Table 1. Demographics.

	Placebo n=22	NNC0109-00121 n=45
Age, years*	51.1 (28; 65)	50.9 (26; 75)
Women/Men, %	72.7/27.3	77.8/22.2
Duration of RA years*	6.1 (0.4; 16.2)	6.8 (0.5; 17.3)
Duration of MTX therapy, years*	1.9 (0.1; 7.0)	1.9 (2.0; 14.3)
RF-positive, %	63.6	71.1
ACPA-positive, %	68.2	68.9
RF- and ACPA-positive, %	63.6	64.4
DAS28-CRP*	6.0 (3.8; 7.3)	6.0 (3.9; 7.8)
DAS28 Components*		
Tender joints (28)	16.0 (5.0; 28)	17.5 (5.0; 28)
Swollen joints (28)	11.5 (5.0; 24)	13.0 (5.0; 24)
Subject's VAS (cm)	7.1 (2.6; 8.7)	6.9 (0.4; 9.7)
CRP (mg/L)	9.4 (0.6; 77.8)	7.2 (0.8; 69.5)

*Mean (min; max); ACPA=anticitrullinated protein antibody; CRP=C-reactive protein; DAS=disease activity score; MTX=methotrexate; RA=rheumatoid arthritis; RF=rheumatoid factor; VAS=visual analog scale.

At 12 weeks, mean changes in DAS28-CRP were significantly greater for NNC0109-0012 compared with placebo (difference,-0.88; 95% CI for difference, -1.61 to -0.14; p=0.020). Significant reduction of disease activity (-0.5; p=0.011) was observed after 1 week and was maintained for 5 weeks after the end of treatment. The reduction in disease activity was observed primarily in RF- and ACPA-positive patients. Estimated mean difference at 12 weeks was -1.66 [-2.53; -0.79; p=0.0004] and was driven mainly by a reduction in tender and swollen joints. There were no differences for DAS28-CRP changes between anti-IL-20- and placebo-treated patients with seronegative disease.

On the secondary endpoints, treatment with NNC0109-0012 resulted in a significant percentage of subjects who achieved moderate or good EULAR response (75.5%) compared with placebo (54.5%) after 12 weeks of treatment (p=0.02). DAS28-CRP remission (≤2.6) was achieved by approximately 18% of NNC0109-0012 patients. ACR 20/50/70 responses were also significantly higher in NNC0109-0012-treated RF- and ACPA-positive patients, compared with placebo-treated patients (p=0.028, p=0.045 and p=0.018, respectively), although the trial was not powered to detect differences in ACR20/50/70 responses.

The occurrence of adverse events (AEs) was similar in both groups. There was 1 withdrawal because of AEs in the placebo group. Severe AEs were reported by 1 subject in each group. There were more infections in the active treatment group (10 events in 10 patients) compared with placebo (2 events in 1 patient), but only 3 were considered to be related to the study drug. The infections were mild and consisted of upper respiratory and urinary tract infections, bronchitis, herpes simplex, and herpes zoster (placebo). Four patients in the active treatment group experienced mild, reversible injection-site reactions. No deaths, serious AEs, or dose-limiting toxicities were reported.

24-Week Data from the Phase 4 ADACTA Trial

Written by Maria Vinall

Data from several registries and a United States health insurance claims database have shown that approximately one-third of rheumatoid arthritis (RA) patients are being treated with biologics as monotherapy [Yazici Y et al. *Bull NYU Hosp Jt Dis* 2008; Lee SJ et al. *J Rheumatol* 2009], but there have been no head-to-head studies to assist in the choice of monotherapy for these patients. Results from the Multi-center, Randomized, Blinded, Parallel-group Study of the Reduction of Signs and Symptoms During Monotherapy Treatment With Tocilizumab 8 mg/kg Intravenously Versus Adalimumab 40 mg Subcutaneously in Patients With Rheumatoid Arthritis trial [ADACTA; NCT01119859], presented by Cem Gabay, MD, University Hospitals, Geneva, Switzerland, suggest that tocilizumab monotherapy may be more effective than adalimumab monotherapy reducing the signs and symptoms of RA.

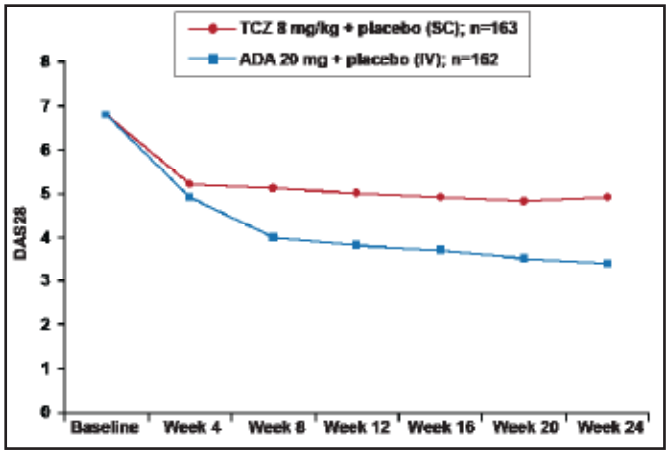
The ADACTA trial was an international, multicenter, randomized, double-blind, 24-week superiority trial that compared tocilizumab with adalimumab monotherapy in patients with RA. Patients were required to have an RA diagnosis of ≥6 months and a Disease Activity Score (DAS) score >5.1 and to be methotrexate-intolerant or judged inappropriate for continued treatment with methotrexate. Patients with prior treatment with a biologic agent were excluded. The primary study endpoint was mean change from baseline in the DAS28 at Week 24. Key secondary endpoints included efficacy at Week 24, based on the proportions of patients who achieved DAS28 remission (<2.6) and low disease activity (≤3.2), ACR 20/50/70 responses, and ACR/EULAR remission. Safety was assessed using adverse events (AEs) and laboratory parameters. Clinical Disease Activity Index (CDAI) responses were assessed as a *post hoc* analysis.

Study participants, aged 53 to 54 years and mainly women (82% in the adalimumab arm; 79% in the tocilizumab arm), had active disease (DAS 6.7 to 6.8; Health Assessment Questionnaire score 1.6 to 1.7) and a disease duration of 6.3 to 7.3 years. Subjects were randomized to intravenous

tocilizumab 8 mg/kg every 4 weeks plus subcutaneous placebo (n=163) or adalimumab 40 mg subcutaneously every 2 weeks plus intravenous placebo (n=163). Patients who did not achieve at least a 20% improvement from baseline in swollen and tender joint count at Week 16 or later could escape to weekly subcutaneous injections of adalimumab/placebo.

At Week 24, the change from baseline in DAS28 was -3.3 for the tocilizumab group versus -1.8 for subjects who received adalimumab (difference, 1.5; 95% CI for difference, -1.8 to -1.1; p<0.0001). Differences were observed, beginning at Week 8 (Figure 1). Significantly (p<0.0001) more subjects in the tocilizumab group also achieved the secondary endpoints of remission and low disease activity compared with those who received adalimumab (39.9% versus 10.5% and 51.5% versus 19.8%, respectively). ACR20/50/70 responses were also significantly (p<0.01) better among the tocilizumab subjects (65.0%, 47.2%, 32.5%) compared with subjects who received adalimumab (49.4%, 27.8%, 17.9%). In the *post hoc* analysis for CDAI response, 47.9% of tocilizumab versus 29.0% of adalimumab subjects (p=0.0003) were considered to be in remission or have low disease activity (CDAI score ≥0 to ≤10).

Figure 1. DAS28: Mean (±SE) Over Time.



TJC=tender joint count; SJC=swollen joint count; TCZ=tocilizumab; ADA=adalimumab; LOCF used for TJC and SJC; ESR and Patient's Global Assessment of Disease Activity VAS; If ESR=0 then ESR=1 is substituted into the DAS28 calculation to enable a non-missing DAS28.
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The incidence of AEs was similar (82.1% in the tocilizumab arm and 82.7% in the adalimumab arm). Serious AEs and serious infections were also similar (tocilizumab: 11.7%, 3.1%; adalimumab: 9.9%, 3.1%). Changes in transaminase, low-density lipoprotein elevations, and neutrophil reductions occurred in both arms, with the proportion of patients with abnormal values higher in the tocilizumab arm. There were 2 deaths in the tocilizumab arm; 1 from sudden death that was considered to possibly be related to the study drug and 1 from illicit drug overdose that was not considered to be related.

Efficacy of Different Doses of Rituximab for the Treatment of RA: Data From the CERERRA Collaboration

Written by Toni Rizzo

The approved dose of rituximab for the treatment of rheumatoid arthritis (RA) is 1000 mg x 2, but some data have suggested similar clinical efficacy with rituximab 500 mg x 2. The objective of this analysis, presented by Katerina Chatzidionysiou, MD, Karolinska Institute, Stockholm, Sweden, was to compare the efficacy of the 2 doses, given as first or second treatment courses.

The data for this analysis were obtained from the European Collaborative Registries for the Evaluation of Rituximab in Rheumatoid Arthritis (CERERRA), which includes 10 European registries. The registries submitted anonymous datasets with demographic, efficacy, and treatment data on patients who had started rituximab therapy. Treatment and retreatment efficacy were assessed by Disease Activity Score (DAS) 28 reductions and EULAR responses after 6 months.

Information on rituximab doses was available for 2873 (88%) of 3266 patients in the registries. A total of 2625 patients (91.4%) received 1000 mg x 2 of rituximab, and 248 patients (8.6%) received 500 mg x 2. Baseline characteristics that were significantly different between the 500 mg x 2 and 1000 mg x 2 groups, respectively, were: age (55.2 vs 52.6 years; p=0.002), disease duration (13.6 vs 10.9 years; p<0.0001), number of prior biologics (0.7 vs 1.0; p <0.0001), number of prior disease-modifying antirheumatic drugs (DMARDs; 2.6 vs 2.4; p=0.04), baseline DAS28 (5.7 vs 5.9; p=0.02), concurrent DMARDs (72.6% versus 83.1%; p<0.0001), concurrent corticosteroids (65.7% vs 59.3%; p=0.03), and TNF-naïvete (42% vs 62.5%; p<0.0001).

There were no significant differences in DAS28 or Health Assessment Questionnaire (HAQ) responses between the 2 dose groups at 3 months and 6 months. The change in ΔDAS28 at 3 months was 1.3±1.3 in the 500 mg x 2 group versus 1.8±1.4 in the 1000 mg x 2 group (p=0.005, corrected for baseline difference in DAS28). The Δ HAQ at 3 months was 0.3±0.5 in the 500 mg x 2 group versus 0.5±0.6 in the 1000 mg x 2 group (p=0.02). There was no significant difference between the 2 groups in change in DAS28 or HAQ at 6 months. No significant difference was seen in EULAR response or remission rates between the 2 dose groups.

Data on 622 patients who received a second cycle with 2 rituximab infusions were available at 6±1 months. At 6 months after retreatment, the 1000 mg x 2 group versus the 500 mg x 2 group had significant improvements in