial comparing MTX with ADA + MTX in patients with early RA) were used to perform this analysis. Data were from patients (N = 525) randomized to MTX or ADA + MTX. DAS28 was time-averaged (TA-DAS28) over 3 intervals from baseline: 26, 52, and 104 weeks, and multivariate analyses were performed to assess the impact of treatment and TA-DAS28 on change in JSN after 26, 52, and 104 weeks of treatment. To control for continuous between-group variations in DAS28, we compared groups by TA-DAS28 quartile.
Results: All results are changes in JSN expressed by quartile (range) of TA-DAS28. In the MTX group, JSN increased as TA-DAS28 increased [Week 26 (observed): Q1 (<3.6): 0.38; Q2 (3.6-<4.4): 0.39; Q3 (4.4-<5.1): 0.64; Q4 (≥5.1): 2.43. Week 52 (observed): Q1 (<3.2): 0.60; Q2 (3.2-<4.0): 1.05; Q3 (4.0-<4.8): 1.38; Q4 (≥4.8): 3.97. Week 104 (linear imputation): Q1 (<3.3): 0.82; Q2 (3.3-<4.2): 2.11; Q3 (4.2-<5.1): 2.98; Q4 (≥5.1): 8.14]. However, this relationship was not apparent in the ADA+MTX group [Week 26: Q1 (<3.6): 0.15; Q2 (3.6-<4.4): 0.17; Q3 (4.4-<5.1): -0.06; Q4 (≥5.1): 0.63. Week 52: Q1 (<3.2): 0.52; Q2 (3.2-<4.0): 0.43; Q3 (4.0-<4.8): 0.55; Q4 (≥4.8): 0.53. Week 104: Q1 (<3.3): 0.56; Q2 (3.3-<4.2): 0.90; Q3 (4.2-<5.1): 1.02; Q4 (≥5.1): 1.60]. Wk-104 results were similar using either observed data or linear imputation.
Conclusions: The typical relationship between TA-DAS28 and progression of JSN was observed in patients treated with MTX; however, this relationship was not apparent in patients treated with ADA+MTX. These results suggest that ADA + MTX may have direct protective effects on cartilage that are beyond its ability to control for disease activity, potentially through the inhibition of catabolytic activities in chondrocytes.
Disclosure statement: M.C., B.G. and K.P. are full-time employees of Abbott and may hold Abbott stock or stock options. M.G. has received research grants and honoraria from Abbott, research grants from Merck Serono, consultancy fees or other remuneration from NicOx and Pfizer, and honoraria from Fidia Farmaceutici. E.K. has received consultancy fees or other remuneration from Abbott, UCB, Pfizer, Roche, Amgen and Bristol-Myers Squibb. R.L. is/has been a member of speakers' bureaus for, and has received research grants, consultancy fees or other remuneration from Abbott, Amgen, Centocor, Pfizer/Wyeth, UCB and Bristol-Myers Squibb. J.S. has received research grants, consultancy fees or other remuneration from Abbott, Bristol-Myers Squibb, Centocor, Schering-Plough (MSD), Roche, UCB and Pfizer/Wyeth. D.vdH. has received consultancy fees or other remuneration from, Abbott, Amgen, Bristol-Myers Squibb, Centocor, Chugai, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB and Wyeth.

186. MAINTAINING PATIENTS WITH RHEUMATOID ARTHRITIS IN REMISSION ON REDUCED BIOLOGIC THERAPY DOSAGE

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Background: Treatment with biologic therapies such as tumour necrosis factor (TNF) blockade has increased remission rates in patients with rheumatoid arthritis (RA). The objective of this study was to explore whether RA patients attending BCU-West Biologic clinic could be maintained in remission on a reduced TNF blocker dosage.
Methods: Among 96 patients on TNF blocker therapy for RA, 26 had their doses reduced as they had achieved remission. Remission was defined as DAS28<2.6 for 6 months or longer. The original dose of TNF blocker was restarted in the event of a relapse (DAS>3.2).
Results: A minimum of 6 month data was achieved for 20 out of the 26 patients. The other 6 patients were excluded from the analysis as they had less than 6 months data. The TNF blocker therapy was etanercept in 15 cases and adalimumab in the other 5 cases. Seven patients were taking concomitant DMARD therapy (methotrexate n = 5, other n = 2) and 2 patients were taking longterm prednisolone at a dose range of 5 - 7.5 mg daily. Fifty five per cent of the patients were female. The 20 patients had a mean age of 61.5 years (range 40-83 years), a mean disease duration of 12.05 years (range 7-19 years) and a mean TNF blocker therapy duration before dose reduction of 57.3 months (range 13-101 months). Sixty per cent of the 20 patients were rheumatoid factor positive. The mean DAS28 score prior to starting TNF blocker therapy was 5.49 (range 3.028 - 7.32). The number of patients still in remission after TNF blocker dose reduction was 17/20 at 6 months. At 12 months, 12/17 (71%) patients remained in remission. Whilst on a reduced dose, 3(18%) patients relapsed and returned to their original dose of TNF blocker (etanercept = 3, rheumatoid factor positive = 3). All 3 patients achieved remission on the original dosage. The 17 patients that remained in remission had varied reduced dosages. Etanercept doses ranged from 50 mg/25 mg on alternate weeks to 25 mg monthly and adalimumab from 40 mg every 3 weeks to 40 mg every 5 weeks. A total cost saving of £120,000 has been made by reducing the doses of patients who achieved remission.
Conclusions: Maintenance of disease remission was achieved in 85% and 71% of cases on a reduced dose of TNF blocker after 6 and 12 months respectively. Relapsing patients responded well to resumption of original TNF blocker dosage. The optimal duration and dose of expensive biologic agents in patients who attain remission is unknown. There have been a number of studies that have shown relapes when biologics agents have been discontinued but there is very little information regarding reducing doses. As a first step we have shown that clinical remission can be acheived with reduced biologic doses at 1 year. There is an economical and clinical need to explore these issues, so more patients can be treated with these drugs without massively increasing drug budgets within the NHS.
Disclosure statement: The authors have declared no conflicts of interest.

187. POST-TREATMENT CHANGES IN SERUM C-REACTIVE PROTEIN LEVELS AND CLINICAL RESPONSE IN RHEUMATOID ARTHRITIS

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Background: With the availability of many effective therapies for RA, biomarker(s) that can reliably predict response to a treatment would be useful in clinical practice. Serum CRP levels have been known to be associated with disease activity including radiographic progression. It is however not clear if early changes in serum CRP levels in response to treatment can predict sustained clinical response at later time points. To evaluate if early post-treatment changes in CRP can reliably predict clinical response, we evaluated the association of early post-treatment changes in serum CRP levels with clinical response at a later time point.
Methods: Sera were collected at wk0, 4 & 24 from GO-BEFORE (MTX naïve RA patients; 477 golimumab [GLM]+/-MTX, 160PBO+MTX), GO-FORWARD (active RA patients despite MTX; 311GLM+/-MTX, 133PBO+MTX) and GO-AFTER (active RA patients previously treated

with TNF inhibitors; 304GLM, 155PBO) studies. Samples were tested for CRP levels using Roche Tinaquant assay. CRP levels at baseline (BL), wk4 & 24 in GLM±MTX and PBO+/-MTX patients achieving and not achieving multiple measures of clinical response (ACR & EULAR/DAS response criteria) were evaluated. Logistic regression models were used to test for marker associations with clinical endpts. Positive predictive value (PPV) & Negative predictive value (NPV) were calculated.

Results: Patients achieving remission tend to have lower CRP at BL, wk4&24, compared to patients not achieving remission, and patients treated with GLM had in general lower CRP levels than patients treated with MTX or PBO. Changes from BL in CRP levels were analyzed in 3 RA populations and decreases from BL at wk4 in patients with BL CRP>1 mg/dL were significantly associated with remission at wk24 in GLM±MTX patients from GO-BEFORE (OR = 1.4; $p < 0.002$; PPV = 67%; NPV = 53%), GO-FORWARD (OR = 2.1; $p < 0.000$; PPV = 70%; NPV = 68%) and GO-AFTER (OR = 1.3; $p = 0.06$; PPV = 51%; NPV = 64%). Reductions from BL CRP of >50% at wk4 in these pt subsets were also significantly associated with multiple measures of clinical response including remission.

Conclusions: While changes in CRP levels associate with clinical response and may be a good measure of disease activity in RA at any time point, it is not a reliable predictor of clinical response to treatment.

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188. GOLIMUMAB AND CARDIOVASCULAR DISEASE MARKERS IN INFLAMMATORY ARTHRITIDES

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Background: The purpose of this study was to assess the effect of golimumab (GLM), a human anti-tumor necrosis factor (TNF) agent, +/- methotrexate (MTX), on serum lipid profiles and inflammatory markers associated with cardiovascular disease (CVD).

Methods: Serum lipids, including LDL subfractions and inflammatory CV markers (e.g., high sensitivity [hs]CRP, VEGF, ICAM-1, SAA, fibrinogen, IL-6) and markers of insulin sensitivity (fasting glucose, fasting insulin, HbA1c, HOMA-IR, QUICKI) were assessed in 2 phase 3 GLM trials in RA pts (MTX-naïve in GO-BEFORE and MTX inadequate responders [IR] in GO-FORWARD). Changes from baseline to wk14 or 24 were compared between the PBO + MTX (n = 293) and combined GLM (50&100 mg) + MTX (n = 496) groups (grps).

Results: In GO-FORWARD, median total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels increased in the GLM + MTX compared with PBO + MTX grp (8.4 vs 1.0 mg/dL[$p \leq 0.001$], 5.4 vs 0.0 mg/dL[$p \leq 0.01$], 11.6 vs 3.3 mg/dL [$p \leq 0.01$], respectively), whereas atherogenic ratios (TC/HDL, LDL/HDL, Apo B1/A1) were not substantially changed. Favourable changes in LDL subfractions (increase in large, decrease in small LDL, increase in mean LDL particle size) were seen in GLM grps(+21.5 mg/dL and -10.5 mg/dL, respectively). In GO-BEFORE, increases in TC and LDL and favorable changes in LDL subfractions were seen in both the MTX and GLM grps; in contrast, HDL increase and Apo B/A1 decrease were observed in GLM but not MTX grp. Most inflammatory CV markers improved significantly with GLM+MTX vs PBO + MTX in both studies (hsCRP:-70.7 vs -10.4 mg/dL[$p \leq 0.001$]in GO-FORWARD, -71.7 vs -49.6 mg/dL[$p \leq 0.05$]in GO-BEFORE; ICAM-1:-12.2 vs 0.0 ng/mL[$p \leq 0.001$]in GO-FORWARD, -12.5 vs -0.7 ng/mL[$p \leq 0.001$] in GO-BEFORE. Markers of insulin sensitivity remained unchanged at wks14/24 in patients treated with GLM.

Conclusions: This is the first demonstration of favorable changes in LDL subfractions with anti-TNF therapy. Despite increases in TC and LDL, atherogenic indices remained stable and CV-related inflammatory markers improved with GLM treatment. These findings are consistent with published epidemiologic data suggesting, a beneficial effect of anti-TNF agents on CV events. No significant changes in insulin sensitivity parameters were observed.

Disclosure statement: J.B., R.F., M.G., B.K., E.M. and M.W. have received research grants from Centocor Research & Development, Inc. E.H., H.L. and M.R. are employees of Centocor Research & Development, Inc.

189. TREATMENT WITH INFLIXIMAB IMPROVES CLINICAL RESPONSE AND PHYSICAL FUNCTION IN PATIENTS WITH MODERATE OR SEVERE RHEUMATOID ARTHRITIS ACTIVELY SWITCHED FROM ETANERCEPT OR ADALIMUMAB THERAPY

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Background: Evidence suggests that RA pts with active disease, despite tx with SC TNFα inhibitors, respond to infliximab (IFX). The dosing flexibility of IFX allows for the tx of continued active disease with targeted clinical outcomes. The aim was to evaluate the safety and efficacy of IFX in RA pts with moderate or severe RA despite tx with etanercept (ETN) or adalimumab (ADA).

Methods: This is a Phase4, open-label, assessor-blinded,active switch study of IFX in active RA pts who received MTX and had inadequate response(DAS28≥3.6, SJC≥6,& TJC≥6) to ETN or ADA. Pts were on stable dose of MTX for ≥4wks prior to screening. Pts receiving ETN were switched no less than 1wk and no more than 2wks after the last dose; pts receiving ADA were switched no less than 2wks and no more than 4wks after last dose. Pts received IFX 3 mg/kg infusions at wks0, 2&6. Pts who either achieved/maintained EULAR response at wks14 or 22 remained on current IFX dose. IFX dose was increased by 2 mg/kg for pts who did not achieve/lost response. EULAR response was evaluated at wk10 post induction(primary endpt) and following incremental increases in IFX dose in pts not adequately responding to initial doses. Physical function was assessed using HAQ.

Results: Data for 197/203pts enrolled were evaluable. 60.9% and 39.1%pts were previously treated with ETN or ADA, respectively. EULAR response was achieved by 49.7%pts at wk10(55.6%,per protocol)and 51.8% at wk26(61%,per protocol) with/without dose adjustment. Among pts responsive to 3 mg/kg induction dose, 45% maintained response through wk26. ACR20,50&70 responses were achieved in 28.4%,12.2% &1.5%pts at wk10, respectively; responses improved to 35.5%, 18.3%, &7.1%, respectively, at wk26. Mean CDAI and SDAI were 40.1 and 41.2, respectively, at baseline and significantly improved to 21.45($p < 0.001$) and 22.28($p < 0.001$), respectively, at wk26. 48.3%pts previously treated with ETN and 57.1%pts previously treated with ADA achieved a EULAR response at wk26. Changes from baseline at wks10&26 in DAS28, HAQ, SJC, and TJC are described (Table 1). At least 1AE and serious AE were reported in 70.4% and 4.9%pts, respectively; 6.9%pts experienced at least 1infusion reaction (1.6%infusions were associated with an infusion reaction).

Conclusions: RA pts actively switched from tx with ETN or ADA to IFX, without a washout period, demonstrated a statistically significant and clinically important improvement in EULAR response and physical function. IFX was generally well-tolerated with no new safety signals observed.

Disclosure statement: R.B., D.D. and R.D. are employees of Centocor Ortho Biotech Services, LLC. H.E., R.F., J.G., H.K., M.L. and E.Z. have received research grants from Centocor Research & Development, Inc. J.W. is an employee of Johnson & Johnson Pharmaceutical Research and Development, LLC.

TABLE 1.

	Baseline	Change from baseline to wk10	Change from baseline to wk26
DAS28 (ESR)	6.193 (0.981)	−1.076 (1.146)*	−1.468 (1.437)*
DAS28 (CRP)	5.701 (0.896)	−1.088 (1.090)*	−1.436 (1.312)*
HAQ improvement	1.334 (0.577)	−0.173 (0.455)*	−0.223 (0.497)*
SJC	17.335 (10.537)	−6.960 (10.686)*	−8.283 (11.380)*
TJC	30.188 (16.893)	−10.460 (14.067)*	−13.197 (14.304)*

*$p < 0.001$

190. SUBCUTANEOUS GOLIMUMAB SUSTAINS EFFECTS OF INTRAVENOUS GOLIMUMAB IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS: RESULTS OF THE GO-LIVE LONG TERM EXTENSION

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Background: The objective of this study was to evaluate the efficacy and safety of SC golimumab (GLM) in RA pts who previously received IV GLM q12 wks with and without MTX.
Methods: Adult RA pts (n = 643), with persistent disease activity while receiving MTX > 15 mg/wk for at least 3mos, were randomized to IV placebo + MTX (n = 129) or GLM 2- or 4 mg/kg, both with and without MTX, q12wks (n = 514) up to Wk96 [median 68.4 wks]. Pts who received IV GLM completing the Wk48 database lock were eligible to participate in the long term extension (LTE) and receive open label GLM 50 mg SC q4wks for an additional 24wks (E-0 to E-24) and 16wks of safety follow-up (E-24 to E-40) with and without MTX. At Wk E-14, changes in concomitant RA medication (including MTX) were permitted at the investigators discretion.
Results: Of the 505 pts who entered the LTE, 186 pts who did not change dosing strategy during the IV phase (GLM IV 2 mg/kg IV + MTX [n = 82]; GLM IV 4 mg/kg + MTX [n = 104]) participated in the LTE at Wk E-0; baseline demographics and disease characteristics were comparable between both groups. Through Wk E-0, ACR20, ACR50, and DAS28-CRP (good or moderate) response was achieved by 67.5%, 61.9%, 43.4% and 39.2%, 87.7% 82.1% in the IV GLM 2 mg/kg and 4 mg/kg groups, respectively. Overall efficacy (ACR20, ACR50) and improvements in ACR components were sustained or improved in a majority of pts through Wk E-24 regardless of GLM IV dose: ACR20 was achieved by 85.7% IV GLM 2 mg/kg patients and 90.8% IV GLM 4 mg/kg patients, ACR50 was achieved by 77.8% and 82.1%, respectively. Compared with the IV phase, DAS 28 response and CRP measures improved with SC GLM. The rates of GLM SC discontinuations from Wk E-0 through Wk E-24 were 2.4% and 4.8% in pts previously treated with IV GLM 2- and 4 mg/kg, respectively, most commonly for adverse events (AEs). A total of 77.5% and 83.0% of patients in the GLM IV 2- and 4mg/kg groups, respectively, experienced >1 AEs through Wk E-0. Rates of infusion reactions remained lower in GLM-treated pts compared with placebo-treated pts. During the LTE (Wk E-0 through Wk E-40), 69.5% of SC GLM-treated pts experienced >1 AE; 13.7% and 14.0% of pts previously treated with GLM IV 2- and 4 mg/kg, respectively, experienced >1 serious AE. Injection site reactions were rare [0.6% (19/3443)].
Conclusions: In pts switched to SC GLM 50 mg through the LTE, overall efficacy was sustained or improved regardless of whether pts previously received IV GLM 2-or 4 mg/kg. Both IV and SC GLM were well tolerated with acceptable safety profiles.
Disclosure statement: D.B., L.K. and A.M. are employees of Centocor Research & Development, Inc. J.K., C.R. and P.T. have received research grants from Centocor Research & Development, Inc.

191. MALIGNANCIES ASSOCIATED WITH TNF INHIBITORS IN REGISTRIES AND PROSPECTIVE OBSERVATIONAL STUDIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Tumour necrosis factor (TNF) is an important component of host surveillance mechanisms for malignancy but also may be involved in spread of some cancers. Patients with rheumatoid arthritis have increased risk of lymphoma and some other cancers but a reduced risk of colon cancer. It is important that the effect of treatment with TNF-inhibitors (TNF-I) on cancer risk is evaluated. This project was undertaken to assess the risk of malignancy in patients with rheumatoid arthritis treated with TNF inhibitors in clinical practice as recorded in prospective, observational studies.
Methods: We undertook comprehensive searches of Medline, Embase, the Cochrane Database of Systematic Reviews and ACR, EULAR and BSR conference abstracts according to a pre-specified protocol. Publications that met the inclusion criteria were assessed for quality. Data on malignancy, including type, site, percentages of patients with malignancy, incidence rates, standardised incidence ratios (SIR) and relative risk were extracted and meta-analyses undertaken.
Results: The searches identified totals of 2039 papers and 1979 abstracts of which 20 full-texts and 7 conference abstracts met the inclusion criteria. Six studies contained sufficient data on malignancy to be included in the meta-analysis. The pooled estimate was 0.91 (95% CI 0.82, 1.01) indicating that treatment with TNF-I was not associated with an overall increased risk of malignancy compared with non-exposed RA patients. There was no evidence that longer duration of exposure increased the risk of malignancy nor that prior malignancy increased the relative risk, although the absolute rates of malignancy in both exposed and non-exposed patients was higher than in patients without a prior history of cancer.

Comparisons of incidence ratios of lymphoma in exposed and non-exposed patients were reported in three studies. The pooled estimate was 1.11 (95% CI 0.70, 1.61). Results from four studies showed that patients treated with TNF-I have a significantly increased risk of developing an NMSC (1.45; 95% CI 1.15, 1.85). Additionally, patients may be at an increased risk of developing melanoma, as the pooled estimate, that included two studies, was 1.79 (95% CI 0.92, 2.89).
Conclusions: This systematic review and meta-analysis provides reassurance to physicians and patients that treatment of RA patients with TNF-I does not increase the risk of malignancy in general or of lymphoma in particular but does appear to increase the risk of skin cancer, including melanoma. The confidence intervals however do not preclude an effect of treatment on risk of malignancy and researchers should be encouraged to publish additional analyses to add to the evidence base.
Disclosure statement: P.E. has received research grants and honoraria from Abbott, Bristol-Myers Squibb, Pfizer, Roche, Schering-Plough and UCB. R.H. and R.L. have received research grants from Pfizer. X.M. has received honoraria for talks and advisory boards from Pfizer, Roche and UCB. M.M. has received lecture fees from Actelion, Bristol-Myers Squibb, Roche and Pfizer, and research grants from Actelion, Pfizer, Centocor and Schering-Plough. K.P. has received consultancy fees from Abbott, Pfizer, Roche and Schering-Plough. A.R. has received consultancy fees from Napp, and is a previous employee of, holds share options with, and has received consultancy fees from Pfizer. P.T. has received lecture and consultancy fees from Abbott, Bristol-Myers Squibb, Centocor, Pfizer, Roche, Schering-Plough and UCB, and research grants from Roche and Glaxo Smith Kline. R.V. has received research grants and honoraria from Abbott, Bristol-Myers Squibb, Pfizer, Roche, Schering-Plough and UCB. C.W. has received a research grant from Pfizer.

192. SELECTION OF NON-BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS DEPENDING ON CLINICAL, LABORATORY AND RADIOLOGICAL CHARACTERISTICS OF RHEUMATOID ARTHRITIS

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Background: it has now been well established that early treatment of RA with DMARDs should be initiated to control the inflammatory activity and slow the structural damage. Unfortunately, very little

information is available on the efficacy of DMARDs depending on clinical, laboratory and radiological characteristics of RA.
Methods: 402 pts with RA (45.4% with early RA, including 11.9% pts with very early RA) were studied. Average age at inclusion was 50.4 ± 0.63 yrs, mean disease duration - 51.5 ± 3.31 mth. 78.9% of the pts were women; 62.6% were positive for rheumatoid factor (RF) and 75.7% - for antibodies against cyclic citrullinated peptides (anti-CCP AB). Outcomes after 2 yrs treatment were assessed by disease activity score (DAS28) and X-ray changes (modified Sharp-van der Heijde scoring method). Using the stepwise multiple logistic regression analysis, the most important prognostic factors of RA progression were found. Analysis of treatment efficacy depending on the duration, clinical (presence of extraarticular manifestations /EAM/), laboratory (RF, anti-CCP AB, elevated C-reactive protein (CRP) level) and X-ray (presence of erosive changes) characteristics, disease activity of RA was performed.
Results: in 24 months, ACR20% response rate with MTX in low and medium doses was similar (43.8% vs 53.7%, $p > 0.05$), but MTX in medium doses was better than MTX in low doses in ACR50/70% response rates (29.8/8.77% vs 13.4/1.81%, $p < 0.01$). Remission was achieved more often in pts received medium doses of MTX then low doses (12.4% vs 3.63%, $p < 0.05$). X-ray changes after 2 yrs were more than twice as apparent in group with low doses of MTX. For the following analysis only pts received medium doses of MTX was included. By the results of the stepwise multiple logistic regression analysis the most important prognostic factors of RA progression are presence of anti-CCP AB ($B = 12.8$, $p < 0.001$), the basic change in the total X-ray score ($B = 6.7$, $p < 0.001$) and presence of RF ($B = 3.3$, $p < 0.001$). The other factors (titer of RF, presence of EAM, level of anti-CCP and CRP, basic disease activity) had significant but less essential impact on RA progression.
Conclusions: anti-CCP AB must be measured even in RF(+) pts as the most significant prognostic factor of RA progression. SS can be prescribed for pts with low disease activity; for pts with higher activity but RF(-), anti-CCP(-) RA, without EAM and erosive RA. LF is better for early and late anti-CCP(+) RA, including pts with high CRP level. MTX (≥15 mg/w) can be prescribed for all pts except pts with early and late anti-CCP(+) RA. In case of ineffectiveness of MTX or LF for pts with moderate or high activity, CBT must be prescribed: for very early anti-CCP(+) RA with high CRP level; for early anti-CCP(+) RA despite of CRP level; for all pts with late RA except for non-erosive pts.
Disclosure statement: The authors have declared no conflicts of interest.

193. EFFICACY SUSTAINED AFTER DOSE DE-ESCALATION OF CERTOLIZUMAB PEGOL IN RHEUMATOID ARTHRITIS PATIENTS: POST-HOC ANALYSIS OF THE RAPID 2 OPEN-LABEL EXTENSION

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Background: In the RAPID studies, certolizumab pegol (CZP) 200 mg or 400 mg every other week (EOW) + methotrexate (MTX) was efficacious and well tolerated in patients (pts) with active rheumatoid arthritis (RA); the 2 CZP doses showed similar efficacy and safety (CZP 400 mg EOW is not licensed in the UK). Pts who completed these studies (completers) were eligible to enter open-label (OL) extensions (OLE) of CZP 400 mg EOW + MTX. Increasing the CZP dose from 200 to 400 mg EOW upon OLE entry in CZP 200-mg completers did not, on average, provide additional efficacy benefit compared with pts treated with CZP 400 mg throughout. Pts have now been followed to 3 years (yrs) (148 weeks [wks]) from the RAPID 2 baseline, during which time the CZP dose was decreased from 400 to 200 mg EOW per protocol (after ≥ 6 months in the OLE) in some pts. The purpose of this analysis is to investigate the impact of CZP dose decrease on efficacy in RA pts.
Methods: This analysis includes all RAPID 2 CZP 200- and 400-mg completers who received CZP 400 mg EOW + MTX in the OLE and who subsequently had the CZP dose decreased to 200 mg EOW by the 3-yr data cut. CZP dose decrease was mandatory after ≥6 months in the OLE. As the dose decrease in pts occurred at different times, data are shown up to 48 wks of CZP exposure following dose decrease, with Wk 0 (for this analysis) set as the last efficacy assessment visit prior to dose decrease; CZP dose decrease occurred between Wks 0 and 10. Wk 12 is therefore the first visit after dose decrease. Analyses include mean DAS28 (ESR) and HAQ-DI scores (last observation carried forward [LOCF]) and ACR responses (non-responder imputation). Data are shown by treatment originally received in RAPID 2 (200 or 400 mg EOW + MTX). RAPID 2: NCT00160602; RAPID 2 OLE: NCT00160641.
Results: Of 342 RAPID 2 completers who received OL CZP 400 mg + MTX, the CZP dose was decreased in 287 (139 CZP 200-mg and 148 CZP 400-mg completers) by the 3-yr data cut. All 287 pts received OL CZP 400 mg for ≥ 1 yr prior to dose decrease, with 126 and 132 CZP 200- and 400-mg completers, respectively, having reached up to 48 wks exposure following dose decrease (Wk 48 of this analysis). Mean DAS28 scores were 3.77 (SD: 1.22) and 3.54 (1.08) in CZP 200- and 400-mg completers at Wk 0 and remained similar after dose decrease to Wk 48. Mean HAQ-DI scores were 0.91 (0.61) and 0.90 (0.56) in CZP 200-mg and 400-mg completers, respectively, at Wk 0 and were similar to Wk 48 (0.87 [0.59] and 0.84 [0.56], respectively). The ACR50 response rates at Wk 48 after dose-decrease were 47% and 42% for CZP 200-mg and 400-mg completers, respectively; the ACR70 response rates were 24% and 22%, respectively.
Conclusions: In RA pts who had an initial response to CZP, efficacy was maintained in the OLE after CZP dose decrease from 400 mg to 200 mg EOW + MTX.
Disclosure statement: J.C. and D.V. are consultants for UCB. A.K., J.S. and R.V. have received research support from and are consultants for UCB. K.L. is an employee of UCB.

194. PROBABILITY OF ACHIEVING LOW DISEASE ACTIVITY AT 52 WEEKS IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH CERTOLIZUMAB PEGOL DEPENDS ON TIME TO AND LEVEL OF INITIAL RESPONSE

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Background: The relationship between an early response to biologic therapy and longer-term clinical outcomes has not been well characterized. We conducted a post hoc analysis to determine the relationship between initial improvement in DAS28(ESR) score within 12 weeks (wks) and probability of achieving low disease activity (LDA; DAS28 ≤3.2) at Wk 52 in RA patients (pts) treated with CZP.
Methods: The proportion of pts treated with CZP (200 or 400 mg*) + MTX who had LDA at Wk 52 was assessed among pts who achieved or failed to achieve various DAS28 responses (ie, DAS28 decrease from baseline [BL] <0.3, 0.6, 0.9, 1.2, 1.5 and 1.8 units) by Wks 1, 2, 4, 6, 8, 10, or 12. The results were analyzed for the ITT (LOCF) population. Pts

with nonimputable missing data during the first 12 wks of treatment were excluded from the analysis. *CZP 400 mg every other week is not licensed in the UK.
Results: Of the 783 pts randomized to CZP + MTX, 98% had DAS28 > 5.1 at BL; 30% achieved LDA by Wk 52. By Wk 12, 98%, 87%, and 74% of CZP-treated pts had DAS28 decreases from BL ≥ 0.3, ≥ 1.2, and ≥ 1.8, respectively. CZP-treated pts who improved their DAS from BL by < 0.3 up to Wk 6 (N = 41) had 0% probability of achieving LDA at Wk 52 (Table 1). Similarly, pts who improved their DAS from BL by <0.6 or 0.9 up to Wk 10 (N = 45 and N = 76, respectively) had 0% chance to achieve LDA at Wk 52. Pts who had a change of <0.3 at Wk 4, <0.6 and 0.9 at Wk 6, <1.2 at Wk 8, or <1.5 and 1.8 at Wk 12 had a <5% probability of achieving LDA at Wk 52 (bolded rows of Table 1).
Conclusions: Long-term response to CZP can be estimated early in the course of treatment. The majority of RA pts respond within the first 12 wks of CZP treatment. Furthermore, the probability of not achieving LDA at Wk 52 can be predicted by a combination of the change in DAS28 from BL and the time at which DAS28 was assessed after starting CZP treatment.

TABLE 1. Percentage[a] of CZP-treated patients with LDA at Week 52 out of those who failed to achieve DAS decreases up to week of follow-up for the first 12 weeks

DAS28 Change	Week						
	1	2	4	6	8	10	12
<0.3	19.5 (N = 220)	11.6 (N = 112)	**3.2 (N = 63)**	**0 (N = 41)**	**0 (N = 27)**	**0 (N = 19)**	**0 (N = 14)**
<0.6	21.0 (N = 352)	14.8 (N = 209)	7.1 (N = 126)	**2.5 (N = 79)**	**3.2 (N = 63)**	**0 (N = 45)**	**0 (N = 34)**
<0.9	22.8 (N = 457)	17.0 (N = 317)	8.9 (N = 202)	**4.2 (N = 144)**	**2.8 (N = 106)**	**0 (N = 76)**	**0 (N = 67)**
<1.2	24.7 (N = 546)	19.1 (N = 418)	12.8 (N = 288)	7.5 (N = 214)	**4.5 (N = 157)**	**3.1 (N = 129)**	**1.0 (N = 103)**
<1.5	26.1 (N = 605)	21.5 (N = 492)	16.5 (N = 369)	11.7 (N = 281)	7.2 (N = 221)	5.5 (N = 182)	**2.1 (N = 145)**
<1.8	27.9 (N = 656)	24.4 (N = 573)	17.4 (N = 448)	12.3 (N = 357)	9.5 (N = 294)	7.3 (N = 245)	**4.9 (N = 206)**

[a]N numbers are denominators for % calculations and are the number of patients not achieving the DAS28 change threshold at the week presented.

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195. DETERMINATION OF THE CRITICAL DIFFERENCE IN DISEASE ACTIVITY: A NEW DEFINITION FOR INDIVIDUAL TREATMENT RESPONSE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Normal fluctuations in disease activity measurements due to short-term situational effects and measurement errors complicate the evaluation of a clinically meaningful therapeutic response. We have addressed this difficulty by using a statistical approach to determine a critical difference (dcrit) that defines valid criterion for response as assessed by the Disease Activity Score-28 joints (DAS28).
Methods: The reference population was derived from two clinics and consisted of 101 RA patients with stable responses to DMARD or biologic therapy. Therapy was not changed in these patients and their disease course remained stable from months 12 to 24 after therapy initiation. To evaluate changes in DAS28 scores, we subjected patients' DAS28 scores at 12, 18, and 24 months to an ANOVA model to establish a 95% one sided confidence interval (95% CI) for normal fluctuations; this value was used to define the dcrit for individual changes. DAS28 changes less than the dcrit value represented the normal variation in DAS28 scores during stable disease and stable treatment, while changes that were equal to or greater than the dcrit can be considered to represent a therapeutic response.
Results: The overall dcrit value in the 101-patient reference population was 1.70. Values for dcrit were comparable regardless of treatment center, class of therapy (DMARDs or biologics), or baseline disease activity (Table 1). Male patients had a lower dcrit value than female patients, possibly due to the relatively small number of males in this population. In all subgroups except one, the dcrit value fell below 1.8. We thus conclude that DAS28 improvements of 1.8 or higher are outside the normal variation and represent a real therapeutic response.
Conclusions: Based on our data, a dcrit value of 1.8 (DAS28 improvement of 1.8 points) signifies a positive individual therapeutic response that exceeds the threshold of random fluctuation. The dcrit value determined by statistical analysis of normal variation in DAS28 scores is higher than the DAS28 change required to achieve a good EULAR response (1.2 points) and is independent of baseline disease activity, which may make it more convenient for clinical use. Further studies in larger populations will be required to confirm the utility of the dcrit value in determining therapeutic response. However, preliminary data suggest that a dcrit value of 1.8 has the potential to guide treatment decisions in daily clinical practice and to facilitate research on treatment responders.
Disclosure statement: F.B., H.B. and H.T. have received research grants from Abbott. G.W. has received honoraria from Abbott. All other authors have declared no conflicts of interest.

TABLE 1. dcrit value (DAS28 decrease) in patients subgroups

Clinical center		Class of therapy		Disease activity at month 12		Gender	
Goethe-University Frankfurt	Wuerzburg University	DMARDs	Biologic	DAS < 3.2	DAS > 3.2	Male	Female
n = 51	n = 50	n = 41	n = 60	n = 76	n = 25	n = 22	n = 79
1.71	1.69	1.83	1.61	1.50	1.79	1.39	1.78

196. A COMPARISON OF THE USE OF ANTI-TNFα AGENTS BEFORE AND AFTER A DECISION TO USE TRIPLE COMBINATION THERAPY AT BASELINE IN EARLY RA

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Background: The Early Rheumatoid Arthritis Network (ERAN)is an observational study of the secondary care management of early RA in the UK and Eire. The decision to use combination therapy for early RA was made in Oct 2006 in Hereford.This has since been demonstrated as feasible in real life clinical practice and as making a statistically significant difference in outcome in Hereford. Objective: To explore any differences in the use of Anti-TNFα agents before and after the decision to use combination therapy as standard first line treatment in early RA
Methods: Since October 2006 a combination of Methotrexate (MTX), Sulfasalazine (SSZ) and Hydroxychloroquine (HCQ) has been offered to the majority of patients with early RA and is started within 3 months of a decision to treat, usually at the time of diagnosis.This is escalated to maximum tolerated doses within 3 months.Patients failing to respond are offered either an alternative DMARD or a biologic agent depending on clinical assessment and NICE recommendations for the use of biologics. Standardised data comparable with that collected for the BSR biologics registry including details of drug therapy and rationale for discontinuation has been collected and has been analysed using the ERAN database. This data has been verified with the case notes by an external monitor. The cohort has been divided into groups A and B; pre and post decision to use combination therapy as standard respectively.
Results: Baseline demographics are similar across the two groups. Data is available on 231 participants at baseline.Group A pre decision to use combination therapy as standard mean age 57, Female 65.1%, erosions 20.5% 63.7% sero-positive. Group B post decision to use combination therapy as standard mean age 61. Female:65.7%, erosions:21.5%, 65% sero positive.Analysis using Pearson Chi-Square tests show no statistically significant difference in the use of anti-TNFα agents between the two groups.
Conclusions: There is no change in the percentage of patients treated with biologics since the introduction of aggressive combination therapy for RA in the first 3 years from diagnosis. The use of combination therapy in early RA is part of a strategy of tight disease control. It was expected to rapidly define a population of refractory RA patients eligible for biologic therapy, and therefore to increase the use of biologics. These data do not support this hypothesis.
Disclosure statement: The authors have declared no conflicts of interest.

TABLE 1.

Year	Drugs	GROUP A	GROUP B
1		Total n = 117	Total n = 61
	combination	9%	64%
	anti-TNF	3%	5%
2		Total n = 108	Total n = 29
	Combination	9%	65%
	Anti-TNF	7%	7%
3		Total n = 104	Total n = 6
	combination	8%	83%
	Anti-TNF	15%	17%

197. CLINICAL AND RADIOGRAPHIC IMPLICATIONS OF TIME TO TREATMENT RESPONSE IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS

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Background: Recent publications advocate treatment adjustment at 12 weeks for patients with rheumatoid arthritis (RA); still, data support the possibility of later responses to therapy. Our objective was to evaluate the association of early (12 weeks) and delayed (24 weeks) clinical responses with rates of clinical remission, low-disease activity (LDAS), and rapid radiographic progression (RRP) at 52 weeks in patients with early RA treated with MTX monotherapy or adalimumab (ADA) + MTX combination therapy in the PREMIER trial.
Methods: PREMIER was a 104-week, phase 3, randomized, placebo-controlled trial in a MTX-naïve population with early RA. In this post hoc analysis, observed data comparing MTX with ADA + MTX therapy are presented. Clinical outcome measures included the 28-joint Disease Activity Score (DAS28) and mean change from baseline in modified Total Sharp Score (ΔmTSS) at 52 weeks. Patients were categorized on the basis of clinical response (DAS28 improvement >1.2 or 20/50/70% improvement in ACR score) at 12 and 24 weeks: ''early responders'' achieved the clinical target at week 12 and maintained the response at week 24; ''delayed responders'' did not meet the clinical target until week 24. The percentages of patients at 52 weeks with LDAS (DAS28 <3.2), clinical remission (DAS28 <2.6), and RRP (ΔmTSS >3 units/year) in each group were determined.
Results: In both treatment groups, early clinical responses were associated with better long-term outcomes than delayed responses. Achieving early or delayed ACR70 responses did not result in treatment group differences in the proportion of patients achieving LDAS or clinical remission at week 52. However, delayed responses to MTX resulted in a high proportion of patients with RRP. Indeed, delayed ACR70 responses were associated with an RRP prevalence of 40%. In addition, even an early improvement of DAS28 >1.2 with MTX was insufficient to slow radiographic progression (41% RRP). In contrast, early or delayed clinical responses to ADA + MTX resulted in low proportions of RRP at 52 weeks, even for patients with a delayed ACR20 response (11% RRP). Of note, ADA + MTX delayed responders had less RRP than MTX-treated early responders.
Conclusions: MTX-treated patients with early RA who fail to achieve an ACR70 within 12 wks of treatment are at risk for RRP and should be considered for treatment adjustment. In contrast, ADA + MTX treatment is associated with better clinical outcomes and less severe radiographic progression at 52 wks, even among patients with a delayed clinical response.
Disclosure statement: B.G., N.M. and K.P. are full-time employees of and may hold stock or stock options with Abbott. A.K. conducted research studies on behalf of Abbott. E.K. has received consultancy fees or other remuneration from Abbott, UCB, Pfizer, Roche, Amgen and Bristol-Myers Squibb. M.W. has received research grants, consultancy fees or other remuneration from Abbott, and consultancy fees or other remuneration from Amgen, Pfizer, Centocor, UCB, Roche and Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

198. 4.2-YEAR RESULTS: LONG-TERM EFFICACY OF TOCILIZUMAB TREATMENT FOR RA

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Background: Randomised Phase III trials have demonstrated the efficacy and safety of tocilizumab (TCZ) in patients with RA. The majority of patients continued therapy in the long-term extension studies (GROWTH95, GROWTH96, open-label phase of LITHE) and data from 2904 patients with moderate-to-severe RA and an inadequate response to DMARDS (DMARD-IR patients) treated with TCZ plus DMARDS for up to 4.2 years are presented here.
Methods: Patients were assessed every 4 weeks in the original studies and every 8 or 12 weeks in the extension studies, from first dose to 28 August 2009. Data were assigned to the nearest 12-week point. There was no imputation of missing data.
Results: TCZ increased absolute numbers of DMARD-IR patients achieving ACR50, LDA and DAS28 remission through Week 96 and ACR70 through Week 120. However, these data must be interpreted with caution due to lower absolute numbers over time. ACR70 response rates were maintained for 24 consecutive weeks by Week 144 in 20% of assessed DMARD-IR patients. At Week 120, 52.3% of assessed patients had ≤1 swollen joint count and 38.4% had ≤1 tender joint count. HAQ scores of ≤0.5 were achieved in 38.4% of patients.
Conclusions: Efficacy during long-term TCZ treatment was demonstrated by increasing patient numbers achieving ACR50/70 and LDA/DAS28, maintained over time. These data support TCZ as an effective, long-term treatment for DMARD-IR RA patients.

199. CHANGES IN GENE EXPRESSION IN SYNOVIAL TISSUE FROM REFRACTORY RHEUMATOID ARTHRITIS PATIENTS TREATED WITH RITUXIMAB

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Background: To determine the effects of the B cell depleting drug rituximab on gene expression in synovial tissue from patients with

TABLE 1. Long-term efficacy of TCZ in DMARD-IR patients

Week	0	24	48	72	96	120	144	168	192
ACR50		**35**	**45**	**50**	**53**	**56**	**56**	**61**	**66**
		929/2693	1088/2439	1162/2312	1183/2227	1154/2047	1028/1825	802/1323	469/716
ACR70		**16**	**24**	**30**	**31**	**35**	**35**	**43**	**45**
		423/2693	581/2439	692/2312	698/2227	714/2047	638/1825	562/1323	325/716
LDA	**2**	**43**	**54**	**62**	**65**	**68**	**69**	**70**	**73**
	50/2889	1137/2658	1302/2396	1403/2261	1409/2158	1352/1978	1208/1755	887/1268	500/689
DAS28	**1**	**27**	**40**	**47**	**50**	**54**	**54**	**57**	**61**
remission	22/2889	722/2658	962/2396	1066/2261	1083/2158	1061/1978	951/1755	718/1268	420/689

refractory rheumatoid arthritis (RA) who have been on rituximab for 2 years.
Methods: Synovial tissue biopsies were collected from 19 patients with refractory rheumatoid arthritis at baseline, and 3 months after the first infusion of rituximab. 117 genes of interest were selected for analysis, including immune cell genes and fibrosis genes. Analysis was carried out using microfluidic real-time q-PCR and CT values were then obtained using the fluidigm gene expression data analysis software (version 2.1.1 Fluidigm Corporation).
Results: B cell depletion was evident in both responders and non responders of rituximab between baseline and 3 months as assessed by CD19 and CD20 gene expression. A number of genes were differentially expressed in responders compared to non responders of rituximab at baseline. An unsupervised hierarchical cluster analysis revealed the presence of two groups of RA patients. One with high inflammation at baseline and one with low inflammation at baseline. The high inflammation group had significantly higher DAS28, higher erythrocyte sedimentation rate, higher C-reactive protein levels and a greater change in DAS28 over 3 months.
Conclusions: These results show the existence of two distinct RA patient subgroups, where high inflammation tissue is associated with more severe disease and a better response to rituximab.
Disclosure statement: J.vL. did the gene expression analysis in collaboration with Roche. All other authors have declared no conflicts of interest.

200. SWITCHING BETWEEN BIOLOGIC THERAPIES IN CLINICAL PRACTICE

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Background: Treatment with Tumour necrosis factor-alpha inhibitors (TNFi) is standard therapy for patients with severe rheumatoid arthritis (RA) despite conventional DMARDs. Significant numbers of patients do not respond or experience adverse events to TNFi. We explored the hypothesis that patients who do not initially respond to TNFi (primary failure) respond less well to subsequent TNFi therapy than those switching for secondary failure or adverse events.
Methods: Patients with RA who had received TNFi prior to March 2010 were identified from existing databases. Medical notes were reviewed for all those with available 6 month follow up data. Changes in DAS28, ESR, CRP, EULAR responses were recorded, as well as reasons for discontinuation and response to subsequent therapy.
Results: 297 patients were identified. 248 (83%) patients were female. Patients had active (median DAS28 5.9; IQR 1.1) longstanding (median 13, IQR 14 years) disease, most were seropositive and erosive (78%). 146 (69%) were on methotrexate (median dose 21 mg/wk, IQR 10 mg) and had taken median 3 DMARDs previously (IQR 1). Good or moderate EULAR responses were seen in 219 patients (74%). 51 patients (17%) did not respond, and 27 patients experienced early adverse events. 74 patients deteriorated (secondary failure) after median 18 (IQR 12) months. 19 patients experienced late adverse events leading to a change in therapy. Patients discontinuing their initial TNFi had higher disease duration at baseline (median 14 vs. 12 $p = 0.03$), but there were no other differences in baseline characteristics. 158 patients switched to other TNFi, and had available response data at 6 months. 102 patients (65%) had good or moderate responses to their next drug, and there was no increase in adverse events (19%, 30 patients). However, 53 patients (34%) did not respond to their second drug. Successful treatment was less common if the first drug had been stopped due to primary failure (34% good/moderate responses, $p < 0.0001$ vs. switching for adverse event or secondary failure). Conversely, 85% patients with an adverse event to the first drug responded to the second, and 75% responded after switching because of secondary failure. There were no differences in response if there was a change from an antibody to a receptor construct or between two different antibodies (e.g. IFX to ADA).
Conclusions: We report high initial response rates to TNFi therapy, but many patients are unable to continue therapy long term. The most common reason for discontinuation was secondary failure, which may be due to development of antibodies specific to a TNFi. Current NICE guidelines state that these patients should be treated with rituximab. We suggest that patients who fail their initial TNFi course because of adverse events or secondary failure should receive a second TNFi. Response rates after primary failure of TNFi were poor in our cohort supporting the use of therapies with an alternative mode of action in this group.
Disclosure statement: B.K. has participated in advisory boards for Pfizer, Centocor, Abbott, Bristol-Myers Squibb, Roche and UCB, and has received research grants from Pfizer, Centocor and Abbott. All other authors have declared no conflicts of interest.

201. JOINT SPACE NARROWING HAS A STRONGER IMPACT ON PHYSICAL FUNCTION THAN JOINT EROSION: RESULTS FROM EIGHT YEAR LONGITUDINAL ANALYSES

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Background: Structural damage, assessed by the modified Total Sharp Score (mTSS), has been shown to be related to physical function. Thus far, it remains unclear to what extent the individual components of the mTSS contribute to long-term physical function. The objective of this analysis was to characterize the longitudinal relationship between physical function and Joint Space Narrowing (JSN) or Joint Erosion (JE) in patients with advanced RA.
Methods: DE019 was a 52-week, phase 3, randomized, placebo-controlled trial for the treatment of moderate to severe advanced RA, in which patients with an inadequate response to methotrexate (MTX) were randomized to weekly placebo, weekly adalimumab (ADA) 20 mg, or ADA 40 mg every other week (eow), alongside concomitant MTX therapy. Patients completing the double-blind study were eligible to receive open-label ADA 40 mg eow + MTX for an additional 7 years. This post hoc analysis evaluated the 8-year completers cohort with radiographs available at baseline and years 5, 6, and 8. 28-joint Disease Activity Score (DAS28) was used to assess clinical levels of disease activity. Physical function was assessed through the Health Assessment Questionnaire (HAQ). Radiographic damage was assessed using the modified Total Sharp Score (mTSS). Longitudinal generalized linear modeling was used to characterize the dependence of the HAQ on concurrent DAS28, total mTSS, JSN, and JE values, following adjustment for baseline age and gender and for concurrent CRP.
Results: Over time, DAS28 was linearly associated with the HAQ ($P < 0.001$). Similarly, the mTSS was significantly associated with the HAQ throughout treatment duration ($P < 0.001$). A 1 unit increase in DAS28 and a 20 unit increase in mTSS were associated with 0.22 and 0.044 increases in the HAQ, respectively. A breakdown of mTSS into the individual components revealed that JSN more strongly impacted the HAQ over time than JE, although both were significant determinants ($P < 0.001$ for both). A 20 unit increase in JSN and JE were associated with 0.1 and 0.06 increases in the HAQ, respectively. Interestingly, negative changes in mTSS trended towards lower HAQ values over time.
Conclusions: For patients with advanced disease, long-term physical functioning is associated with both the level of disease activity (DAS28) and the extent of radiographic damage (mTSS). Of the contributors to the mTSS, JSN had a greater impact on the HAQ over time than JE, suggesting that therapies with high potency for inhibiting both the progression of JSN and JE should be considered.
Disclosure statement: B.G. is a full-time employee of Abbott and may hold Abbott stock or stock options. E.K. has received consultancy fees or other remuneration from Abbott, Amgen, Bristol-Myers Squibb, UCB, Pfizer and Roche. R.L. has received research grants, consultancy fees or other remuneration from, and is/has been a member of speakers' bureaus for Abbott, Amgen, Centocor, Pfizer/Wyeth, UCB and Bristol-Myers Squibb. K.P. and S.R. are full-time employees of Abbott and may hold Abbott stock or stock options. D.V. has received consultancy fees or other remuneration from Abbott, Amgen, Bristol-Myers Squibb, Centocor, Chugai, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB and Wyeth.

202. GOLIMUMAB AND RADIOGRAPHIC PROGRESSION IN RHEUMATOID ARTHRITIS: RESULTS OF GO-BEFORE AND GO-FORWARD STUDIES

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Background: The objective of this study was to evaluate the effect of golimumab (GLM) on radiographic progression in pts with RA.
Methods: In both GO-BEFORE (MTX-naïve pts; n = 637) and GO-FORWARD (MTX-inadequately responding (IR) pts; n = 444) pts were randomized to PBO + MTX, GLM 100 mg + PBO, GLM 50 mg + MTX, or GLM 100 mg + MTX. Subcutaneous injections were administered q4 wks. GO-BEFORE had a control period of 52wks with early escape [EE] at wk 28 and GO-FORWARD had a control period of 24wks with EE at wk16. Pts in control grps meeting EE criteria start receiving GLM 50 mg + MTX. Radiographs of hands and feet at baseline, wk24 (wk16 for EE pts) and wk52 in GO-FORWARD, and baseline, wk 28, and wk 52 in GO-BEFORE were scored by 2 independent readers and an adjudicator using the van der Heijde -Sharp score (vdHS). Different readers were used for the two trials. Linear extrapolation was used for radiographs taken at EE visits.
Results: In the MTX-naïve population, mean vdHS changes (±SD) from baseline to wk52 (co-primary endpoint) in both the 50 mg and 100 mg GLM + MTX grps were significantly lower compared with those in the PBO + MTX grp (0.74 ± 5.23[p = 0.015] and 0.07 ± 1.83 [p = 0.025] versus 1.37 ± 4.56, respectively, in GO-BEFORE; 0.93 ± 4.86[p = 0.855] and 0.15 ± 1.64[p = 0.221] versus 1.10 ± 4.68, respectively, in GO-FORWARD). In the MTX-IR population, vdHS changes from baseline to wk 24 (primary analysis) were minimal in all grps, preventing any significant effect of GLM to be detected. The proportion of pts with change in vdHS above the smallest detectable change (SDC = 2.58 for the study) was 4 % in the PBO + MTX group. The lack of progression in the PBO grp may have been due to the short PBO-control period (in PBO + MTX grp 32% EE at wk16 and remaining pts crossed over at wk 24 to receive GLM) and relatively less active pt population (median CRP of 0.9, lower joint counts, lower baseline vdHS scores) than in previously reported trials in similar populations.
Conclusions: Both GLM 50 + MTX & GLM100 mg + MTX demonstrated statistically significant and comparable inhibition of radiographic progression in MTX-naïve population compared with MTX alone. In the MTX-IR population the minimal radiographic progression in the MTX alone grp prevented any effect of GLM to be detected.
Disclosure statement: A.Ba., A.Be., E.H., M.R. and W.X. are employees of Centocor Research & Development, Inc. P.C., P.E., R.F., M.G., E.K. and D.V. have received research grants from Centocor Research & Development, Inc.

203. HOW MANY PATIENTS WITH RHEUMATOID ARTHRITIS START AND REMAIN ON DMARD MONOTHERAPY OVER THREE YEARS AND WHAT IS THEIR OUTCOME?

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Background: Current guidelines for management of early Rheumatoid Arthritis (RA) include the principles of treating to a low disease activity target, such as the 28 joint disease activity score (DAS28). Strategies to achieve this include conventional disease modifying anti-rheumatic drugs (DMARDs) used sequentially or in combinations and if these fail and DAS28 remains >5.1, the use of biologic agents. This study examines actual clinical practice in the management of early RA from 25 centres in the UK since 2002.
Methods: The Early RA Network (ERAN) is a multi-centre inception cohort which was started in the UK in 2002 to record secondary care management of RA and examine RA outcomes over time. Standardised clinical and laboratory data is collected at entry and yearly. Outcomes include measures of function (HAQ & SF36), disease activity (DAS28), radiological erosions of hands/feet, work disability and all interventions including drug therapies and orthopaedic surgery.
Results: 557 patients have completed three year follow up out of a total of 1189 recruited into the study. 542 patients were on DMARD therapy. Demographics and baseline characteristics were mean age 55.5yrs, 66% women, 61% rheumatoid factor positive, 29% had erosions on X-rays. The time in months from first RA symptoms to first rheumatology outpatient assessment was median 7 months, and from the latter to start of first DMARD was 1 month. First DMARD use was as follows: Methotrexate 45%, Sulphasalazine 37%, other monotherapy 7%, miscellaneous combination therapy 7%, triple therapy 4%. By 3 years, 48% were on monotherapy, 12% were on sequential monotherapy, 29% were on 'step up' ('add on') combination therapies and 11% had combination therapies from start. 53 (10%) of the patients had anti-TNF agents added to their DMARD therapies. Table 1 shows the mean DAS28 over 3 years in the different DMARD groups. The mean DAS28 was significantly lower at 6 months and 1 year in the monotherapy group compared to each of the other groups ($p < 0.0001$). The results were similar at 3 years, except there was no significant difference in DAS28 between the monotherapy and combination therapy groups (mean 3.1 vs 3.2 respectively).
Conclusions: These results show that nearly half of these patients remained on monotherapy over 3 years as DAS28 values were controlled. The findings also suggest that if patients who are started on monotherapy do not achieve a low DAS28 by 6-12 months, then more intensive combination therapies with or without anti-TNF agents, should be considered.
Disclosure statement: The authors have declared no conflicts of interest.

TABLE 1. DAS 0-3 years by drugs at FUp year - ERAN 2002–2010

	Drugs 3 years			
	Mono Rx	Seq Mono	CombAddon	Comb Rx
DAS 0yr mean	4.4	4.3	5.1	4.9
DAS 6mth mean	3.5	3.9	4.5	4.2
DAS 1yr mean	3.2	4.1	4.2	3.8
DAS 2yr mean	3.2	3.8	4.1	3.5
DAS 3yr mean	3.1	4.1	3.7	3.2

204. AN AUDIT OF THE USE OF RITUXIMAB AGAINST NICE TA195

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Background: In August 2010, NICE released TA195 for the use of rituximab and other agents following the failure of a TNF inhibitor in the treatment of RA. This study compared the historical use of rituximab within our department with TA195 to determine if there is a difference in response between those who were TA195 compliant, and those who received rituximab according to the clinical gestalt of the consultant rheumatologists.
Methods: A proforma captured data from all RA patients prescribed rituximab. Patients were NICE compliant if they satisfied three criteria: 1.Patient received concomitant methotrexate (MTX) 2.Prior history of anti-TNF use 3.Multiple treatment cycles were at least 6 months apart. Patients were NICE non-compliant if they failed to satisfy any of these criteria. Change in DAS28 score between baseline and three months post-treatment was used to determine each patient's EULAR response to each treatment cycle. The EULAR response between the NICE compliant and non-compliant groups was compared after the first and second cycles of treatment (where applicable).
Results: Of 62 RA patients treated since 2006, 25 were NICE compliant (40.3%), and 37 were non-compliant (59.7%). 20/37 were not on MTX. A DAS28 score was lacking for 1 patient at follow-up, and 12 patients were still within the three month follow-up period. Response to the first treatment cycle was determined for 49 of the 62 patients. Median DAS28 change was 1.985 (range -1.54 to 5.13). To compare the NICE compliant and non-compliant groups, good and moderate EULAR responses were considered together as responders (Table 1). A χ^2 analysis tested the null hypothesis that NICE compliance does not influence response. A χ^2 result of 1.400 with 1 degree of freedom was obtained (P = 0.2).

37 patients had at least 2 treatment cycles. 2 patients died prior to follow-up, and 8 patients were still within the three month follow-up period. EULAR response to the second treatment cycle was determined for 27 of the 37 patients. Median DAS28 change was 2.95 (range -0.01 to 5.31). Responders and non-responders were compared as above. A χ^2 result of 0.391 with 1 degree of freedom was obtained (P = 0.5).

Conclusions: There was no apparent difference in response between those who were NICE compliant and non-compliant for the first and second treatment cycles. The majority of non-compliant patients were those who could not be prescribed concomitant MTX. According to TA195, they should have been prescribed adalimumab or etanercept as monotherapy. However, our clinical experience is of a good response to rituximab irrespective of TA195 compliance. Further published data is required to address rituximab efficacy without MTX.
Disclosure statement: D.H. has performed consultancy work for Roche. All other authors have declared no conflicts of interest.

TABLE 1.

Responder?	NICE Compliant (n = 19)	NICE Non-compliant (n = 30)	P-value
CYCLE 1			
YES	14	21	0.2
NO	5	9	
Responder?	**NICE Compliant (n = 12)**	**NICE Non-compliant (n = 15)**	**P-value**
CYCLE 2			
YES	10	13	0.5
NO	2	2	

205. SAFETY OF RITUXIMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS AND CONCOMITANT LUNG DISEASE

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Background: A variety of lung diseases are more common in patients with rheumatoid arthritis (RA) - including interstitial lung disease (ILD) and infectious conditions - and they may be considered contraindications to or cause toxicity in patients receiving DMARDs or anti-TNF agents. Many such patients may therefore be treated with rituximab (RTX). The safety of RTX in lung disease in RA has not been fully assessed and such patients are often excluded from clinical trials. This ongoing observational study aimed to evaluate the safety of patients with RA and lung disease that received RTX.
Methods: The records of patients who received RTX for RA at one Unit were reviewed and patients with lung disease before RTX were identified. Data were recorded on type of lung disease; mortality; and serious respiratory infections (i.e. necessitating admission to hospital or intravenous antibiotics). Patients underwent CT scanning and pulmonary function tests at time of diagnosis of lung disease. All patients received 2 infusions of 1,000 mg RTX with methylprednisolone; this repeated on return of RA disease activity, at not less than 6 monthly intervals.
Results: 347 patients received RTX for RA between 2004 and 2010. 67 patients (19.3%) had lung disease when treated with RTX. 56 (83.6%) of these patients were female, mean age was 60.3 +/- 13.5 years, mean disease duration was 15.1 +/- 9.4 years. 34 patients (50.7%) had received at least 2 cycles of RTX. Total follow up duration was 173.5 patient years (median 2.36, range 0.65 - 6.58 years). 48 patients had (71.6%) had ILD; 14 patients had chronic obstructive pulmonary disease (COPD); 5 patients had bronchiectasis; 2 patients had previous pulmonary empyema. After RTX, 3 deaths were recorded (2 patients with ILD, 1 patient with COPD). Causes of death were: infective exacerbation of COPD (12 months after 3rd cycle of RTX); pneumonia and possible acute progression of ILD - clinical and CT changes attributable to either condition were observed(4 weeks after 1st cycle of RTX) and suicide (3 months after 1st cycle of RTX). 3 patients had single episodes of serious respiratory tract infection (as defined above).
Conclusions: No definite new significant safety signals were observed beyond that which might be expected in this patient population (longstanding severe RA and concomitant lung disease). However, we note that 1 death occurred due to respiratory deterioration closely temporally related to RTX. Analysis of follow up respiratory function and HRCT data is in progress, as well as ongoing safety review.
Disclosure statement: M.B., S.D. and E.V. have received honoraria from Roche. P.E. has received consultancy fees from Roche. All other authors have declared no conflicts of interest.

206. SUSTAINED EFFICACY IS ACHIEVED WITH MULTIPLE COURSES OF RITUXIMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS WITH AN INADEQUATE RESPONSE TO ONE OR MORE TNF INHIBITORS

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Background: To determine the effect of multiple courses of rituximab in patients with severe, refractory RA (TNF-IR population).
Methods: Further courses of rituximab (2 x 1000 mg IV, 2 weeks apart) were permitted in TNF-inhibitor (TNF-IR) patients who entered the open-label extensions of the Phase II or III studies of the rituximab RA clinical programme. Eligibility for re-treatment included a response to the initial course (≥20% reduction in swollen and tender joint counts [SJC/TJC]), with courses administered no more frequently than every 16 weeks. Re-treatment criteria were SJC and TJC ≥8 or DAS28 ≥2.6 (depending on the study). Efficacy at 24 weeks post-rituximab course was determined relative to pre-rituximab baseline. Two populations were analysed: observed data on all patients (All patients); and observed data on all patients with efficacy data at 24 weeks following each of their first 5 courses of rituximab (within patient, within visit [WW]).
Results: A total of 500 patients had been exposed to ≥1 course of rituximab and had efficacy data at Week 24. The WW population comprised 119 evaluable patients. Greater responses were observed in all patients with rituximab re-treatment than with a single course (Table 1). However, re-treatment criteria may cause this population to become enriched with rituximab responders, as patients were required to achieve a response to the first course. Responses were maintained when analysed in the WW population (Table 1). Furthermore, 5 courses of rituximab resulted in a doubling of the proportion of patients in the WW population achieving DAS28 low disease activity (LDA) or remission. No unexpected findings for rates of infection (including serious infection) were found with rituximab re-treatment over multiple courses.
Conclusions: Multiple courses of rituximab produce sustained efficacy and tolerability in TNF-IR patients with active RA
Disclosure statement: M.D. has received research grants and consultancy fees from, and is/has been a member of speakers'

TABLE 1.

	Populations analysed									
	All patients					WW				
Response	C1	C2	C3	C4	C5	C1	C2	C3	C4	C5
ACR responses (n)	500	360	289	222	153	119	119	119	119	119
ACR20 (%)	61.0	70.8	70.9	65.8	65.4	68.9	72.3	71.4	67.2	70.6
ACR50 (%)	30.2	41.4	46.4	43.2	42.5	35.3	41.2	45.4	42.9	44.5
ACR70 (%)	12.0	18.9	25.3	22.5	20.3	16.0	18.5	23.5	21.0	22.7
EULAR responses (n)	489	355	288	215	149	112	112	112	112	112
Good response (%)	15.7	25.4	33.3	28.8	28.2	10.7	20.5	25.9	23.2	30.4
DAS28 LDA (%)	16.2	25.6	33.7	28.8	28.2	11.6	20.5	25.9	23.2	30.4
DAS28 remission (%)	8.4	14.4	17.7	17.2	16.1	6.3	8.9	9.8	15.2	15.2
Change in DAS28	489	355	288	215	149	112	112	112	112	112
Mean change	−2.15	−2.64	−2.93	−2.88	−2.93	−2.29	−2.63	−2.83	−2.85	−3.08
SD	1.43	1.43	1.46	1.59	1.73	1.32	1.46	1.46	1.67	1.66

C: course; LDA: DAS28 ≤3.2; remission: DAS28 <2.6.

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207. NURSE-SPECIALIST-LED CLINICS SIGNIFICANTLY IMPROVE PATIENT CONCORDANCE WITH DMARD THERAPY IN RA: A CRITICAL STEP IN ACHIEVING REMISSION

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Background: In the absence of a cure, the ultimate goal of treatment for Rheumatoid Arthritis (RA) is remission, which is associated with improved long-term outcomes. Goal directed therapy is necessary to achieve the target of remission. Tight control with rapid optimization of DMARD therapy and patients understanding the goal of therapy are essential if this is to be achieved. The RA Centre aims to achieve remission defined by a DAS28 score <2.6 in all patients if possible, using all available medication within national guidelines. We have investigated the outcomes of consultations over several years to understand the detail of this strategy and the obstacles to achieving it. One such obstacle was patients declining treatment and two audits in 2004 and 2006 showed that 35% of patients were declining an increase in treatment.
Methods: A retrospective notes review using the same pro-forma as previous audits was carried out for sequential RA consultations. The primary question investigated reasons for no change in therapy if DAS28 was >2.6. There were six categories identified for no change in therapy and we also analysed patient related factors influencing treatment decisions. We compared the results of this audit with two previous audits of outcome of consultations conducted using the same pro-forma in 2004 and 2006.
Results: 200 patient visits were reviewed and there were 160 women and 40 men, 130 had a change in treatment and 70 had no change. The majority of the patients (151) were white/white British, age range 22-89 years, disease duration less than 1 year to 43 years and DAS28 scores ranging from 2.7 to 7.5. A number of factors were identified as to why there was no change in treatment (see Table 1).
Conclusions: This study shows that the number of patients declining treatment has decreased significantly form 35% in the first two audits to only 8%. The reasons for this change are probably multifactorial. The RA Centre clinic has evolved and the ethos of goal directed therapy is now firmly embedded at the centre of patient care and has become part of routine practice, it is expected that remission can be achieved. We believe that the most important change over the last four years has been the introduction of the clinical nurse specialist role to provide support to newly diagnosed patients guiding them through the first few months of diagnosis and treatment, providing education and encouragement. Patients are seen on a monthly basis for a review of their medication and dose escalation of DMARDs.
Disclosure statement: The authors have declared no conflicts of interest.

TABLE 1.

Reasons	2010	2006	2004
Number of patients	70	29	81
Declined	8%	35%	34%
Pain score>inflammation	30%	20%	5%
Contraindications	8%	17%	22%
Flare-up only	4%	10%	15%
Waiting for previous treatment to take effect	28%	6%	12%
Other reasons	22%	12%	12%

208. DISEASE REMISSION, NORMALIZED PHYSICAL FUNCTION AND RADIOGRAPHIC NON-PROGRESSION ARE ACHIEVED BY THE MAJORITY OF PATIENTS WITH EARLY RHEUMATOID ARTHRITIS TREATED WITH ABATACEPT + METHOTREXATE: RESULTS FROM THE 2-YEAR AGREE TRIAL

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Background: Earlier, more intensive treatments in early RA pts have made disease remission and normalized physical function attainable goals. Prevention of radiographic progression early in disease is pivotal to minimizing detrimental long-term outcomes. We evaluated clinical and radiographic outcomes with abatacept (ABA) + methotrexate (MTX) over 2 yrs in MTX-naïve early RA pts.
Methods: In AGREE, early RA pts with poor prognostic factors were randomized to ABA ($\sim$10 mg/kg) + MTX or placebo (PBO) + MTX in a 1-yr double-blind period; all pts received ABA + MTX in a 1-yr open-label (OL) period. Efficacy and safety were assessed for pts who received ≥ 1 dose of OL ABA. Disease Activity Score 28 (DAS28 [CRP])-defined remission (DAS28 <2.6) and tender/swollen (active) joints (28-joint count) were assessed for the modified intent-to-treat population (dropouts = non-responders). Normalized physical function (Health Assessment Questionnaire-Disability Index [HAQ-DI] score ≤ 0.5) and radiographic progression (mean change in Genant-modified Sharp total scores [TS] and non-progression = change from baseline in TS ≤ 0) were assessed as-observed.
Results: 459 pts (both arms) completed Yr 1 and continued in Yr 2; 94.3% completed Yr 2. Mean baseline DAS28 (CRP) = 6.3; HAQ-DI score = 1.7; TS = 7.5. Proportion of pts randomized to ABA + MTX achieving remission was maintained (46.1 vs 55.2% at Yrs 1 and 2). Of pts in remission at Yr 2, 63.5% had 0 active joints; 11.9, 7.1 and 17.5% had 1, 2 and ≥ 3 active joints, respectively. For the PBO + MTX arm, 26.9% achieved remission at Yr 1; after switching to ABA + MTX, 44.5% achieved remission at Yr 2. HAQ-DI normalization was maintained over 2 yrs for the ABA + MTX arm, with rates of 49.1 and 54.7% at Yrs 1 and 2; rates for the PBO + MTX arm were 35.6% at Yr 1 and 47.6% at Yr 2 after addition of ABA. Pts randomized to ABA + MTX had significantly less structural damage progression in Yr 2 vs Yr 1 (change in TS: 0.65 from baseline to Yr 1 vs 0.18 from Yr 1-2; $p < 0.001$). For pts randomized to PBO + MTX, change in TS was 1.48 from baseline to Yr 1 vs 0.25 from Yr 1-2; $p<0.001$. Changes from baseline to Yr 2 were significantly lower for the original ABA + MTX arm vs those who switched at Yr 1; 0.84 vs 1.75, $p = 0.001$. The rate of non-progression over 2 yrs was 56.8% in the ABA + MTX arm vs 43.8% in the PBO + MTX arm; 91.1% of pts randomized to ABA + MTX who were non-progressors at Yr 1 remained non-progressors at Yr 2. AEs, including serious infections, malignancies and autoimmune events, in Yr 2 were consistent with those in Yr 1.
Conclusions: Early introduction of ABA + MTX combination therapy results in greater sustainable clinical and radiographic benefits and normalization of function in the majority of MTX-naïve early RA pts vs MTX alone, supporting use of ABA + MTX earlier in disease.
Disclosure statement: J.B. has received Grant or research support from Biogen Idec and Pfizer and is a consultant for Crescendo Biosciences. J.B. is an employee and shareholder of Bristol-Myers Squibb and has a self-directed pension plan with Bristol-Myers Squibb. A.C. is an employee of Bristol-Myers Squibb. P.D. is/has been a member of speakers' bureaus for Wyeth, Bristol-Myers Squibb and Schering-Plough. H.G. has received grants or research support from and is a consultant for Bristol-Myers Squibb, Roche, Genentech, Amgen and Merck, has received research support from Pfizer, Servier and Biogen Idec, and is a consultant and shareholder of Synarc. R.W. has received research support from UCB, is/has been a consultant and member of speakers' bureaus for Bristol-Myers Squibb and Schering-Plough, and is a consultant for Roche Belgium. All other authors have declared no conflicts of interest.

209. SAFETY, EFFICACY AND HEALTH-RELATED QUALITY OF LIFE THROUGH 5 YEARS OF ABATACEPT TREATMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS AND AN INADEQUATE RESPONSE TO ANTI-TUMOUR NECROSIS FACTOR THERAPY

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Background: Abatacept (ABA) has shown sustained efficacy and consistent safety over the long term in patients (pts) with RA and an inadequate response (IR) to anti-TNF therapy in the ATTAIN trial. Here we evaluate the safety, efficacy and health-related quality of life (HRQoL) of ABA through 5 years (yrs) in anti-TNF inadequate responders.
Methods: Pts in this placebo-controlled Phase III trial had active RA and an IR to $\geq$ 3 months anti-TNF therapy. Pts completing a 6-month double-blind (DB) period entered a long-term extension (LTE) to receive ~10 mg/kg ABA + background DMARDs. Pts left the study after 5 yrs of treatment or when ABA became commercially available in their country. Safety was assessed for pts who received $\geq$ 1 ABA dose during the LTE up to November 2008 (~5 yrs). Disease Activity Score 28 (DAS28, based on C-reactive protein [CRP]), Health Assessment Questionnaire-Disability Index (HAQ-DI) and Short Form (SF)-36 scores (physical component summary [PCS] and mental component summary [MCS]) were assessed for pts randomized to ABA who entered the LTE, using as-observed data. DAS28 (CRP) data are presented to Yr 4.5 (6-month DB + 4-yr LTE) and HAQ-DI and SF-36 data to Yr 4 (6-month DB + 3.5-yr LTE).
Results: 317/322 completers of the DB period entered the LTE (218/317 had been randomized to DB ABA). ABA-treated pts who entered the LTE had mean DAS28 (CRP) of 6.5 and mean HAQ-DI score of 1.8 at baseline. Mean exposure (range) to ABA was 42.2 (3.7-65.5) months. During the LTE, 69/317 (21.8%) and 36/317 (11.4%) pts discontinued due to lack of efficacy and adverse events (AEs), respectively. Incidence rates (per 100 pt-yrs) of serious AEs and serious infections were 26.0 and 5.3 versus 19.6 and 3.4 in the DB period vs the LTE, respectively. No cases of tuberculosis or opportunistic infections occurred in the LTE. Rates of malignancies and autoimmune events per 100 pt-yrs, respectively, were 3.5 and 1.8 in the DB period vs 2.2 and 1.5 in the LTE. Five deaths (respiratory distress, asphyxia, staphylococcal wound infection, metastatic neoplasm, natural cause) occurred in the LTE. Reductions in DAS28 were observed through the LTE: mean changes (95% CI) from baseline were -2.0 (-2.2, -1.8) at Month 6 vs -2.9 (-3.1, -2.6) at Yr 4.5. Reductions in HAQ-DI score were maintained from Month 6 through the LTE: -0.5 (-0.6, -0.4) at Month 6 and -0.6 (-0.7, -0.5) at Yr 4. Improvements from baseline in PCS and MCS were maintained during the LTE, with 7.5 (6.1, 8.8) and 5.8 (4.2, 7.5) at Month 6 vs 8.7 (6.9, 10.5) and 5.4 (3.2, 7.6) at Yr 4, respectively.
Conclusions: During the ATTAIN LTE, ABA was well tolerated with consistent safety relative to the DB period. Improvements in disease activity, physical function and HRQoL observed in the DB period were sustained in the LTE, supporting long-term use of ABA in anti-TNF inadequate responders.
Disclosure statement: R.A. is and employee and shareholder of Bristol-Myers Squibb. J.B. is an employee and shareholder of Bristol-Myers Squibb and has a self-directed pension plan. M.D. has received research support from and is a consultant for Bristol-Myers Squibb, Abbott, Wyeth, Centocor and Schering-Plough, and is a member of speakers' bureaus for Bristol-Myers Squibb, Abbott and Wyeth. A.E. and M.L. are employees and shareholder of Bristol-Myers Squibb. M.G. has received research grants and consultancy fees from, and is a member of a speakers' bureau for Bristol-Myers Squibb. T.L. was an employee and shareholder of Bristol-Myers Squibb at the time of the study. M.L. has received research support from Bristol-Myers Squibb. M.S. has received research support from and is a consultant for Bristol-Myers Squibb.

210. EFFICACY AND SAFETY OF CERTOLIZUMAB PEGOL PLUS METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS: 3-YEAR DATA FROM THE RAPID 2 STUDY

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Background: Certolizumab pegol (CZP) every other week (EOW) + methotrexate (MTX) demonstrated rapid and sustained efficacy with an acceptable tolerability profile over 2 years (yrs) in patients (pts) with active rheumatoid arthritis (RA) despite MTX. The purpose of this analysis is to evaluate sustainability of improvements in RA signs and symptoms, inhibition of joint damage progression and tolerability of CZP + MTX over 3 yrs in pts who completed 24 weeks (wks) of double-blind treatment with CZP 200 or 400 mg EOW + MTX (completers) in RAPID 2, and entered an open-label extension (OLE) of CZP 400 mg EOW + MTX (CZP 400 mg EOW is not licensed in the UK).
Methods: ACR responses, DAS28(ESR), HAQ-DI, pain VAS (0-100 mm scale) were measured over 3 yrs (148 wks) from RAPID 2 baseline (BL) for CZP completers who entered OLE; modified Total Sharp Scores (mTSS) were measured over 2.5 yrs (128 wks). Pts who withdrew from the OLE for any reason or took rescue medication in the OLE had data imputed from that timepoint onward. For mTSS, linear extrapolation was used. For DAS28, HAQ-DI, and pain VAS, last observation carried forward was used for any missing data. For ACR responses, both non-responder imputation (NRI) and observed data are reported. AEs were assessed in all pts at each visit (after first study drug administration) from RAPID 2 BL. Safety analyses were based on the ITT population. AEs and serious AEs (SAEs)/100 pt-yrs are presented for all pts who received $\geq$1 CZP dose. RAPID 2: NCT00160602; RAPID 2 OLE: NCT00160641.
Results: Of 494 pts treated with CZP + MTX, 355 completed RAPID 2; of these, 342 (96%) entered the OLE. Completers entering OLE had high disease activity at RAPID 2 BL (mean: DAS28: 6.8; HAQ-DI: 1.6; pain VAS: 60.7); mean mTSS at RAPID 2 BL was 33.6. After 3 yrs, 79% of CZP completers continued to receive OL CZP; only 2 pts withdrew due to lack of efficacy. ACR responses and improvements in DAS28, HAQ-DI and pain from BL were sustained in the OLE to 3 yrs in CZP completers. After 3 yrs, 60% and 32% of patients were ACR50 and ACR70 responders, respectively (observed case analysis). Similar response patterns were obtained using NRI. Mean change from BL at 3 yrs in DAS28, HAQ-DI and pain VAS was −3.0, −0.65 and −29.2, respectively. Inhibition of progression of structural damage observed during the placebo-controlled phase was sustained up to the last x-ray evaluation at 2.5 yrs (mTSS mean change from BL: 0.75). The incidence of AEs by Wk 148 was 108/100 pt-yrs, and SAEs 13/100 pt-yrs. Most AEs were mild to moderate; no new safety signals were identified.
Conclusions: In pts with active RA despite MTX, the addition of CZP provides clinical improvements that are sustained over 3 yrs, inhibits joint damage progression, and is well tolerated.
Disclosure statement: A.F. is an employee of UCB. A.K., J.S. and R.V. have received research support from and are consultants for UCB. V.S. and D.V. are consultants for UCB. J.V. is/has been a member of a speakers' bureau for UCB.

211. ARE VENOUS THROMBOTIC EVENTS INCREASED IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH ANTI-TNF THERAPY? RESULTS FROM THE BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS REGISTER (BSRBR)

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Background: Case reports have shown that TNF decreases platelet activation and inhibits thrombus formation, and so blocking TNF may contribute to thrombus formation. Research looking at the role of such therapies on venous thrombotic events (VTE) in RA patients been conflicting. The aims of this analysis were (1) to compare rates of VTE

in RA patients treated with anti-TNF vs. non-biologic disease modifying anti-rheumatic drugs (nbDMARDs) alone and (2) to compare the rates between each individual anti-TNF and nbDMARDs.
Methods: To 31/10/2009, 11,173 anti-TNF and 3,214 biologic-naive nbDMARD control patients had been recruited to the BSRBR, a UK national register of active RA patients on biologic therapy. All patients were followed by regular hospital and patient questionnaires. This on-drug analysis, limited to first biologic only, followed all patients until first VTE (deep venous thrombosis or pulmonary embolism), death, treatment discontinuation or last follow-up date, whichever came first. Cox proportional hazards models were used to compare rates of VTE between cohorts. Inverse probability of treatment weighting (IPTW) was used to adjust for the confounding effect of baseline differences between groups, including age, gender, steroid use, smoking, disease duration, and severity amongst others. Surgery was included as a time-varying covariate, with patients viewed as being at increased risk for 90 days post-procedure. Missing baseline data were accounted for using multiple imputation.
Results: The anti-TNF cohort was younger (mean 56 v 60 years), had a higher proportion of females (76 v 72%) and more severe disease (mean DAS28/HAQ: anti-TNF 6.6/2.0, nbDMARD 5.1/1.5). The median duration of follow up was 4.3 years (IQR 2.9, 5.4) in the anti-TNF cohort, and 3.0 years (IQR 1.7, 4.2) in the nbDMARD cohort. A total of 161 first VTE's were reported (129 anti-TNF, 32 nbDMARD). 14% of anti-TNF and 6% of nbDMARD VTE events were reported within 90 days of hip or knee replacement. Overall there was no difference in the rate of VTE between anti-TNF and nbDMARD treated patients (adjusted HR 1.2 (95% CI 0.6, 2.1) (Table 1). The risk was similar across all anti-TNF agents.
Conclusions: Anti-TNF therapy is not associated with an increased risk of VTE in RA patients. There is also no difference in VTE risk between the anti-TNF drugs.
Disclosure statement: The authors have declared no conflicts of interest.

212. LONG-TERM SAFETY OF ABATACEPT: INTEGRATED ANALYSIS OF CLINICAL PROGRAMME DATA OF UP TO SEVEN YEARS OF TREATMENT

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Background: Integrated analyses of clinical trial data are important to assess long-term (LT) safety and detect rare events. Here we present an integrated analysis of safety data from the abatacept RA clinical trial program up to December 2009, including 12,132 patient-years (p-y) of exposure.
Methods: Data from eight abatacept RA clinical trials were classified into short-term (ST) and LT periods and analyzed. ST data included six double-blind (6- or 12-month), placebo-controlled periods, one non-randomized Phase II study and one non-randomized Phase III study. The LT data included the open-label (OL) periods of these eight studies. Safety assessments, presented for all patients receiving $\geq$1 dose of abatacept, included adverse events (AEs), serious AEs (SAEs), mortality and events of clinical interest. All events are presented as incidence rates (IRs) per 100 p-y with 95% CIs.
Results: The cumulative period (ST and LT) included 4149 patients with 12,132 p-y of exposure; 1165 had $\geq$5 years' exposure. Mean (range) exposure was 35.6 (1.9-104.2) months. The ST period included 3173 patients (2331 p-y) and the LT period included 3256 patients (9752 p-y). In the cumulative period, IRs (95% CIs) for SAEs, deaths, serious infections and autoimmune events were 14.61 (13.85-15.41), 0.60 (0.47-0.76), 2.87 (2.57-3.19) and 1.99 (1.74-2.26), respectively and were generally consistent with IRs in the ST period. Annual IRs (95% CIs) for SAEs did not increase with increasing abatacept exposure: Year 1, 19.13 (17.67-20.67); Year 2, 14.39 (12.80-16.11); Year 3, 12.82 (11.09-14.74); Year 4, 10.53 (8.76-12.57); Year 5, 10.18 (8.11-12.62); Year 6, 7.09 (4.54-10.55); Year 7, 8.90 (4.74-15.22). During the cumulative period, the IR (95% CI) of hospitalized infection was 2.64 (2.35-2.95). There were few opportunistic infections (0.36 [0.27-0.49]), with only eight cases of tuberculosis (0.07 [0.03-0.13]) observed overall. IRs (95% CIs) for malignancies (not including non-melanoma skin cancer [NMSC]), NMSC and solid tumors in the cumulative period were 0.73 (0.58-0.89), 0.73 (0.58-0.90) and 0.59 (0.46-0.75), respectively and were consistent with the ST. IRs (95% CIs) for lung cancer and lymphoma were 0.15 (0.09-0.23) and 0.07 (0.03-0.14), respectively. Acute infusional events, occurring within one hour of the start of the infusion, were reported at an IR (95% CI) of 3.90 (3.52-4.32; based on 6 studies).
Conclusions: Integrated safety data from 4149 patients with 12,132 p-y of exposure up to 7 years demonstrate that abatacept is generally well tolerated. No new safety events were identified over time, and the types and IRs of safety events (including events of clinical interest) in the LT and cumulative periods were generally consistent with those in the ST period, indicating that the abatacept safety profile remains stable with increasing duration of exposure.
Disclosure statement: R.A., I.D., S.K. and A.L. are employees and stock holders of Bristol-Myers Squibb. R.C. has received consultancy fees from Bristol-Myers Squibb and Human Genome Sciences. S.G., N.K., R.P., K.Q. and A.T. are employees of Bristol-Myers Squibb. M.H. has received consultancy fees from Abbott, Amgen, Bristol-Myers Squibb, Genentech, Biogen Idec, Roche and UCB. L.M. has received consultancy fees from and is a member of speakers' bureaus for Bristol-Myers Squibb, Genentech and Biogen Idec. R.W. has received consultancy fees from Bristol-Myers Squibb, Centocor, Roche, Schering-Plough and UCB, and is a member of a speakers' bureau for Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

213. ACT-SURE PRELIMINARY RESULTS: TOCILIZUMAB TREATMENT OF PATIENTS WITH RA AND AN INADEQUATE RESPONSE TO DMARDS AND/OR TNF INHIBITORS IN A SETTING CLOSE TO CLINICAL PRACTICE

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Background: The safety and efficacy of tocilizumab (TCZ) have been demonstrated in patients (pts) with RA and previous inadequate response to DMARDs (DMARD-IR) or TNF inhibitor (TNF-IR) therapy in

TABLE 1. Patient characteristics and incidence of VTEs

	nbDMARD	All anti-TNF	ETN	INF	ADA
Subjects (n)	3214	11173	3968	3347	3858
Exposure (pyrs)	8702	33638	14797	8909	9932
Surgeries (n)	1145	5310	2405	1341	1564
Hip/knee replacement (n)	521	3135	1426	815	894
VTEs (n)	32	129	47	47	35
VTE within 90 days of surgery, n (%)	4 (13)	23 (18)	9 (19)	9 (19)	5 (14)
VTE within 90 days of hip/knee replacement, n (%)	2 (6)	18 (14)	7 (15)	8 (17)	3 (9)
VTE incident rate/1000 pyrs	3.8 (2.5,5.2)	3.8 (3.2,4.6)	3.2 (2.3,4.2)	5.3 (3.9,7.0)	3.5 (2.5,4.9)
VTE adjusted HR	Ref	1.2 (0.6,2.1)	1.0 (0.5,1.9)	1.5 (0.8,2.8)	1.1 (0.5,2.3)

7 Phase III controlled studies. However, data regarding pts switching to TCZ without TNF inhibitor washout are limited.
Methods: ACT-SURE was a 6-month, Phase IIIb, open-label, single-arm study of DMARD-IR and TNF-IR pts treated with TCZ 8 mg/kg q4wk as monotherapy or in combination with DMARDs in a clinical setting (tertiary academic centres, non-academic centres and private practice). For analysis pts were stratified by pre-study TNF inhibitor use (TNFi-naive [DMARD-IR] pts; previous TNFi users [>2 months since use] or recent TNFi users [≤2 months since use]). A separate sub-analysis was performed on patients receiving TCZ as monotherapy.
Results: 1,681 pts were evaluated; mean age was 54 yrs and 81% were female. Overall, 58% of pts were DMARD-IR, 18% were previous TNFi users and 24% recent TNFi users. Baseline DAS28 was similar between groups (5.9-6.2) and mean RA duration was 8.2 years for DMARD-IR pts vs 11.2/11.7 years in previous/recent TNFi users. Overall, 12.8% of pts withdrew, 4.8% for safety reasons, with infections the most common safety-related cause of withdrawal (1.1%, 1.8/100 patient-years [PY]). AE, SAE and infection rates were lower in DMARD-IR pts. Few pts experienced clinically significant ALT shifts. Onset of efficacy was rapid and increased over time: 24%-38% of pts achieved DAS28 remission at Wk 8 and 49%-62% of pts at Wk 24. Responses were similar for recent and previous TNFi pts and better among DMARD-IR pts. Mean DAS28 values at Wk 24 were 2.83/2.76 for previous/recent TNFi users, and 2.34 for DMARD-IR pts. Improved physical function was seen in 74.1%, 71.1% and 70.2% of DMARD-IR pts, previous TNFi users and recent TNFi users. With TCZ monotherapy, ACR20/50/70 response rates were 66.9%/43.5%/23.8% at Week 24, with a DAS28 remission rate of 49.8%.
Conclusions: In a setting close to clinical practice, the TCZ safety profile demonstrated in previous Phase III trials was confirmed. TCZ showed rapid and increasing efficacy over time as monotherapy or in combination with DMARDs, as first-line biologic in DMARD-IR pts and in TNFi-IR pts. Safety results did not differ between previous and recent TNFi users, supporting switching to TCZ without a washout.
Disclosure statement: C.B. and V.B. have received consultancy fees from Roche. J.I. has received research grants from Actelion Pharmaceuticals US, Merck Sharp & Dohme, Pfizer and Roche, and consultancy fees from Actelion Pharmaceutical US. M.N. has received research grants from Abbott Immunology Pharmaceuticals, Bristol-Myers Squibb, Roche, Sanofi-Aventis, Schering-Plough and Wyeth, is/has been a member of speakers' bureaus for Abbott Immunology Pharmaceuticals and Bristol-Myers Squibb, and has eceived consultancy fees from Roche. K.P. has received consultancy fees from Roche. A.S. is an employee of Roche. J.A. has received consultancy fees from Roche and UCB, Inc. A.O. has received consultancy fees from Abbott Laboratories, Bristol-Myers Squibb, GlaxoSmithKline, AsahiKASEI, Merck Serono, Roche, Schering-Plough, UCB and Wyeth, and is a member of speakers' bureaus for Abbott Laboratories, Bristol-Myers Squibb, Chugai, Merck Serono, Roche, Schering-Plough and UCB. All other authors have declared no conflicts of interest.

TABLE 1.

Week 24	AE rate/ 100 PY	SAE rate/ 100 PY	Serious infection rate/100 PY	Infusion reactions* % (n)	ALT shift from baseline to > 3 x ULN % (n)
DMARD-IR	551.1	18.6	4.2	6.8 (66)	2.4 (23)
TNFi-IR, previous	654.4	28.7	7.6	7.4 (22)	3.0 (9)
TNFi-IR, recent	652.6	18.0	6.0	6.1 (25)	0.7 (3)
	ACR20 % (n)	ACR50 % (n)	ACR70 % (n)	ACR90 % (n)	DAS28 rem. % (n/n)
DMARD-IR	70.5 (688)	51.9 (507)	31.8 (310)	10.3 (101)	61.6 (534/867)
TNFi-IR, previous	60.7 (181)	35.2 (105)	17.8 (53)	6.4 (19)	48.5 (117/241)
TNFi-IR, recent	62.7 (255)	42.3 (172)	19.7 (80)	6.6 (27)	50.4 (175/347)

n/n: no. of patients who responded/no. of evaluable patients. *Infusion reaction: AE occurring during infusion of TCZ.

214. THE IMPACT OF ESR ON TREATMENT RESPONSE RATES IN PATIENTS TREATED WITH TOCILIZUMAB IN DAILY CLINICAL PRACTICE: FINDINGS FROM THE GERMAN BIOLOGICS REGISTER (RABBIT)

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Background: Tocilizumab, a human anti-interleukin (IL)-6 receptor antibody, has demonstrated high clinical response and remission rates in clinical studies of patients with RA and has recently been approved for the treatment of this condition. IL-6 receptor blockade leads to a direct inhibition of acute-phase protein production by hepatocytes. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), which are measures of the acute-phase response, are important components of the disease activity score (DAS28) used to determine treatment effectiveness in RA. The present study investigated the contribution of single components of the DAS28 to treatment response in tocilizumab-treated patients in daily rheumatological care.
Methods: The RABBIT register is a prospective cohort study containing data on all licensed biologic agents prescribed to RA patients in Germany since 2001. Following the approval of tocilizumab in Germany in January 2009, patients starting treatment with tocilizumab were enrolled in the study. All patients included in the register will undergo 5 years' follow-up, including regular assessments of clinical status and therapy, with disease activity measured using DAS28 (ESR).
Results: Of 6,861 enrolled patients in the register, 243 patients received treatment with tocilizumab. Mean age and median disease duration at start of treatment were 57 years and 10 years. Of patients with 3 months' follow-up (n = 119), 36% achieved a good EULAR response with a further 29% achieving a moderate response. DAS28 remission (DAS28 < 2.6) was achieved by 27% of patients. Of 55 patients with 6 months' follow-up, 49% had a good EULAR response, with an additional 29% having a moderate response; 40% of patients were in DAS28 remission. With regard to single DAS28 components, similar changes in joint counts and patient global assessment were observed in patients treated with tocilizumab compared to patients receiving other biologics whereas the decrease in ESR levels was significantly greater. The percental change of the ESR after 6 months was 80% under treatment with tocilizumab compared to 33% under anti-TNF treatment. In a high number of patients treated with tocilizumab the decrease in ESR was already sufficient to reach EULAR response.
Conclusions: A substantial proportion of RA patients treated with tocilizumab in clinical practice benefit from high response and remission rates. However, when considering treatment efficacy based on DAS28 and EULAR responses, the significant impact of ESR changes on these outcome measures must be taken into account.
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Disclosure statement: A.S. has received honoraria from Pfizer, Roche and Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

215. CHANGE IN CRP AT 12 WEEKS PREDICTS THE RISK OF RAPID RADIOGRAPHIC PROGRESSION AT TWO YEARS IN METHOTREXATE-TREATED PATIENTS WITH EARLY RHEUMATOID ARTHRITIS

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Background: In patients with rheumatoid arthritis (RA), radiographic progression is an important contributor to long-term disability. Hence, identifying patients at risk of rapid radiographic progression (RRP) early in the course of disease is an important goal of medical management, as it affects therapeutic decision-making. The objective of this study was to determine whether change in CRP after 12 weeks of treatment can indicate risk of RRP in patients with early RA.
Methods: We examined data from methotrexate (MTX)-naïve patients with early RA in the PREMIER study, a 104-week, phase 3, placebo-

controlled trial in which patients were randomized 1:1:1 to the following: weekly MTX, adalimumab (ADA) 40 mg every other week, or ADA + MTX. This post hoc analysis evaluated patients from the intent to treat population who had CRP measures available at baseline and at week 12, as well as radiographs available at baseline and week 104. RRP was defined as an increase of >3 units/year in the modified Total Sharp Score (mTSS). Using week 12 data, quartiles (Qs) of CRP absolute values and percent change from baseline (%ΔCRP) were used to assess relationships with RRP following 2 years of treatment.
Results: Overall, RRP was significantly more likely to occur among patients treated with MTX monotherapy (33.5%) than among patients treated with ADA + MTX (6.7%). In the MTX-treated population, there was an association between increasing Qs of %ΔCRP (less improvement) and RRP prevalence; 26.5%, 27.9%, 32.2%, and 48.5% in the Q1 (−98.61 - <−80.34), Q2 (−80.34 - <−61.28), Q3 (−61.28 - <−16.67), and Q4 (−16.67 - +661.36) quartiles, respectively, demonstrated RRP. In contrast, this association was absent in the ADA + MTX population, where the risk of RRP was universally low; 6.7%, 5.2%, 8.0%, and 6.9% in the Q1, Q2, Q3, and Q4 quartiles, respectively, demonstrated RRP. In both treatment groups, lower CRP improvement at week 12 was observed in the majority of patients ultimately identified with RRP at year 2; 84% of the MTX-treated RRP patients and 54% of the ADA + MTX-treated RRP patients exhibited CRP improvement ≤80% after 12 weeks of treatment. Interestingly, increasing Qs of CRP at 12 weeks produced comparable results to those from the %ΔCRP.
Conclusions: CRP changes from baseline to 12 weeks or absolute CRP levels at 12 weeks were associated with the prevalence of RRP. Of note, association of CRP with poor radiographic prognosis applied mainly to patients treated with MTX monotherapy, as RRP rates were low in patients treated with ADA + MTX and CRP changes were not correlative with frequency of RRP during combination therapy. Based on these data, changes in CRP or CRP levels at 12 weeks appear to be useful tools for early identification of MTX-treated patients who will fail to achieve long-term disease control, as evidenced by significant radiographic damage.
Disclosure statement: P.E has receieved research grants, consultancy fees or other remuneration from Abbott, Merck, Pfizer, Roche and Bristol-Myers Squibb. B.G., H.K., N.M. and K.P. are full-time employees of Abbott and may hold Abbott stock or stock options. E.K. has received consultancy fees or other remuneration from Abbott, UCB, Pfizer, Roche, Amgen and Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

216. SAFETY OF SUBSEQUENT BIOLOGIC THERAPY IN RA PATIENTS WHO DISCONTINUED RITUXIMAB

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Background: B cell (CD20+) depletion with rituximab (RTX) may be long lasting, therefore the purpose of this analysis is to describe the rate of serious infection events (SIEs) in patients treated with RTX, who subsequently received a biologic disease-modifying antirheumatic drugs (DMARDs).
Methods: Patients with moderate to severe, active RA receiving RTX + methotrexate who withdrew from clinical studies entered a safety follow-up (SFU). During SFU, peripheral B cell counts were monitored at regular intervals for ≥48 weeks and patients were permitted to receive other biologics. SIEs, defined as serious adverse events or infections that required IV antibiotics, were recorded throughout the SFU.
Results: As of Sept 2009, 3189 RA patients had received ≥1 RTX course, which amounted to 9342 patient-years of follow-up. Overall, SIE rate was 4.35 (95% CI 3.94-4.79) per 100 patient-years. Of patients who entered the SFU, 283 were subsequently treated with another biologic (median time 8.5 [range 0.1-52] months after last RTX infusion); most (n = 230) received TNF inhibitors. Median follow-up after receipt of the subsequent biologic was 11 (range 7-17) months. For the majority of patients (83%), peripheral B cell CD19 levels were depleted below the lower limit of normal (<80 cells/μL) at the time of receiving subsequent biologic. 87 (30.7%) patients received subsequent biologic within 6 months of their last RTX infusion. B cell depletion appeared to have little impact on the emergence of infections with subsequent biologic therapy, as the proportion and rate of SIEs was similar before and after the biologic (Table 1). Median time to SIE after initiating biologic therapy was 11 (range 2-21) months. In 43 patients receiving abatacept post-RTX, there was one SIE before and after this subsequent biologic (total 97.7 patient-years). In general, infections were typical for RA patients with no opportunistic or fatal infections. In a subgroup analysis of 174 patients with very low B cell counts (CD19+ count <20 cells/μL) at the time of receipt of subsequent biologic, SIE rate was 6.28 (95% CI 3.79-10.42) per 100 patient-years. In patients who received biologic <6 months (n = 87) or ≥6 months (n = 196) post-RTX, SIE rates were 5.04 (95% CI 2.26-11.22) and 4.94 (95% CI 2.66-9.18), respectively.
Conclusions: In this updated analysis, the use of subsequent biologics in RA patients previously treated with RTX was not associated with an increase in the rate of serious infections. The rate of serious infections is consistent with rates seen in long-term safety analyses.
Disclosure statement: L.B. is an employee of Roche. A.C. is an employee of Genentech. S.C. has received consultancy fees from Genentech and Biogen Idec. P.E. has received research grants and consultancy fees from Roche and Abbott. M.G. has received research grants from Biogen Idec, Genentech and Roche, and consultancy fees from Biogen Idec and Genentech. E.K. has received consultancy fees from and is a member of speakers' bureaus for Genentech, Biogen Idec and Roche, and has received research grants from Roche. E.M. has received research grants from Biogen Idec and Genentech. W.R. is an employee of Genentech. T.S. is an employee of Roche and may hold Roche stock or stock options. M.S. holds Biogen Idec stock or stock options. All other authors have declared no conflicts of interest.

Table 1. SIEs in patients receiving biologic DMARDs following RTX treatment

	Subsequent biologic post-RTX (n = 283)		TNF inhibitor post-RTX (n = 230)	
	Before biologic	After biologic	Before TNFi	After TNFi
Exposure, patient-years	365.83	321.64	282.16	265.89
No. of SIEs	22	16	17	12
SIE rate per 100 patient-years (95% CI)	6.01 (3.96, 9.13)	4.97 (3.05, 8.12)	6.03 (3.75, 9.69)	4.51 (2.56, 7.95)

217. ANTI-CD3 MAB INDUCES CD8 + FOXP3 + T CELLS FROM THE PBMC OF RA PATIENTS

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Background: The use of anti-CD3 monoclonal antibody (mAb) for the treatment of type 1 diabetes and prevention of transplant rejection has been well studied and linked with the induction of regulatory T cell (Treg) populations in vivo. Based on observations made in a mouse model of rheumatoid arthritis (RA) that anti-CD3 therapy can suppress collagen-induced arthritis (CIA), the aim was to understand its immunomodulatory capacity in the context of RA. Suppression of CIA was associated with the induction of CD8 + Foxp3 + T cells that were capable of regulating Th1 and Th17 responses. CD8 + Foxp3 + T cells constitute less than 1% of peripheral CD8 + T cells in healthy and RA patients; therefore, very little is known about their induction or their ability to regulate immune responses. As anti-CD3 therapy is now about to enter clinical trials for use in RA, we investigated its ability to induce CD8 + Foxp3 + T cells from the peripheral blood mononuclear cells (PBMC) of patients with RA.
Methods: PBMC were co-cultured in vitro with various doses of anti-CD3 mAb. To understand further the conditions required for the induction of CD8 + Foxp3 + T cells, the role of TNF alpha, TGF beta and IL-6 were determined by adding neutralising antibodies to in vitro induction assays. Depletion assays were used to ascertain the origin of the cytokines responsible for the induction of CD8 + Foxp3 + T cells in vivo.
Results: Co-culture of PBMC with low dose anti-CD3 mAb resulted in optimal induction of CD8 + Foxp3 + T cells. These cells did not express the transcription factor Helios, suggesting they are induced and not expanded from pre-existing peripherally derived CD8 + Foxp3 + T cells. Furthermore, they expressed high levels of TNF Receptor 2 (TNFR2) and CD25 and produced negligible amounts of IFN gamma and IL-2. These are characteristics of Tregs rather than activated T cells. Co-culture of RA PBMC with anti-CD3 mAb and anti-TGF beta mAb or anti-IL-6 mAb revealed that neither TGF beta nor IL-6

were required for the induction of CD8 + Foxp3 + T cells. However, long-term cultures suggested that IL-6 may be required for their maintenance. In contrast, blockade of TNF alpha inhibited the induction of CD8 + Foxp3 + T cells by approximately 50% ($P < 0.01$). Culture of PBMC depleted of monocytes with anti-CD3 mAb abolished the production of TNF alpha and the induction of CD8 + Foxp3 + T cells ($P < 0.001$), revealing that the induction of CD8 + Foxp3 + T cells was entirely dependent on the presence of monocytes.

Conclusions: Weak stimulation of PBMC from RA patients with anti-CD3 mAb can potently induce CD8 + Foxp3 + T cells that have a similar phenotype to CD4 + Tregs. Their induction is dependent on the presence of monocytes and the production of TNF alpha. The induction of CD8 + Foxp3 + T cells by anti-CD3 mAb has the potential to be harnessed therapeutically, provides insight into its mechanism of action and could be used as a predictor of patients who will respond successfully to anti-CD3 mAb.

Disclosure statement: The authors have declared no conflicts of interest.

218. THE ROSE STUDY: EFFICACY AND SAFETY OF TOCILIZUMAB IN RA PATIENTS WITH PREVIOUS INADEQUATE RESPONSE TO DMARDS

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Background: Early and aggressive treatment of RA is associated with improved disease outcomes. The 24-week Rapid Onset and Systemic Efficacy (ROSE) study enrolled patients with moderate to severe RA and inadequate response to DMARDs (DMARD-IR) to assess the efficacy of tocilizumab (TCZ) + DMARDs for the reduction of RA signs and symptoms.

Methods: Patients (N = 619) were randomly assigned to receive TCZ 8 mg/kg (n = 412) or placebo (n = 207), in combination with DMARDs, for 24 weeks. Patients were assessed every 4 weeks, with the primary efficacy endpoint ACR50 response at Week 24. A subset of 62 patients was assessed for disease activity at Week 1. Safety and laboratory assessments continued throughout the study.

Results: More patients in the TCZ group achieved the primary endpoint vs patients in the control group (30.1% vs 11.2%, $p < 0.0001$). ACR20 and ACR50 response rates between Weeks 4 and 24 were significantly higher for TCZ patients, while the ACR70 response rate was significantly higher in the TCZ group from Week 8 until Week 24. Significant improvements in RAPID3 scores were evident in the TCZ group from Week 4 to Week 24 and in FACIT-Fatigue scores from Week 8 through Week 24. Early improvements in CRP and Hb in the TCZ group at Week 4 were sustained through Week 24, with significant CRP improvement maintained throughout the study ($p < 0.0001$). TCZ-treated patients assessed at Week 1 demonstrated significant improvements in DAS28, patients' pain and global assessment scores and normalised CRP levels ($p \leq 0.01$ vs control). SAE rates/100PY (95% CI) were 24 (17, 33) in the TCZ group and 19 (11, 31) in the control group. Serious infections occurred in 2.9% and 0.5% of patients in the TCZ and control groups and malignancies were reported in 0.7% and 1.5% of patients. ALT shifts to $> 3 \times$ ULN occurred in 3.2% and 1.1% of TCZ and control patients. Grade 3/4 decreases in neutrophil counts were reported in 2.9% of TCZ patients vs 0% of controls. There were no Grade 3/4 decreases in platelet counts.

Conclusions: Significant benefits of TCZ in reducing disease activity were demonstrated as early as Week 4, with DAS28 improvements as early as Week 1 and sustained improvements over 24 weeks. Safety findings were consistent with the known safety profile of TCZ. These results demonstrate the early and sustained efficacy of TCZ, confirming it as an effective treatment option for DMARD-IR RA patients

Disclosure statement: H.B. has received research grants from Roche. C.C. and R.M. are employees of Genentech, a member of the Roche Group. J.C. has received research grants from Amgen, Inc., Centocor, Inc., Corrona and Roche, consultancy fees from Centocor, Inc., Corrona, Roche and UCB, Inc., and is/has been a member of speakers' bureaus for Roche and UCB, Inc. A.I. is/has been a member of speakers' bureaus for Abbott Laboratories, Amgen, Inc. and Wyeth Pharmaceuticals. A.K. has received consultancy fees from and carried out clinical research on behalf of Roche. Y.Y. has received consultancy fees from Bristol-Myers Squibb, Celgene, Centocor, Corrona, Roche and UCB, has received research grants from Centocor, Corrona and Roche, and is/has been a member of speakers' bureaus for Bristol-Myers Squibb, Roche and UCB.

TABLE 1.

	ACR20			ACR50			ACR70		
Week	TCZ	Control	p	TCZ	Control	p	TCZ	Control	p
4	34.2	17.6	<0.0001	12.5	3.4	0.0002	4.4	1.5	0.0627
8	46.5	25.4	<0.0001	20.8	5.4	<0.0001	6.8	0.5	0.0002
24	44.7	25.4	<0.0001	30.1	11.2	<0.0001	15.4	1.5	<0.0001
	RAPID3 score*			FACIT-fatigue score*			CRP, mg/dl†		
4	−1.27	−0.52	<0.0001	3.97	2.99	0.0152	0.41	1.71	<0.0001
8	−1.70	−0.75	<0.0001	5.71	3.72	0.0110	0.28	1.72	<0.0001
24	−2.30	−1.37	<0.0001	8.49	5.76	0.0188	0.25	1.37	<0.0001

*Adjusted mean change from baseline. †Mean values, p based on change from baseline

219. TARGETING THERAPEUTICS TO ARTHRITIC JOINTS

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Background: The aim of our study is to target anti-inflammatory proteins to arthritic joints, in order to improve efficacy and reduce side-effects of current therapies.

Methods: We chose type II collagen (CII) as a target as it is uniquely present in cartilage. In the arthritic joint, CII is damaged by reactive oxidant species (ROS) generated in the inflammation process. We used ROS-modified CII to select a single chain antibody (scFv) specific to ROS-CII. In order to target therapeutic proteins to the inflamed joints, we have fused anti-ROS-CII scFv to anti-inflammatory proteins via an MMP cleavage site linker. MMPs are up-regulated in arthritis, and therefore when the fusion protein is localised to inflamed areas by the scFv, the therapeutic is liberated, and is free to engage its target.

Results: We were able to demonstrate binding of this scFv, 1-11E to damaged cartilage from rheumatoid arthritis (RA) and osteoarthritis (OA) patients but not to intact cartilage.

Accordingly, imaging studies have shown that fluorescently labelled 1-11E scFv localises specifically to inflamed joints in arthritic mice. 1-11E fused to mTNFR2-Fc is able to bind modified CII in ELISA, and is cleaved at the linker site by incubation with MMP-1. Biological activity of the fusion protein was also demonstrated in vitro. Moreover, we show that by fusing mTNFR2-Fc to 1-11E, the therapeutic efficacy in arthritic mice is enhanced.

Conclusions: We have a proof of principle that therapeutics targeted by anti-ROS-CII to the joints have augmented anti-inflammatory properties. Future work will involve optimising the fusion proteins with a view to development towards the clinic, including targeting alternative therapeutic molecules.

Disclosure statement: The authors have declared no conflicts of interest.

220. LONG-TERM SAFETY OF RITUXIMAB: FOLLOW UP OF THE RHEUMATOID ARTHRITIS CLINICAL TRIALS

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Background: To evaluate the long-term safety of rituximab (RTX) in RA patients (pts).
Methods: Pooled observed case analysis of safety data from pts treated with RTX + methotrexate in a global clinical trial programme. Pts were offered RTX retreatment based on physician decision of clinical need and criteria for retreatment included assessment of active disease (either SJC and TJC ≥8 or DAS28 ≥2.6). Pts who received placebo during placebo-controlled study periods were pooled to provide a placebo population.
Results: As of September 2009, 3189 pts had been treated with RTX providing 9342 pt-yrs exposure. Over 1500 pts were followed for >3 yrs and 587 pts for >5 yrs with 2417, 1724, 1392, 1036 and 656 pts receiving ≥2, ≥3, ≥4, ≥5 and ≥6 courses, respectively; some pts had >9 yrs of follow-up with up to 15 courses of RTX. Other than infusion-related reactions (IRRs), the safety profile of RTX was similar to the placebo population. In RTX pts, the most frequent AEs were IRRs; most were CTC grade 1 or 2 and occurred after the first infusion of the first course (23.0%) with 0.5% considered serious (over all courses). SAE and infection rates generally remained stable over time and over multiple RTX courses, and in pts in long-term follow-up (Table 1). The overall serious infection rate was 4.35 events/100 pt-yrs (3.19 events/100 pt-yrs in pts treated for >5 yrs) and was comparable to that observed in the placebo population (4.29 events/100 pt-yrs). Lower respiratory tract infection, predominantly pneumonia (2%), was the most frequent serious infection. Serious opportunistic infections were rare, with the rates comparable between RTX and placebo (0.04 and 0.1 events/100 pt-yrs, respectively). Rates of myocardial infarction (0.49 events/100 pt-yrs) and stroke (0.25 events/100 pt-yrs) were consistent with rates in the general RA population (0.48-0.59 and 0.51-0.76 events/100 pt-yrs, respectively) [1-4].
Conclusions: In the long-term follow-up of RA pts treated with RTX in clinical trials, no new safety signals were observed in all exposed pts, including pts with >5 yrs of follow-up. RTX has remained well tolerated over time and over multiple courses, with a safety profile similar to that of the pooled placebo population and consistent with published data on pts with moderate to severe RA.
Disclosure statement: C.B. has received research grants from Genetech, Wyeth, Bristol-Myers Squibb and UCB, and consultancy fees from Wyeth, Bristol-Myers Squibb, UCB, Abbott, Cypress Bioscience, Amgen, Genentech, Novartis, Osiris Therapeutics, Roche and Targeted Genetics. P.E. has received research grants from Roche. P.F. is an employee of Genentech. R.F. has received research grants and consultancy fees from Amgen, Abbott, Centocor, UCB, Genentech, Pfizer, Bristol-Myers Squibb and Lexicon, and research grants from Eli Lilly, Celgene, Biogen Idec, Sanofi-Aventis and Regeneron. D.F. has received consultancy fees from Actelion, Gilead, UCB, Genentech, Bristol-Myers Squibb, Abbott, Encysive, Novartis, Nitec, Roche, TAP, Wyeth, Xoma, GlaxoSmithKline, Centocor, Biogen Idec, Array and Amgen, and research grants from Actelion, Gilead, Novartis, Roche, UCB, Genentech, Celgene and Bristol-Myers Squibb. E.K. has received research grants and consultancy fees from Abbott Laboratories, Amgen, Inc., Bristol-Myers Squibb, Centocor, Inc., Schering-Plough Corporation, Wyeth Pharmaceuticals and UCB, and research grants from AstraZeneca Pharmaceuticals, F. Hoffmann-LaRoche, Inc., Novartis Pharmaceuticals and Pfizer. P.L., S.L. and K.M. are employees of Roche. M.S. is an employee of Biogen Idec and may hold stock or stock options. R.V. has received consultancy fees and research grants from Roche.

TABLE 1.

	All exposure (n = 3189)	Long term (> 5 years) (n = 587)	Pooled placebo (n = 818)
Total pt-yrs	9342	3386	979
AE rate/100 pt-yrs (95% CI)	309.4 (305.9, 313.0)	285.1 (279.5, 290.9)	353.1 (341.5, 365.0)
SAE rate/100 pt-yrs (95% CI)	16.2 (15.4, 17.0)	15.5 (14.2, 16.9)	15.5 (13.2, 18.2)
Infection rate/ 100 pt-yrs (95% CI)	94.3 (92.3, 96.3)	83.2 (80.2, 86.3)	100.8 (94.7, 107.3)
Serious infection rate/100 pt-yrs (95% CI)	4.35 (3.94, 4.79)	3.19 (2.64, 3.85)	4.29 (3.17, 5.80)

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221. LITHE THREE-YEAR RESULTS: INHIBITION OF RADIOGRAPHIC PROGRESSION AND IMPROVEMENT IN PHYSICAL FUNCTION WITH TOCILIZUMAB IN RA PATIENTS

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Background: LITHE is a Phase III randomised double-blind study comparing the safety and efficacy of tocilizumab (TCZ) vs placebo (PBO) in patients (pts) with moderate-to-severe active RA and inadequate response to methotrexate (MTX).
Methods: 1,190 pts were randomised to receive TCZ (4 mg/kg [TCZ4] or 8 mg/kg [TCZ8]) or PBO every 4 wks, all with MTX 10-25 mg/wk. In Yr 2 pts could switch to open-label TCZ8. Hand and feet radiographs were analysed by Genant-modified Total Sharp Score (GmTSS) from all pts with baseline (BL), Wk 52, Wk 104, and at least one post-Wk 104 radiograph (linear extrapolation was used if a pt had a post-Wk 104 but not a Wk 152 value). Pooled data are reported for all pts who received ≥1 TCZ dose (All TCZ). Data from the first TCZ dose to 28 Aug 2009 are presented (mean treatment duration 2.43y). LOCF was used for missing TJC/SJCs; no imputation was used for missing HAQ, CRP, ESR and VAS.
Results: The radiographic population consists of ~80% of pts entering Year 3 with a post-Wk 104 assessment (704 pts: 244 TCZ8, 241 TCZ4, 219 PBO). Only 19% of TCZ4 and 9% of PBO pts remained on original treatment at 1 yr. By Yr 3, most pts had received open-label TCZ8 for 2 yrs. Most radiographic progression in the PBO group occurred in the first year. Mean change in GmTSS was 60% lower in patients who had initially received TCZ, and more patients in the TCZ groups had no radiographic progression at 3 years. Signs and symptoms and safety were assessed in 1,149 pts (All TCZ) with 2,790 pt-years' (PY) exposure. ACR response and DAS28 remission rates remained high, demonstrating continued clinical efficacy. The proportion of pts with HAQ scores of <0.5 at Yr 2 was maintained through Yr 3. SAEs and serious infection rates were 11.0 and 3.2/ 100PY; overall deaths and deaths from infections were 0.39 and 0.14/ 100 PY. Malignancies occurred at a rate of 0.7/100PY (solid cancers [0.6/100PY] and non-melanoma skin cancer [n = 1; 0.0/100PY]).
Conclusions: TCZ treatment continued to inhibit radiographic progression. Improvements in physical function and clinical responses were maintained. The safety profile is consistent with the 2-yr analysis.
Disclosure statement: R.B. has received consultancy fees from and is/has been a member of speakers' bureaus for Abbott Laboratories, Pfizer, Inc., Roche, Schering-Plough and Wyeth Pharmaceuticals. J.D. has received consultancy fees from Amgen, Inc., Gebro Pharma, MSD, Pfizer, Inc. and Roche. R.F. has received research grants from Roche. D.F. has received consultancy fees from Abbott Laboratories, Actelion Pharmaceuticals US, Biogen Idec, Bristol-Myers Squibb, Centocor, Inc., GlaxoSmithKline, Merck, Nitec, Novartis Pharmaceuticals, Amgen, Genentech, Gilead, Xoma, Roche, UCB and Wyeth Pharmaceuticals, research grants from Abbott Laboratories, Actelion Pharmaceuticals US, Amgen, Inc., Bristol-Myers Squibb, Gilead Sciences, Novartis Pharmaceuticals,

Genentech, UCB and Wyeth Pharmaceuticals, and is employed by Corrona. J.K. has received research grants and consultancy fees from Genetech and Roche. C.M. and E.V. are employees of Roche.

TABLE 1. Outcomes, Week 152

GmTSS	TCZ8 n = 244	TCZ4 n = 241	Control n = 219
Mean (S.D.) change from BL	0.72 (2.56)*,†	0.71 (2.14)†,‡	1.78 (3.64)
Pts with no progression (GmTSS change from BL ≤ 0), % (n)	69 (169)*,§	67 (162)§,‖	51 (111)
Signs and Symptoms		All TCZ	
ACR20, % (n/n)		80 (472/591)	
ACR50, % (n/n)		59 (346/591)	
ACR70, % (n/n)		36 (212/591)	
DAS28 remission, % (n/n)		57 (325/572)	
TJC and SJC = 0, % (n/n)		21 (137/656)	
HAQ < 0.5 % (n/n)		37 (202/552)	

n/n: no. patients achieving end point/no. patients reaching timepoint with valid assessments. *$p < 0.0001$ vs control. †p calculated by Van Elteren test stratified by region. ‡$p = 0.0002$ vs PBO. §p calculated by logistic regression analysis adjusted for region. ‖$p = 0.0008$ vs control.

222. PEPTIDYLARGININE DEIMINASE FROM PORPHYROMONAS GINGIVALIS AS A POTENTIAL TARGET FOR THE TREATMENT AND PREVENTION OF RHEUMATOID ARTHRITIS

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Background: Porphyromonas gingivalis (P. gingivalis) is a major bacterium in the pathogenesis of periodontitis. Several epidemiological studies have shown an association between periodontitis and rheumatoid arthritis (RA). We demonstrated cross-reactivity between citrullinated human α-enolase and P. gingivalis enolase, and that the anti-citrullinated α-enolase response links with DR4 alleles and smoking, common susceptibility factors for RA and periodontitis. Recently, we reported that P. gingivalis peptidylarginine deiminase (PPAD) catalyses the citrullination of carboxy-terminal arginines to citrulline, in both bacterial and human peptides. Bacterial citrullination might therefore be aetiologically important in a subset of RA by driving the autoimmune response to citrullinated proteins. Hence, we investigated the PPAD enzyme as a potential new therapeutic target.
Methods: Recombinant full-length PPAD was expressed in E. coli, purified, and tested for enzymatic activity. A specific antibody to PPAD was developed by immunising rabbits with recombinant protein. The subcellular localisation of PPAD was investigated by fractionation of P. gingivalis and blotting with anti-PPAD antibody. Cross-reactivity with human PADs was examined by western blot. PPAD inhibition studies were performed using tetracycline, doxycycline, minocycline, sulfasalazine, methotrexate, and 2-chloroacetamidine. Site-directed mutagenesis was performed to investigate the contribution of a conserved cysteine residue to enzyme activity.
Results: Full-length PPAD was active and citrullinated α-enolase and fibrinogen peptides harbouring carboxy-terminal arginines, but not peptides with internal arginines. Blotting of subcellular fractions with a PPAD-specific antibody demonstrated that the enzyme is located on the cell surface of various P. gingivalis strains. Anti-PPAD antibody did not cross-react with human PADs. 2-chloroacetamidine proved an effective inhibitor with half-maximal inhibition (IC50) at ~25 μM. Tetracycline, doxycycline, minocycline, sulfasalazine or methotrexate did not inhibit PPAD activity. The substitution of cysteine-351 with alanine completely abolished PPAD activity.
Conclusions: The cell-surface localisation identifies PPAD as a putative virulence factor and suitable pharmaceutical target. Cysteine-351 as a crucial catalytic residue indicates that agents targeting cysteines can be effective inhibitors. This is confirmed by the inhibitory activity of 2-chloroacetamidine in the low μM-range. Our combined results suggest that PPAD and human PADs have different three-dimensional structures but share a similar, although not identical, catalytic mechanism. Our findings form the basis for further characterisation, such as crystallisation and the development of more potent and specific inhibitors with the potential to prevent RA by inhibiting the generation of the autoantigens which drive the disease.
Disclosure statement: The authors have declared no conflicts of interest.

Scleroderma and related disorders

223. LONG TERM OUTCOME IN A CONTEMPORARY SYSTEMIC SCLEROSIS COHORT

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Background: We have previously compared outcome in two groups of systemic sclerosis (SSc) patients with disease onset a decade apart and we reported data on 5 year survival and cumulative incidence of organ disease in a contemporary SSc cohort. The present study examines longer term outcome in an additional cohort of SSc followed for 10 years.
Methods: We have examined patients with disease onset between years 1995 and 1999 allowing for at least 10 years of follow-up in a group that has characteristics representative for the patients we see in contemporary clinical practice.
Results: Of the 398 patients included in the study, 252 (63.3%) had limited cutaneous (lc) SSc and 146 (36.7%) had diffuse cutaneous (dc) SSc. The proportion of male patients was higher among the dcSSc group (17.1% v 9.9%, $p = 0.037$) while the mean age of onset was significantly higher among lcSSc patients (50 ± 13 v 46 ± 13 years ± SD, $p = 0.003$).

During a 10 year follow-up from disease onset, 45% of the dcSSc and 21% of the lcSSc subjects developed clinically significant pulmonary fibrosis, $p < 0.001$. Among them approximately half reached the endpoint within the first 3 years (23% of dcSSc and 10% of lcSSc) and over three quarters within the first 5 years (34% and 16% respectively). There was a similar incidence of pulmonary hypertension (PH) in the two subsets with a steady rate of increase over time. At 10 years 13% of dcSSc and 15% of lcSSc subjects had developed PH (p=0.558), with the earliest cases observed within the first 2 years of disease. Comparison between subjects who developed PH in the first and second 5 years from disease onset demonstrated no difference in demographic or clinical characteristics, but 5-year survival from PH onset was better among those who developed this complication later in their disease (49% v 24%), with a strong trend towards statistical significance ($p = 0.058$). Incidence of SSc renal crisis (SRC) was significantly higher among the dcSSc patients (12% v 4% in lcSSc, $p = 0.002$). As previously observed, the rate of development of SRC was highest in the first 3 years of disease-10% in dcSSc and 3% in lcSSc. All incidences of clinically important cardiac disease developed in the first 5 years from disease onset (7% in dcSSc v 1% in lcSSc, $p < 0.001$) and remained unchanged at 10 years. As expected, 10-year survival among lcSSc subjects was significantly higher (81%) compared to that of dcSSc patients (70%, $p = 0.006$). Interestingly, although over the first 5 years the death rate was much higher in the dcSSc cohort (16% v 6% in lcSSc), over the following years it became very similar for both subsets (14% and 13% between years 5 and 10, and 18% and 17% between years 10 and 15 for dcSSc and lcSSc respectively).
Conclusions: Even though dcSSc patients have higher incidence for most organ complications compared to lcSSc subjects, the worse survival among them is mainly due to higher early mortality rate. Mortality rate after first 5 years of disease becomes comparable in the two disease subsets.
Disclosure statement: The authors have declared no conflicts of interest.

224. SYSTEMIC SCLEROSIS MANAGEMENT: ARE WE DOING AS WELL AS WE COULD?

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Background: 2009 EULAR guidelines set clear standards for the treatment of systemic sclerosis (SSc). We wanted to assess our