OPEN ACCESS

EXTENDED REPORT

Clinical and radiographic outcomes at 2 years and the effect of tocilizumab discontinuation following sustained remission in the second and third year of the ACT-RAY study

T W J Huizinga,[1] Philip G Conaghan,[2] Emilio Martin-Mola,[3] Georg Schett,[4] Howard Amital,[5] Ricardo M Xavier,[6] Orrin Troum,[7] Maher Aassi,[8] Corrado Bernasconi,[8] Maxime Dougados[9]

Handling editor Tore K Kvien

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2014-205752).

For numbered affiliations see end of article.

Correspondence to
Professor T W J Huizinga, Department of Rheumatology, Leiden University Medical Center, PO Box 9600, Leiden 2300 RC, The Netherlands; t.w.j.huizinga@lumc.nl

Received 15 April 2014
Revised 21 July 2014
Accepted 10 August 2014
Published Online First 28 August 2014

To cite: Huizinga TWJ, Conaghan PG, Martin-Mola E, *et al*. *Ann Rheum Dis* 2015;**74**:35–43.

ABSTRACT

Objective To assess the efficacy and safety of tocilizumab (TCZ) plus methotrexate/placebo (MTX/PBO) over 2 years and the course of disease activity in patients who discontinued TCZ due to sustained remission.

Methods ACT-RAY was a double-blind 3-year trial. Patients with active rheumatoid arthritis despite MTX were randomised to add TCZ to ongoing MTX (add-on strategy) or switch to TCZ plus PBO (switch strategy). Using a treat-to-target approach, open-label conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), other than MTX, were added from week 24 if Disease Activity Score in 28 joints based on erythrocyte sedimentation rate (DAS28-ESR) >3.2. Between weeks 52 and 104, patients in sustained clinical remission (DAS28-ESR <2.6 at two consecutive visits 12 weeks apart) discontinued TCZ and were assessed every 4 weeks for 1 year. If sustained remission was maintained, added csDMARDs, then MTX/PBO, were discontinued.

Results Of the 556 randomised patients, 76% completed year 2. Of patients entering year 2, 50.4% discontinued TCZ after achieving sustained remission and 5.9% achieved drug-free remission. Most patients who discontinued TCZ (84.0%) had a subsequent flare, but responded well to TCZ reintroduction. Despite many patients temporarily stopping TCZ, radiographic progression was minimal, with differences favouring add-on treatment. Rates of serious adverse events and serious infections per 100 patient-years were 12.2 and 4.4 in add-on and 15.0 and 3.7 in switch patients. In patients with normal baseline values, alanine aminotransferase elevations >3×upper limit of normal were more frequent in add-on (14.3%) versus switch patients (5.4%).

Conclusions Treat-to-target strategies could be successfully implemented with TCZ to achieve sustained remission, after which TCZ was stopped. Biologic-free remission was maintained for about 3 months, but most patients eventually flared. TCZ restart led to rapid improvement.

Trial registration number NCT00810199.

INTRODUCTION

International task force recommendations state that treatment of patients with rheumatoid arthritis (RA) should aim to reach a target of remission or low-disease activity in as short a time as possible.[1 2] Remission should represent the absence of inflammation and no advancement of joint deterioration. The newly updated European League Against Rheumatism (EULAR) recommendations for the management of RA emphasise the importance of using a treat-to-target approach. The EULAR Task Force suggests that in cases of persistent remission, after tapering glucocorticoids, patients and physicians may decide together to titrate the dose of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or consider tapering biological DMARDs.[2] Initial data suggest that patients who have achieved and maintained remission may be able to discontinue biological treatment[3–6]; however, clinical trial definitions of remission and flare differ, discouraging meaningful comparisons across studies.

ACT-RAY is a 3-year phase 3b randomised clinical trial in patients with moderate-to-severe RA who have an inadequate response to methotrexate (MTX). The first 24 weeks of ACT-RAY evaluated the safety and efficacy of adding tocilizumab (TCZ) to ongoing MTX (add-on strategy) versus switching to TCZ monotherapy (switch strategy), with results of the primary efficacy analysis at week 24 demonstrating that the add-on strategy was not statistically superior to the switch strategy.[7] From week 24 through year 3, ACT-RAY employed a treat-to-target strategy, where all patients continued on TCZ therapy+blinded MTX/placebo (PBO) but could add open-label csDMARDs based on disease activity.[8] After week 52, the open-label treat-to-target strategy was adapted based on response where study medication could be tapered, continued, intensified or maintained with the goal of achieving drug-free remission. This article reports on secondary objectives of the ACT-RAY study concerning the 2-year and 3-year results.

PATIENTS AND METHODS

Study design

Patients

This report covers the planned analysis for the 2-year and 3-year results of the double-blind, PBO-controlled, parallel-group clinical trial (NCT00810199, EudraCT No. 2008-001847-20; figure 1A). This study was approved by all institutional review boards and/or ethics committees.

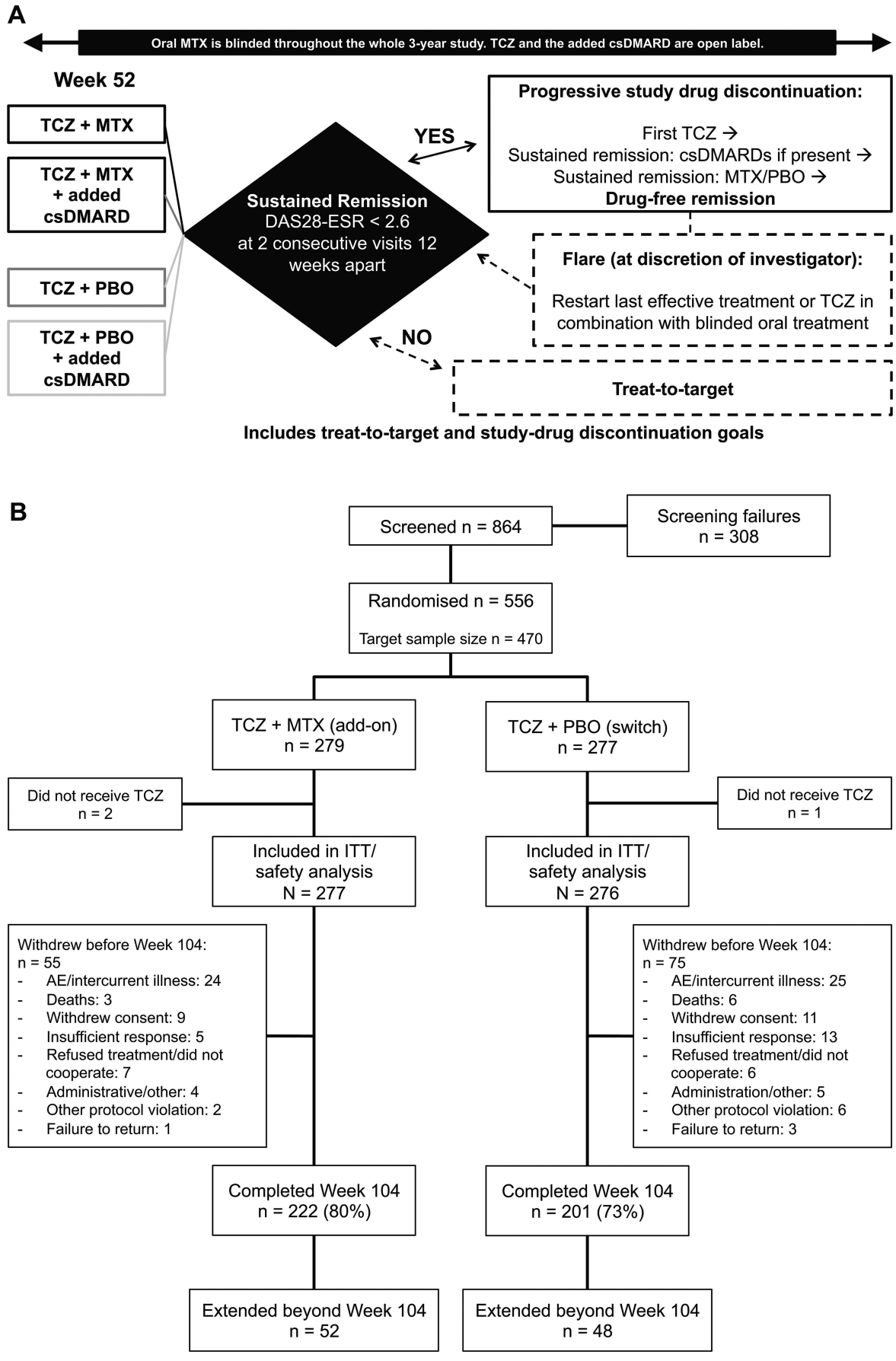

Figure 1 (A) Schematic of study design and (B) patient disposition through 3 years. AE, adverse event; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate; ITT, intent-to-treat population; MTX, methotrexate; OL, open-label; PBO, placebo; TCZ, tocilizumab.

Eligibility criteria have been previously described.[7 8] Briefly, patients had RA according to the 1987 American College of Rheumatology (ACR) classification criteria with moderate-to-severely active disease defined as Disease Activity Score in 28 joints based on erythrocyte sedimentation rate (DAS28-ESR) >4.4 at baseline and an inadequate response to a stable dose of MTX (≥15 mg/week for ≥6 weeks). Major exclusion criteria included severe comorbidities, prior use of any biologics and use of csDMARDs other than MTX 1 month (3 months for leflunomide) before the baseline visit.

Study treatment

Treatment strategies during the first 52 weeks of ACT-RAY have been previously described.[7 8] Briefly, during the first 24 weeks, all patients were randomised either to continue oral MTX with the addition of open-label TCZ 8 mg/kg intravenously every 4 weeks (add-on strategy) or switch to TCZ alone with PBO (switch strategy). Between weeks 24 and 52, treatment with TCZ plus blinded MTX/PBO continued unchanged; however, if DAS28-ESR was >3.2 at week 24, an open-label csDMARD (sulfasalazine, leflunomide, hydroxychloroquine or azathioprine; choice and dose at investigator's discretion) was added. If DAS28-ESR was >3.2 at week 36 with an added csDMARD, the patient was moved to the maintenance arm (TCZ+blinded MTX/PBO+open-label csDMARD) for the remainder of the study, with the option to receive an additional open-label csDMARD per the investigator's discretion.

Between weeks 52 and 104, open-label treatment was adapted based on response every 12 weeks, and patients continued the study in one of four treat-to-target strategies (see online supplementary figure S1):

1. Treatment tapering: If DAS28-ESR was <2.6 at two consecutive assessment visits 12 weeks apart, TCZ was discontinued at the second assessment visit (TCZ-free remission). If DAS28-ESR was <2.6 over two consecutive assessment visits after discontinuation of TCZ, for patients on an open-label csDMARD, the added csDMARD was stopped; for patients without added csDMARDs, the blinded oral treatment was stopped, and drug-free remission was achieved. For patients with an added csDMARD, drug-free remission could be achieved after an additional two assessment visits with DAS28-ESR <2.6. In patients who experienced flare, defined at the investigator's discretion, the last effective treatment or TCZ in combination with blinded oral treatment was restarted.
2. Continued treatment: If DAS28-ESR was ≥2.6 and ≤3.2, treatment was continued as before.
3. Treatment intensification: If DAS28-ESR was >3.2, an open-label csDMARD was added if the patient had not yet received an open-label csDMARD. If the patient received an open-label csDMARD at the previous assessment visit, treatment was continued unchanged.
4. Maintenance: If DAS28-ESR was >3.2 and an open-label csDMARD was added at each of two consecutive visits, the patient switched to TCZ 8 mg/kg every 4 weeks plus blinded MTX/PBO plus the added csDMARD. An additional (third) csDMARD may have been added at the discretion of the investigator. Patients receiving maintenance therapy did not receive step-up or step-down treatment and were treated according to the investigator's discretion.

For patients who stopped TCZ due to sustained remission before week 100, the study continued for 52 weeks after TCZ discontinuation. All other patients completed treatment at week 100. Patients returned 4 weeks after completion of the treatment for a safety follow-up visit.

Oral corticosteroids were permitted if the dose was ≤10 mg/day (prednisone or equivalent) and stable for ≥25 out of 28 days prior to the start of study treatment. The corticosteroid dose was not to be changed during the first 24 weeks of the study, but could be reduced stepwise by 2.5 mg/day beginning at any visit thereafter. The dose could not be reduced to <5 mg/day in the first year.

Collected patient data and assessments

Clinical and laboratory data were collected at baseline and every 4 weeks thereafter.[7] Radiographs of hands/wrists and feet were obtained at baseline and weeks 24, 52 and 104 and were assessed by applying the Genant-modified Sharp Score (GSS) from two independent readers (Perceptive Informatics Medical Imaging Services, Berlin, Germany) who were blinded to treatment assignment, chronological order of radiographs and the patient's clinical status. Two reading campaigns were performed, one for baseline, week 24 and week 52, and one for baseline and week 104. The smallest detectable change (SDC) for GSS was computed based on the observed SD of difference between the three X-ray readers in total participating in the campaign;[9] SDC for total GSS was defined as 2.1 at week 104. Adverse events (AEs) and laboratory values were monitored at each visit. The detailed risk mitigation strategy for patients with elevated liver enzymes has been previously described.[8]

Statistical analysis

Efficacy analyses were performed in the intent-to-treat (ITT) population (randomised patients who received ≥1 administration of study medication) with non-responder imputation of missing data used for binary response variables (eg, DAS28-ESR remission and ACR response). The primary endpoint at 24 weeks has been previously reported.[7] Secondary endpoints included rate and time to TCZ-free and drug-free remission, time to flare after TCZ-free remission and time to restart of treatment after TCZ-free remission.

Radiographic endpoints included progression of joint destruction based on the GSS at weeks 24, 52 and 104, as well as absolute change from baseline in total GSS, erosion and joint space narrowing (JSN). Time to events were analysed using the Kaplan–Meier method, and comparisons between the two treatment groups were performed using the log-rank test. Analyses of covariance models were used for continuous measures (eg, ACR core components, disease activity indices and GSS measures). Binary and categorical response variables were analysed using a logistic regression model similar to that used for the primary analysis. All tests were exploratory and conducted at the 5% statistical significance level.

Safety endpoints included the incidence of AEs, serious AEs (SAEs), serious infections (SIs) and specific laboratory abnormalities, which were analysed in the safety population (all treated patients with ≥1 postbaseline safety assessment, analysed according to the treatment received).

RESULTS

Patient disposition and baseline demographics

Figure 1B summarises the patient disposition through 104 weeks and beyond. Of the 556 randomised patients enrolled at 118 centres, 553 received ≥1 dose of TCZ and blinded MTX/PBO (ITT population). A comparable proportion of patients in both treatment groups received their first or second open-label csDMARD at week 24 or later (see online

supplementary table S1). By week 100, a total of 134 patients (48.4%) in the add-on arm and 147 patients (53.3%) in the switch arm had added a first or second open-label csDMARD. Of the 553 patients included in the ITT population, 138 prematurely discontinued study treatment due to safety (60 patients (10.8%)) or non-safety reasons (78 patients (14.1%)). The proportion of patients who withdrew for safety reasons was similar between the add-on and switch treatment groups (10.1% and 11.6%, respectively); however, a larger proportion of patients in the switch arm withdrew for non-safety reasons (eg, insufficient therapeutic response, failure to return, refused treatment, other protocol violation, withdrew consent and other) compared with patients in the add-on arm (17.8% vs 10.5%). Of the patients who withdrew for non-safety reasons, 14 (5.1%) patients in the switch group and 5 (1.8%) patients in the add-on group withdrew due to insufficient response. Baseline characteristics were similar between treatment groups, except patients in the add-on group had lower baseline GSSs compared with patients in the switch group (table 1).

TCZ-free remission and flare

Of the 472 patients remaining in the study at week 52, 238 (50.4%) achieved TCZ-free remission by week 104, with no significant difference between treatment groups (129 (53.1%) add-on vs 109 (47.6%) switch patients; p=0.170). The median time to TCZ-free remission was 645 days for the add-on group and 786 days for the switch group (figure 2A). Of the 238 patients who achieved TCZ-free remission, 28 (11.8%) achieved total drug-free remission—subsequent discontinuation of open-label csDMARD and blinded oral treatment due to sustained achievement of DAS28-ESR <2.6. A significantly higher proportion of patients in the add-on arm achieved drug-free remission compared with patients in the switch arm (21/243 (8.6%) vs 7/229 (3.1%); p=0.010).

A total of 200 patients subsequently flared following TCZ-free remission, with 82.5% (95% CI 75.4% to 88.5%) and 88.5% (95% CI 81.5% to 93.7%) of patients in the add-on and switch arms, respectively, experiencing flare within 52 weeks after achieving TCZ-free remission. The median time to flare following TCZ-free remission was 113 days in the add-on group compared with 84 days in the switch group (figure 2B). In patients who flared after TCZ-free remission, the mean (SD) DAS28-ESR score steadily increased from 1.82 (0.79) at 12 weeks before flare to 2.38 (0.96) at the visit before flare to 4.37 (1.12) at the time of flare (4.33 for add-on patients, 4.40 for switch patients at time of flare; p=0.098). Mean (SD) tender joint count using 68 joints (TJC (68)) increased from 1.8 (0.8) at 12 weeks before flare to 9.1 (8.8) at the time of flare. Mean (SD) patient global assessment of disease activity also increased from 13.1 (15.2) at 12 weeks before flare to 34.4 (21.9) at the time of flare. The majority of patients (n=186; 94 add-on patients and 92 switch patients) restarted TCZ in response to flare following TCZ-free remission. Patients demonstrated rapid improvements in DAS28-ESR after restarting TCZ, with mean (SD) DAS28-ESR decreasing to 3.01 (1.25), 2.42 (1.18) and 2.19 (1.04), respectively, at three consecutive visits after the flare (figure 2C). The proportion of patients with moderate (DAS28-ESR >3.2 to ≤5.2) or high (DAS28-ESR >5.2) disease activity was 29.7% (52/175), 18.6% (32/172) and 11.7% (19/163), respectively, at three visits following TCZ restart.

Table 1 Patient baseline demographics and clinical characteristics

	Add-on (N=277)	Switch (N=276)
Female, n (%)	227 (81.9)	217 (78.6)
White, n (%)	258 (93.1)	253 (91.7)
Age, mean (SD), years	53.0 (13.4)	53.6 (11.9)
Aged ≥65 years, n (%)	53 (19.1)	52 (18.8)
BMI, mean (SD), kg/m^2	26.3 (5.2)	26.5 (5.1)
Duration of RA, mean (SD), years	8.2 (8.0)	8.3 (8.4)
Categorical duration of RA in years, n (%)		
<2	51 (18.4)	66 (23.9)
2 to <5	76 (27.4)	68 (24.6)
5 to <10	66 (23.8)	63 (22.8)
≥10	84 (30.3)	79 (28.6)
SJC (66), mean (SD)	14.4 (8.9)	15.3 (10.2)
TJC (68), mean (SD)	25.8 (13.9)	26.6 (15.2)
DAS28-ESR, mean (SD)	6.33 (0.98)	6.36 (1.00)
HAQ-DI, mean (SD)	1.46 (0.65)	1.48 (0.60)
GSS,* mean (SD)	36.9 (33.2)	41.2 (40.0)
Annualised progression rate,* mean, units/year	4.50	4.95
MTX dose, mean (SD), mg/week	16.2 (4.4)	16.6 (4.9)
No. of previous csDMARDs (including MTX) prior to study entry, mean (SD)	1.9 (1.1)	1.9 (1.0)
Oral steroid use, n (%)	140 (50.5)	140 (50.7)
Oral steroid dose (prednisone equivalents), median, mg/day	5.0	5.0
Oral steroid dose (prednisone equivalents), mean (SD), mg/day	6.88 (2.7)	6.69 (2.5)

*Campaign 2: X-ray assessments at baseline and week 104.
BMI, body mass index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate; GSS, Genant-modified Sharp Score; HAQ-DI, Health Assessment Questionnaire Disability Index; MTX, methotrexate; RA, rheumatoid arthritis; SJC (66), swollen joint count using 66 joints; TJC (68), tender joint count using 68 joints.

Efficacy outcomes and radiographic progression through week 104

The week 104 efficacy results are summarised in table 2. Overall efficacy was stable after week 52 in both groups despite nearly 50% of patients discontinuing TCZ treatment.

At week 104, the majority of patients demonstrated minimal progression of radiographic structural damage, with differences favouring the add-on group (table 2, figure 3A). The adjusted mean change in total GSS was 0.35 for add-on and 0.95 for switch (p=0.034) and the adjusted mean change from baseline in erosion score was −0.03 for add-on and 0.26 for switch (p=0.037). There was no statistically significant difference between add-on and switch groups in mean change from baseline to week 104 for the JSN score. The SDC from baseline to week 104 in total GSS was 2.1, allowing for detection of changes from baseline >2.1 and <−2.1. When radiographic progression was defined as ΔGSS >SDC at week 104, 94.4% of add-on patients and 91.1% of switch patients did not exhibit radiographic progression (p=0.098). Similar proportions and trends were observed for JSN and erosion scores. The cumulative distribution plot of change from baseline to week 104 in total GSS is shown in figure 3B.

Corticosteroid use

Of patients who received corticosteroids, mean (SD) corticosteroid dose (prednisone or equivalent) decreased from 6.88 (2.7) mg/day at baseline to 6.17 (2.8) mg/day at week 104 in the add-on group and 6.69 (2.5) mg/day at baseline to 5.77 (2.5) mg/day at week 104 in the switch group. Further, the proportion of patients receiving a dose of >7.5 mg/day decreased from

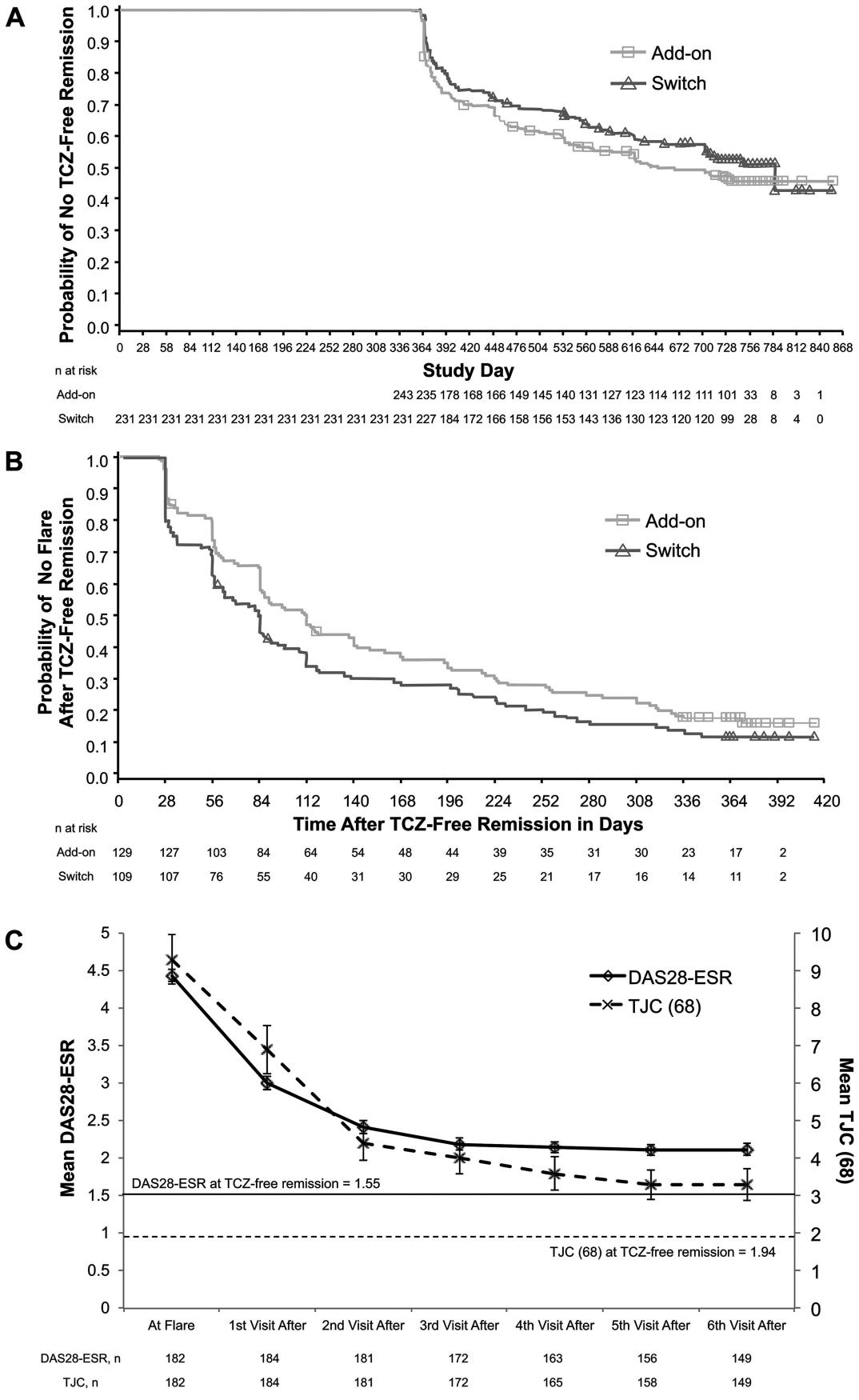

Figure 2 Kaplan–Meier plots of (A) time to TCZ-free remission and (B) time to flare after TCZ-free remission. (C) Evolution of mean DAS28-ESR and TJC (68) after reinitiation of TCZ in patients who restarted TCZ after flare. Error bars represent SD. DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate; TCZ, tocilizumab; TJC (68), tender joint count using 68 joints.

Table 2 Summary of efficacy results at week 104—ITT population

	Week 104		
	Add-on (N=277)	Switch (N=276)	p Value*
DAS28-ESR remission rate, %	38.3	35.1	0.452
Change in DAS28-ESR, mean (SD)	−3.60 (1.47)	−3.61 (1.43)	0.934
EULAR good/moderate responders, %	75.8	66.7	0.056
ACR/EULAR Boolean remission rate, %	14.8	9.4	0.048
SDAI remission rate (≤3.3), %	22.0	19.9	0.627
CDAI remission rate (≤2.8), %	22.7	18.1	0.203
Change in TJC (68), mean (SD)	−20.3 (13.7)	−20.4 (15.1)	0.672
Change in SJC (66), mean (SD)	−12.7 (9.0)	−12.6 (10.3)	0.583
Change in patients' global assessment of disease activity, mean (SD)	−42.1 (25.2)	−41.6 (25.0)	0.743
Change in physicians' global assessment of disease activity, mean (SD)	−46.5 (20.6)	−46.5 (21.2)	0.970
Change in patients' global assessment of pain, mean (SD)	−36.3 (27.2)	−38.1 (24.9)	0.745
Change in RAQoL, mean (SD)	−6.89 (8.69)	−5.24 (8.90)	0.167
Change in HAQ-DI, mean (SD)	−0.67 (0.71)	−0.69 (0.59)	0.833
Change in ESR, mean (SD)	−28.0 (25.0)	−27.2 (26.0)	0.684
Change in CRP, mean (SD)	−1.16 (2.03)	−1.24 (2.34)	0.597
Change in total GSS, adjusted mean (SEM)	0.35 (0.35)	0.95 (0.32)	0.034
Change in JSN score, adjusted mean (SEM)	0.38 (0.22)	0.70 (0.20)	0.078
Change in erosion score, adjusted mean (SEM)	−0.03 (0.17)	0.26 (0.16)	0.037
Patients with no progression in GSS (≤2.1), %	94.4	91.1	0.098

*Between group p values.
ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; GSS, Genant-modified Sharp Score; HAQ-DI, Health Assessment Questionnaire Disability Index; JSN, joint space narrowing; RAQoL, Rheumatoid Arthritis Quality of Life Questionnaire; SDAI, Simplified Disease Activity Index; SEM, SE of the mean; SJC (66), swollen joint count using 66 joints; TJC (68), tender joint count using 68 joints; ITT, intent-to-treat.

35.0% and 29.4% at baseline to 28.6% and 17.9% at week 104 in the add-on and switch groups, respectively, and the proportion of patients receiving a dose of ≤2.5 mg/day increased from 7.1% and 6.6% at baseline to 15.2% and 17.9% at week 104 in the add-on and switch groups, respectively.

Safety

The overall safety profile was similar for both treatment groups (table 3). The frequencies of AEs, SAEs and discontinuations due to AEs were similar between the two treatment groups. There were 10 deaths in the study, including four in the add-on group and six in the switch group (see online supplementary table S2). Overall, SIs occurred at low rates but were numerically higher in the add-on group compared with the switch group (4.4 per 100 patient-years (PY) vs 3.7 per 100 PY, respectively), with three patients in the add-on group each experiencing one opportunistic infection (disseminated tuberculosis, gastrointestinal candidiasis and fungal oropharyngitis). The treatment groups had similar changes in laboratory parameters, including decreased neutrophil, platelet and white blood cell counts; however, the add-on group had a higher proportion of patients with elevation of alanine aminotransferase >3×upper limit of normal than the switch group (14.3% vs 5.4%, respectively).

DISCUSSION

The good clinical efficacy and inhibition of structural damage progression and comparable safety shown in both add-on and switch treatment groups through weeks 24 and 52 of ACT-RAY were maintained through years 2 and 3. The EULAR Task Force recommends the use of all biologics in combination with MTX[2]; however, registry data estimate that approximately one-third of patients are receiving biologics as monotherapy.[10–13] In cases of intolerance to MTX or where continued use of MTX is no longer appropriate, TCZ has supportive evidence to be superior to MTX or other csDMARDs.[14–16] The findings from ACT-RAY provide physicians with further information when considering treatment options for patients requiring biological monotherapy. Patients in persistent remission after tapering glucocorticoids may consider tapering the dose of biologics and csDMARDs.

In ACT-RAY, treat-to-target strategies could be successfully used in patients with an inadequate response to MTX (whether or not currently on MTX) to achieve sustained remission, while a subsequent step-down approach enabled some patients to reach biologic-free or all study drug-free remission. Patients in the switch group were less likely to achieve TCZ-free remission compared with patients in the add-on group; however, analyses that compare elements of the treat-to-target strategy (eg, time to flare) between the treatment groups should be interpreted with care as confounding factors cannot be excluded. The treatment groups may differ slightly at the initial time point of this analysis with respect to disease activity, concomitant medication or time in the study. To reduce variability in background levels of prednisone that patients received during the first year, patients were required to maintain a dose of ≥5 mg/day; however, this study began before recommendations for the management of RA were published, which state that low-dose glucocorticoids should be considered part of the initial treatment strategy, but should be tapered as rapidly as clinically feasible.[2]

The treatment step-down approach in patients who achieved sustained remission (first TCZ discontinuation, then subsequent open-label csDMARDs and blinded MTX/PBO discontinuation) was associated with a high flare risk. Median time to flare, defined at the investigator's discretion, was longer in add-on patients compared with switch patients; however, patients in

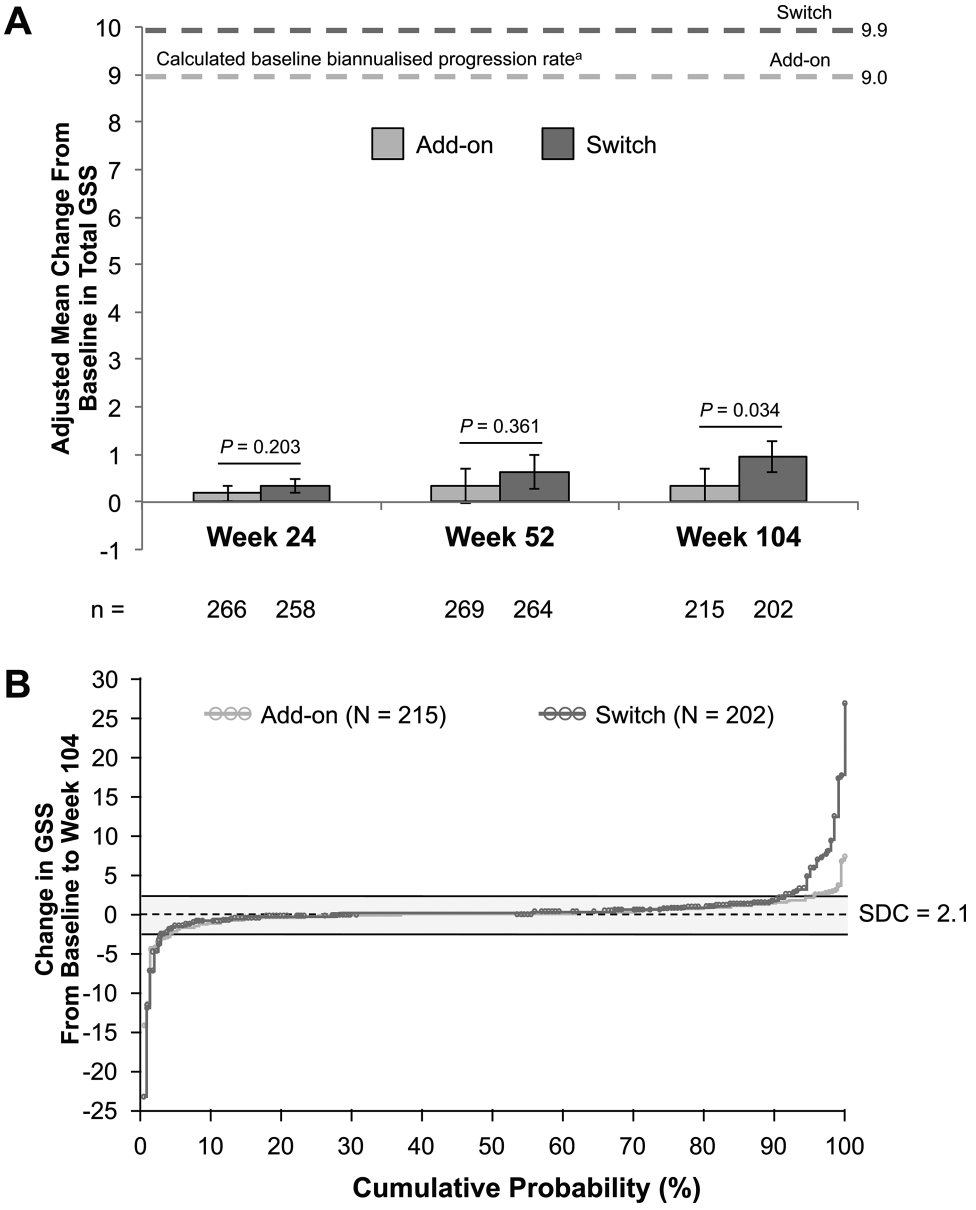

Figure 3 Radiographic results. (A) Mean change from baseline to weeks 24, 52 and 104 in total GSS and (B) cumulative distribution plot of change from baseline to week 104 in total GSS. Area between grey lines is within the SDC for GSS (2.1). [a]Baseline biannualised progression rate was 2×baseline GSS divided by RA duration. Error bars represent the SE of the mean. p Values are from an ANCOVA adjusting for baseline DAS28-ESR, baseline GSS and region. Missing week 52 data were imputed by linear extrapolation if baseline and week 24 values were present. For the week 104 analysis, no imputation of missing data was performed. ANCOVA, analyses of covariance; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate; GSS, Genant-modified Sharp score; RA, rheumatoid arthritis; SDC, smallest detectable change.

both groups who restarted TCZ therapy after a flare achieved rapid improvements in DAS28-ESR and TJC (68). In ACT-RAY, drug discontinuation was not blinded, and the diagnosis of flare was left up to the investigator and closely monitored. Findings from studies of antitumour necrosis factor-α agent withdrawal were rather variable,[3 17–20] which may be attributed to large design differences among studies concerning the conditions leading to withdrawal and the assessment of flare.

Progression of structural X-ray damage was small in both groups, with differences favouring patients in the add-on arm at week 104. These results were consistent with those seen at week 52, with a small percentage of patients benefiting from receiving continuous MTX treatment in the add-on arm.[8]

Overall, the safety findings were similar to previous studies, and no new safety issues were observed. Safety outcomes were similar between both groups at week 104, except patients in the add-on group exhibited numerically higher rates of elevated transaminase levels than patients in the switch group, consistent with week 24 and week 52 results.[7 8] The rates of AEs, SAEs and SIs were comparable between the two treatment groups and consistent with previous clinical studies of TCZ.[21 22]

Taken together, these results demonstrated that the add-on and switch treatment strategies were comparable to achieve clinical remission at week 24 and maintain clinical and radiological benefits through week 104, with combination therapy being preferred; however, TCZ as monotherapy is a viable option in some patients who cannot or do not take MTX. In agreement with EULAR recommendations, the addition of TCZ to MTX may provide added benefit for patients who are able to tolerate MTX.[2] Treat-to-target strategies, in addition to TCZ treatment,

Table 3 Overview of adverse events, deaths and shift from normal at baseline to worst elevations in liver enzymes through the end of study

	Add-on (N=277)	Switch (N=276)
Total TCZ exposure, PY	433.34	431.24
AEs		
Total patients with ≥1 AE, % (n)	89.5 (248)	88.4 (244)
Total no. of AEs	1762	1558
Rate of AEs (95% CI), per 100 PY	325.2 (310.2 to 340.7)	302.5 (287.7 to 317.9)
≥1 AE leading to discontinuation, % (n)	10.1 (28)	11.2 (31)
SAEs		
Total patients with ≥1 SAE, % (n)	17.7 (49)	17.4 (48)
Total no. of SAEs	66	77
Rate of SAEs (95% CI), per 100 PY	12.2 (9.4 to 15.5)	15.0 (11.8 to 18.7)
SIs		
Total patients with ≥1 SI, % (n)	6.9 (19)	4.7 (13)
Total no. of SIs	24	19
Rate of SIs (95% CI), per 100 PY	4.4 (2.8 to 6.6)	3.7 (2.2 to 5.8)
Total no. of deaths	4	6
ALT elevations, % (n)	N*=244	N*=242
>ULN†–1.5×ULN	27.5 (67)	24.4 (59)
>1.5×ULN–3×ULN	30.3 (74)	17.4 (42)
>3×ULN–5×ULN	10.2 (25)	4.1 (10)
>5×ULN	4.1 (10)	1.2 (3)
AST elevations, % (n)	N*=257	N*=249
>ULN‡–1.5×ULN	32.6 (84)	22.1 (55)
>1.5×ULN–3×ULN	20.2 (52)	7.6 (19)
>3×ULN–5×ULN	3.9 (10)	1.6 (4)
>5×ULN	1.2 (3)	0.4 (1)

*Number of patients with normal values at baseline.
†ULN=55 U/L.
‡ULN=40 U/L.
AE, adverse event; ALT, alanine aminotransferase; AST; aspartate aminotransferase; ITT, intent-to-treat population; PY, patient-years; SAE, serious adverse event; SI, serious infection; TCZ, tocilizumab; ULN, upper limit of normal.

permitted achievement of predefined goals of sustained clinical remission in a good number of patients. Following TCZ discontinuation, most patients subsequently flared so that drug-free remission remained an elusive goal except for a minority of patients. However, patients experiencing a flare responded rapidly to reintroduction of study drug. Importantly, these results show that temporary biologic-free remission can be achieved, but further clinical data are required to provide more information on when to discontinue biological treatment or consider drug holidays following achievement of sustained remission.

Author affiliations
[1]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[2]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
[3]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain
[4]Department of Rheumatology, University of Erlangen-Nuremberg, Erlangen, Germany
[5]Department of Medicine 'B', Sheba Medical Center, Tel Hashomer, Israel
[6]Division of Rheumatology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil
[7]Division of Rheumatology, University of Southern California Keck School of Medicine, Santa Monica, California, USA
[8]F.Hoffmann-La Roche Ltd, Basel, Switzerland
[9]Rheumatology B Department, Paris-Descartes University, Cochin Hospital, Paris, France

Acknowledgements Support for third-party writing assistance for this manuscript, furnished by Eric Deutsch, PhD, was provided by F. Hoffman-La Roche Ltd.

Contributors TWJH, PGC, EM-M, GS, MA, CB and MD designed the study and analysed and interpreted the data. TWJH, PGC, EM-M, GS, HA, RX, OT and MD, along with other investigators, were involved in generating the data at their clinical research sites. All authors were involved in writing and reviewing the manuscript and approved the final version submitted.

Funding The ACT-RAY study was funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland (Roche). Roche was involved in developing the study design, in the analysis and interpretation of the data, in the writing of the report and in the decision to submit the paper for publication, through Roche employees, contractors and funding of third-party support, such as contract research organisations. All these activities happened in close collaboration with the independent members of the scientific steering committee.

Competing interests TWJH has been a consultant for Abbott, Axis Shield-Diagnostics, Biotest AG, Bristol-Meyers Squibb, Crescendo Bioscience, Novartis, Pfizer, Roche, Schering-Plough, UCB and Wyeth; PGC has participated in speakers bureau for Bristol-Meyers Squibb, Janssen, Pfizer and Roche; EM-M has no disclosures to declare; GS has no disclosures to declare; HA has research grants from Abbvie and Pfizer and is a consultant for Merck Sharp & Dohme; RMX has been a consultant for Merck, Pfizer and Roche; OT was granted research support from the ACT-RAY clinical trial; MA is an employee of F. Hoffmann-La Roche; Corrado Bernasconi is a contractor of F. Hoffmann-La Roche; MD has received honorarium fees to participate in advisory boards and symposia organised by Abbvie, Bristol-Meyers Squibb, Lilly, Merck, Novartis, Pfizer, Roche, Sanofi and UCB and his department has received research grants from Abbvie, Bristol-Meyers Squibb, Lilly, Merck, Novartis, Pfizer, Roche, Sanofi and UCB.

Ethics approval This study was approved by all institutional review boards and/or ethics committees and was conducted in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice guidelines.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Singh JA, Furst DE, Bharat A, *et al*. 2012 update of the 2008 american college of rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:625–39.
2 Smolen JS, Landewe R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492–509.
3 Allaart CF, Lems WF, Huizinga TW. The BeSt way of withdrawing biologic agents. *Clin Exp Rheumatol* 2013;31(4 Suppl 78):S14–18.
4 Saleem B, Keen H, Goeb V, *et al*. Patients with RA in remission on TNF blockers: When and in whom can TNF blocker therapy be stopped? *Ann Rheum Dis* 2010;69:1636–42.
5 Quinn MA, Conaghan PG, O'Connor PJ, *et al*. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: Results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;52:27–35.
6 van den Broek M, Klarenbeek NB, Dirven L, *et al*. Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: Subanalysis of the BeSt study. *Ann Rheum Dis* 2011;70:1389–94.
7 Dougados M, Kissel K, Sheeran T, *et al*. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). *Ann Rheum Dis* 2013;72:43–50.
8 Dougados M, Kissel K, Conaghan PG, *et al*. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. *Ann Rheum Dis* 2014;73:803–9.
9 Bruynesteyn K, Boers M, Kostense P, *et al*. Deciding on progression of joint damage in paired films of individual patients: Smallest detectable difference or change. *Ann Rheum Dis* 2005;64:179–82.
10 Lee SJ, Chang H, Yazici Y, *et al*. Utilization trends of tumor necrosis factor inhibitors among patients with rheumatoid arthritis in a united states observational cohort study. *J Rheumatol* 2009;36:1611–17.
11 Listing J, Strangfeld A, Rau R, *et al*. Clinical and functional remission: Even though biologics are superior to conventional DMARDs overall success rates remain low—results from RABBIT, the german biologics register. *Arthritis Res Ther* 2006;8:R66.
12 Mariette X, Gottenberg JE, Ravaud P, *et al*. Registries in rheumatoid arthritis and autoimmune diseases: data from the french registries. *Rheumatology (Oxford)* 2011;50:222–9.

13 Soliman MM, Ashcroft DM, Watson KD, *et al*. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the british society for rheumatology biologics register. *Ann Rheum Dis* 2011;70:583–9.
14 Jones G, Sebba A, Gu J, *et al*. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis* 2010;69:88–96.
15 Nishimoto N, Hashimoto J, Miyasaka N, *et al*. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): Evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. *Ann Rheum Dis* 2007;66: 1162–7.
16 Nishimoto N, Miyasaka N, Yamamoto K, *et al*. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod Rheumatol* 2009;19:12–19.
17 Smolen JS, Nash P, Durez P, *et al*. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): A randomised controlled trial. *Lancet* 2013;381:918–29.
18 Smolen JS, Emery P, Fleischmann R, *et al*. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. *Lancet* 2014;383:321–32.
19 Tanaka Y, Hirata S, Saleem B, *et al*. Discontinuation of biologics in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2013;31(4 Suppl 78):S22–7.
20 Smolen JS, Emery P, Ferraccioli GF, *et al*. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: The CERTAIN double-blind, randomised, placebo-controlled trial. *Ann Rheum Dis* 2014. Published Online First: 15 Jan 2014. doi:10.1136/annrheumdis-2013-204632
21 Bykerk VP, Ostor AJ, Alvaro-Gracia J, *et al*. Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: a large, open-label study close to clinical practice. *Ann Rheum Dis* 2012;71:1950–4.
22 Weinblatt ME, Kremer J, Cush J, *et al*. Tocilizumab as monotherapy or in combination with nonbiologic disease-modifying antirheumatic drugs: Twenty-four-week results of an open-label, clinical practice study. *Arthritis Care Res (Hoboken)* 2013;65:362–71.