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SAT0169

NO EVIDENCE THAT CONCOMITANT GLUCOCORTICOID THERAPY AFFECTS EFFICACY AND SAFETY OF TOCILIZUMAB MONOTHERAPY IN RHEUMATOID ARTHRITIS CLINICAL TRIALS

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Background: For rheumatoid arthritis (RA) patients included in clinical trials, background treatment with glucocorticoids (GCs) is quite common (40–60%), but their potential contribution to efficacy and safety of the disease modifying anti-rheumatic drug (DMARD) tested in that trial has rarely been evaluated.

Objectives: To establish whether a stable GC dose at baseline and during the study contributed to the efficacy and safety of TCZ monotherapy initiated in RA patients in 4 TCZ RCTs. In addition, to investigate the same issue in the comparator arms of these trials, in which adalimumab (ADA) or methotrexate (MTX) was initiated.

Methods: Data from 4 randomized controlled double-blind trials (AMBITION, ACT-RAY, ADACTA and FUNCTION) with TCZ monotherapy arms was analysed in this post hoc analysis [1–4]. Study participants were MTX-naïve, intolerant or had an inadequate response to conventional synthetic DMARDs (csDMARD-IR). Because of differences between the studies in region, and baseline RA duration and disease severity, analyses were done separately for each study. Stable GC dose at baseline was allowed and was to be continued unchanged during the first 24 weeks. Analyses of covariance (ANCOVA) of change from baseline to Week 24 in CDAI and DAS28 and logistic regression analyses at Week 24 for CDAI remission and ACR50 were performed. Repeated measures analyses using all visits up to week 24 were also done. Incidence rates of serious adverse events (SAEs) were assessed by GC use.

Table 1 Disease Activities at week 24 of GC Users versus non-GC Users per Treatment per Study

Study	AMBITION				ACT-RAY			
	GC Users	Non-GC Users	GC Users	Non-GC Users	GC Users	Non-GC Users	GC Users	Non-GC Users
Mean (SD)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)
Median	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Range	0–15	0–15	0–15	0–15	0–15	0–15	0–15	0–15
Mean (SD)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)
Median	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Range	0–15	0–15	0–15	0–15	0–15	0–15	0–15	0–15
Mean (SD)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)
Median	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Range	0–15	0–15	0–15	0–15	0–15	0–15	0–15	0–15
Mean (SD)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)
Median	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Range	0–15	0–15	0–15	0–15	0–15	0–15	0–15	0–15
Mean (SD)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)
Median	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Range	0–15	0–15	0–15	0–15	0–15	0–15	0–15	0–15
Mean (SD)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)	10.2 (3.2)
Median	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Range	0–15	0–15	0–15	0–15	0–15	0–15	0–15	0–15

Results: Baseline characteristics were mostly comparable between GC users and non-GC users in each treatment arm for each study. The adjusted differences (95% CIs) of CDAI change at week 24 between GC and non-GC users in TCZ arms of AMBITION, FUNCTION, ACT-RAY and ADACTA were -1.4 (-4.8, 2.1), 0.8 (-2.5, 4.1), 1.2 (-4.0, 6.3) and -4.2 (-9.7, 1.4), respectively (table 1). CDAI remission rates, ACR50 response rates and DAS28 score changes at 24 weeks neither were significantly different between GC users and non-GC users in the TCZ arms, nor in the MTX and ADA arms (table 1). Repeated measures analyses to week 24 showed no significant differences in DAS28 or CDAI. Statistically significant predictors for the various clinical outcomes included baseline CDAI, baseline DAS28, age, sex, RA duration and region. A numerically higher but not significantly different SAE rate was seen in the GC-arms of all four trials, compared to the non-GC-arms.

Conclusions: No evidence was found that GC treatment at baseline and continued at a stable dose affects either clinical efficacy or safety over 24 weeks of TCZ, MTX, or ADA monotherapy initiated at baseline in RA clinical trials.

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SAT0170

ANTI-IL-6 THERAPY MODULATES LEPTIN IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Leptin is an adipocytokine that plays an important role in the regulation of body weight and also participates both in immune homeostasis and inflammatory processes [1,2]. Chronic systemic inflammation is of major importance in the development of atherosclerosis in rheumatoid arthritis (RA) [3]. IL-6 blocker yields a rapid improvement of endothelial function [4].

Objectives: To determine whether the infusion of IL-6 blockade improves the endothelial function by altering circulating Leptin concentrations in patients with RA.

Methods: 50 Spanish patients on treatment with anti-IL-6 monoclonal antibody-Tocilizumab who fulfilled the 2010 classification criteria for RA [5] were recruited. Patients with diabetes mellitus or plasma glucose >110 mg/dl were excluded. Leptin serum levels were determined immediately prior to (time 0) and after (time 60 minutes) Tocilizumab infusion by Enzyme-Linked Immunosorbent Assay (ELISA).

Results: A significant reduction in Leptin concentration was observed following Tocilizumab infusion (mean±standard deviation (SD): 9.24±7.98 ng/ml versus 7.91±7.36 ng/ml, p<0.0011). In addition, a significant positive correlation between Leptin concentration and insulin resistance (HOMA at the time of the study) was found (r= 0.40; p=0.0046). Furthermore, a significant negative correlation between Leptin levels and insulin sensitivity (QUICKI) was disclosed (r= -0.46; p=0.0009).

Conclusions: Our study confirms that circulating Leptin concentrations are modulated by anti-IL-6 treatment. In addition, Leptin concentration correlates with insulin resistance and sensitivity. The beneficial effect of anti-IL-6 blockage on cardiovascular mortality in RA may be mediated by reduction in serum levels of leptin.

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SAT0171

REVERSIBLE DECREASES IN ABSOLUTE NEUTROPHIL COUNT (ANC) IN RHEUMATOID ARTHRITIS (RA) PATIENTS (PTS) ON SARILUMAB: COMPARISON OF DOSE DELAY AND DOSE DECREASE VS CONTINUED TREATMENT

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Background: In randomized studies (RCTs: MOBILITY, TARGET and MONARCH), and open-label [OLE] EXTEND, for those patients who experienced decreases in ANC this typically occurred early after initiating sarilumab. For sarilumab patients with decreased ANC in the RCTs and the OLE, we assessed the outcomes associated with either continuing treatment, decreasing the sarilumab dose or delaying the dose.

Objectives: The effects of a dose decrease (200 to 150 mg), dose delay (>17 days), vs no change in treatment were evaluated in RA patients who experienced decreased ANC while on sarilumab 150 or 200 mg q2w. Outcomes data from patients in MONARCH, MOBILITY and TARGET, and MOBILITY and TARGET patients entering EXTEND were analyzed to compare the three strategies. In MONARCH, patients received sarilumab 200 mg q2w. In MOBILITY and TARGET, patients received sarilumab 150 or 200 mg q2w. In EXTEND, patients were switched to, or initiated on, 200 mg q2w.

Table 1 Outcomes following dose delay, dose decrease, or continued treatment with sarilumab among pts who experienced ANC <1000/mm³ at any time

	RCTs		OLE	
Total treated (N)	1346		1353	
ANC <1000/mm ³ at any time (n, %)	105 (8)		147 (11)	
Pts who did not continue* (n, %)	24 (23)		15 (10)	
Pts that continued, delayed, or decreased sarilumab dose (n, %)	81 (77)		132 (90)	
	Continued without change (n=38)	Dose delay (n=43)	Continued without change (n=31)	Dose delay (n=82)
Normalized on treatment after ≥1 episodes of ANC <1000/mm ³ (n, %)	25 (66)	27 (63)	29 (94)	66 (80)
Median time to normalization for patients with 1 episode (days)	9	15	27	17
Pts with ≥1 episode of ANC <1000/mm ³ who normalized on treatment** (n)	6	6	3	33
Normalized after treatment discontinuation (n, %)	2 (5)	9 (21)	1 (3)	7 (9)
Did not normalize after ≥1 episode of ANC <1000/mm ³ (n, %)	11* (29)	7* (16)	1 (3)	9 (11)
Discontinued treatment due to abnormal ANC after last episode (n)	1	1	1	9
ANC @ last episode (<2000/<1500/<1000/mm ³)	0/1/0	0/0/1	1/0/0	2/6/1
ANC @ last episode (<2000/<1500/<1000/mm ³)	1/4/1			

*10 and % pts enrolled into EXTEND

**ANC<500/mm³ confirmed or had evidence of an infection or had ANC 500 to 1000/mm³ and were discontinued at the investigators discretion.

**pts: ≥1 episode of ANC <1000/mm³ was defined as pts who, at least once, experienced ANC <1000/mm³, then displayed normalized ANC levels and were able to resume treatment, but later experienced ANC <1000/mm³ again.

Methods: In RCTs, patients were required to have baseline neutrophil levels ≥2000/mm³. In RCTs and EXTEND, patients who experienced ANC <500/mm³ (grade 4 [G4] neutropenia) or ≥500 to <1000/mm³ (grade 3 [G3] neutropenia) and signs of infection were required to permanently discontinue treatment. Patients with G3 neutropenia (no signs of infection) temporarily discontinued treatment (or permanently discontinued at the investigators discretion); patients were retested ≤48 hrs after identifying decreased ANC and before the next scheduled dose, and could resume if ANC ≥1000/mm³. In RCTs, patients restarted sarilumab at their randomized dose. In OLE, patients restarted sarilumab at 150 mg q2w, as per the protocol, or otherwise were able to restart at 200 mg q2w at the investigators discretion. In OLE, patients who required a dose decrease to 150 mg q2w sarilumab

received the reduced dose for the remainder of the treatment period. ANC normalization was defined as a return to the patient's baseline or within normal ranges.

Results: Of the 8–11% of patients who experienced ANC <1000/mm³ at any time, 81/105 (RCTs) and 132/147 (OLE) were able to continue or reinstitute sarilumab; the majority of patients who experienced ANC <1000/mm³ one or more times displayed normalized ANC levels and continued treatment when ANC ≥1000/mm³ (25/38 in RCTs; 29/31 in OLE). The majority of patients who dose delayed (27/43 in RCTs; 66/82 in OLE) or dose decreased (51/62, OLE) before ANC normalized resumed treatment.

Conclusions: More than three-quarters of patients who discontinued treatment until ANC normalized were able to reinstitute at their randomized dose (RCT), or at the open-label study dose (200 mg q2w; OLE) or were able to resume at the lower dose (150 mg q2w; OLE).

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SAT0172

LONG-TERM EFFICACY WITH 5-YEAR-RADIOGRAPHIC RESULTS AND SAFETY OF SARILUMAB IN COMBINATION WITH csDMARDs IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Long-term data are being collected on sarilumab in combination with csDMARDs in patients with RA originally enrolled in six trials (TARGET, NCT01709578; MOBILITY, NCT01061736; NCT01764997; NCT01768572; NCT02057250; NCT01217814) including those who continued into extension trials.

Objectives: To assess efficacy and safety of long-term treatment with sarilumab plus csDMARDs in patients with RA.

Methods: Long-term efficacy and safety data were available in patients enrolled in placebo-controlled trials of sarilumab 150 or 200 mg sc q2w who continued into the open-label EXTEND trial of sarilumab 200 or 150 mg sc q2w (NCT0146652). Safety data were evaluated in 2887 patients who received ≥1 dose of sarilumab sc in combination with csDMARDs.

Results: Clinical and radiographic efficacy of sarilumab plus csDMARDs was maintained over 5 years' follow-up (table 1; figure 1). Initial treatment with either dose of sarilumab was associated with significantly better radiographic outcome than placebo. Initial treatment with sarilumab 200 mg portended better radiographic outcome than sarilumab 150 mg or placebo. Mean duration of sarilumab treatment in the safety population was 2.6 years (max 6.8), representing 7412 cumulative patient-years of exposure. Incidence rate of adverse events of special interest (AESIs; table 2) was generally stable over >5 years' treatment, with no signal for increased rate of any AESI (including serious AEs and serious infection) over time. Incidences of injection site reaction, ANC <1 Giga/L, & elevated ALT declined over time.