FRI0252 SUMMARY OF NEUTROPENIA IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH SIRUKUMAB IN THE SIRROUND PHASE 3 CLINICAL TRIALS

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Background: Neutropenia has been reported with interleukin-6 (IL-6) pathway inhibitors and could potentially be associated with increased rates of infection. The reduced neutrophil counts seen with IL-6 inhibitors may be due to effects on margination of circulating neutrophils as opposed to a decrease in bone marrow production or reduced survival. Efficacy of sirukumab (SIR), a human anti-IL-6 cytokine monoclonal antibody, has recently been shown in several phase 3 trials.
Objectives: To assess incidence of neutropenia from completed and ongoing SIRROUND clinical studies.
Methods: Neutrophil counts were compared for SIR 50mg q4w and 100mg q2w doses vs placebo (pbo) in the pbo-controlled period (Wks 0–18) of 2 phase 3 trials and in long-term analysis for the 5-trial, phase 3 program.
Results: 2926 pts received SIR for up to 3.4y with a median duration of 1.46y. For the 18-wk pbo-controlled period, neutropenia was more frequent in both SIR groups compared with pbo. Across all groups, the majority of the decreases in neutrophil counts were National Cancer Institute Common Terminology Criteria for Adverse Events grade 0/1, within the normal range, and the incidence of grade 3/4 decreases was low across groups (Table). Neutropenia began at Wk 2 and persisted through the study period. In long-term analysis, the proportions of pts with grade 1, 2, or 3 neutropenia were slightly higher than in the 18-wk pbo-controlled period, suggesting the majority of events occurred early. No dose relationship was observed in the grade or frequency of neutropenia. Grade 3/4 neutropenia was mostly transient and resolved after interrupting the dose or resolved within the dosing interval such that no change in dose schedule was required. The majority of grade 4 decreases in neutrophils were not correlated with infections; 2 cases of serious infections occurred with grade 4 neutropenia. The distribution of neutropenia by grade was similar in pts who did or did not use disease-modifying antirheumatic drugs (DMARDs) at baseline.

Table 1. Neutropenia by Maximum Toxicity Grade Across Phase 3 Trials (n, %)

Neutrophil count decreased	0–18 wks			Long-term analysis	
	Pbo (N=850)	SIR 50mg q4w (N=848)	SIR 100mg q2w (N=850)	SIR 50mg q4w (N=1454)	SIR 100mg q2w (N=1461)
Grade 0 (≥LLN)	816 (96.9)	576 (68.3)	568 (67.1)	843 (58.0)	806 (55.2)
Grade 1 (3)	19 (2.3)	149 (17.7)	167 (19.7)	313 (21.5)	352 (24.1)
Grade 2 (<1,500–1,000/mm^3)	5 (0.6)	97 (11.5)	94 (11.1)	222 (15.3)	240 (16.4)
Grade 3 (<1,000–500/mm^3)	1 (0.1)	21 (2.5)	16 (1.9)	68 (4.7)	61 (4.2)
Grade 4 (<500/mm^3)	1 (0.1)	0	1 (0.1)	8 (0.6)	2 (0.1)

LLN, lower limit of normal.

Conclusions: Across phase 3 studies, there was no dose effect of SIR on neutropenia, and the use of DMARDs did not have an apparent effect on neutropenia. The majority of grade 4 neutropenia with SIR was not associated with infections.
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FRI0253 PATIENT-REPORTED OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH SUBCUTANEOUS TOCILIZUMAB COMPARED WITH PLACEBO OR INTRAVENOUS TOCILIZUMAB IN COMBINATION WITH CSDMARDS

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Background: Two previous randomized, controlled trials (RCTs), BREVACTA and SUMMACTA, showed subcutaneous tocilizumab (TCZ-SC) was superior to placebo (PBO) and comparable to intravenous TCZ (TCZ-IV) in combination with csDMARDs for improving RA disease activity.[1,2]
Objectives: To compare the efficacy of TCZ-SC with PBO or TCZ-IV + csDMARDs for improvement in patient-reported outcomes (PROs) in 2 RCT populations.
Methods: Both RCTs enrolled patients (pts) with inadequate responses to DMARDs; up to 20% had inadequate responses to tumor necrosis factor inhibitors. In BREVACTA, pts received blinded TCZ-SC 162 mg or PBO every 2 weeks (q2w) + csDMARDs for 24 weeks. In SUMMACTA, pts received TCZ-SC 162 mg weekly or TCZ-IV 8 mg/kg q4w + csDMARDs for the 24-week double-blind period. PROs, assessed at 12 weeks (prior to rescue) in BREVACTA and 24 weeks in SUMMACTA, included patient global assessment (PtGA; visual analog score [VAS], 0–100 mm), pain (VAS), Health Assessment Questionnaire Disability Index (HAQ-DI, 0–3) and Short Form-36 (SF-36) physical and mental component summary (PCS, MCS: 0–50) and domain (0–100) scores. The proportions of pts reporting scores ≥ minimum clinically important differences (MCID) and ≥ age/gender-matched normative values were assessed for each treatment group.
Results: Baseline PRO scores were mostly comparable between treatment groups in each study and between study populations. In BREVACTA, significantly more pts who received TCZ-SC reported scores ≥ MCID for all PROs at week 12 compared with PBO (54% to 73% vs 42% to 55%, respectively; number needed to treat [NNT], 5.2 to 13.0). Compared with 1% to 20% at baseline, 8% to 34% of pts who received TCZ-SC and 4% to 25% of PBO pts reported scores ≥ normative values in all PROs at week 12 (Table). In SUMMACTA, similar proportions of pts who received TCZ-SC and TCZ-IV reported scores ≥ MCID in all PROs at week 24 (61% to 84% vs 64% to 84%, respectively). The proportion of patients who reported scores ≥ normative values was comparable between the TCZ-SC and TCZ-IV groups across all PROs; compared with 0.2% to 23% at baseline, 14% to 41% of pts who received TCZ-SC and 15% to 42% of pts who received TCZ-IV reported scores ≥ normative values at week 24 (Table).

Table. PROs at 12 weeks in BREVACTA and 24 weeks in SUMMACTA.

	Change From Baseline in PROs								
	BREVACTA†					SUMMACTA†			
	LSM Change From Baseline‡		Week 12 Change ≥ MCID, %		NNT	LSM Change From Baseline‡		Week 24 Change ≥ MCID, %	
	TCZ SC q2w	PBO q2w	TCZ SC q2w	PBO q2w		TCZ SC qw	TCZ IV q4w	TCZ SC qw	TCZ IV q4w
Patient global	−25.5	−13.0	72.4***	53.1	5.2	−35.0	−36.0	83.0	83.6
Patient pain	−20.6	−9.63	63.9***	46.0	5.6	−29.2	−31.1	76.2	80.2
HAQ-DI	−0.4	−0.2	58.2**	46.7	8.7	−0.6	−0.6	73.0	74.6
SF-36 PCS	5.6***	2.9	63.1**	51.7	8.8	8.7	8.9	80.0	79.6
SF-36 MCS	6.1***	1.6	58.5***	44.1	6.9	6.4	6.5	63.0	64.2
Physical functioning	8.9***	2.8	59.2*	50.2	11.1	18.9	19.0	77.2	78.0
Role-physical	14.9***	7.7	64.3*	55.0	10.8	20.9	21.3	77.0	77.7
Bodily pain	17.8***	8.6	72.7***	54.5	5.5	25.5	27.5	84.4	83.9
General health	8.5***	4.2	60.9*	51.2	10.3	13.0	13.3	70.9	73.3
Vitality	12.0***	5.3	66.7**	54.5	8.2	16.1	14.8	74.9	74.7
Social functioning	11.0***	4.8	57.3***	41.7	6.4	20.0	20.4	67.8	70.1
Role-emotional	12.2***	4.6	53.5*	45.5	12.5	15.7	16.9	60.9	64.8
Mental health	9.9***	4.6	61.4**	47.9	7.4	10.7	10.9	67.1	65.1
CDAI	−18.8***	−13.0	–	–	–	−24.8	−25.4	–	–
	Patients Reporting Scores ≥ Normative Values, %								
	BREVACTA†					SUMMACTA†			
	Baseline		Week 12			Baseline		Week 24	
	TCZ SC q2w	PBO q2w	TCZ SC q2w	PBO q2w		TCZ SC qw	TCZ IV q4w	TCZ SC qw	TCZ IV q4w
HAQ-DI	3.9	5.5	15.8	10.8		4.3	3.9	33.3	30.1
SF-36 PCS	1.4	0.9	7.9	3.8		0.2	0.8	14.0	14.7
SF-36 MCS	16.3	19.7	31.6	22.6		19.3	20.3	38.7	39.6
Physical functioning	4.4	5.5	12.0	8.0		2.7	4.9	20.8	21.0
Role-physical	3.4	0.9	13.6	8.0		4.3	3.9	19.1	20.3
Bodily pain	3.2	2.3	20.8	13.2		1.3	2.8	29.8	34.5
General health	7.8	9.6	17.2	11.8		9.2	7.3	21.6	22.4
Vitality	13.1	14.7	32.3	23.6		11.7	12.0	37.9	36.1
Social functioning	9.4	12.4	23.0	16.5		10.2	10.1	29.4	31.9
Role-emotional	10.8	8.7	22.0	13.7		11.9	14.2	25.3	28.5
Mental health	18.6	20.2	33.7	24.5		23.2	21.3	41.4	42.1

LSM, least squares mean; NNT, number needed to treat; PBO, placebo; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
† Analyses were performed using the intention-to-treat population in BREVACTA (TCZ SC, n = 437; PBO, n = 219) and the per-protocol population in SUMMACTA (TCZ SC, n = 558; TCZ IV, n = 537).
‡ Adjusted for region and body weight category (< 60 kg; 60 to < 100 kg; ≥ 100 kg).

Conclusions: In BREVACTA, TCZ-SC + csDMARDs resulted in significantly greater improvements across all PROs and significantly more pts reporting scores

≥ MCID at week 12 compared with PBO. Similarly, more pts receiving TCZ-SC reported scores ≥ normative values at week 12 compared with PBO, despite few pts with such scores at baseline. Responses were similar between pts treated with TCZ-SC and TCZ-IV + csDMARDs in SUMMACTA at week 24. These data show TCZ treatment resulted in clinically meaningful improvements in PROs and indicate that attainment of normative scores is a realistic goal in treatment of pts with active RA.

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FRI0254 EFFICACY OF TOCILIZUMAB FOR SUPPRESSING RADIOGRAPHIC PROGRESSION OF CERVICAL LESIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS COMPARISON WITH METHOTREXATE TREATMENT; TWO YEARS OF FOLLOW-UP ～A MULTICENTER REGISTRY STUDY～

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Background: Cervical lesions are known to occur at high frequency as a complication of rheumatoid arthritis (RA). Treatment with biological agents are more clinically effective than the DMARDs that were in use previously, in particular, with their efficacy in suppressing joint destruction having been emphasized. We reported the efficacy of infliximab, anti-tumor necrosis factor antibodies for suppressing the radiographic progression of RA cervical lesions at ACR2009, EULAR2010, 11, 12, 13, 14 and 16. However there is still few studies of efficacy of against RA cervical lesions of Tocilizumab (TCZ), anti-interleukin 6 receptor antibody.

Objectives: To evaluate the efficacy of TCZ for suppressing the radiographic progression of RA cervical lesions comparison with MTX for 2 years.

Methods: We used TCZ or MTX for treating Japanese patients with active RA who fulfilled the ACR criteria in 1987. The final study cohort of each 38 and 71 patients received continuous TCZ and MTX treatment for at least 2 years. For evaluation of cervical lesions, the atlanto-dental interval (ADI), the space available for the spinal cord (SAC), and the Ranawat value were measured by plain lateral radiographs in the flexion position, at initiation and Year 1,2.

Results: In the patients receiving TCZ (n=38) and MTX (n=71), the number of female were each 28 (72%) and 51 (72%) cases (p=0.999). The mean age was 57.3±12.4 and 63.3±10.9 years old (p=0.011); disease duration was 7.0±7.3 and 8.8±9.7 years (p=0.929) and the mean dose of MTX was 9.0±3.4 and 8.3±2.9 mg/w (p=0.335). Clinical findings related to RA were as follows; CRP 3.8±3.1 and 1.5±2.1 mg/dl (p<0.001); ESR 52.7±25.3 and 30.0±20.8mm/h (p<0.001); MMP3 400±300 and 213±356ng/ml (p<0.001); the number of RF-positive 30 (79%) and 58 (82%) cases (p=0.801); DAS28-ESR 5.46±0.92 and 4.24±1.34 (p<0.001); ADI 2.7±1.7 and 2.6±1.6mm (p=0.917); SAC 19.3±2.8 and 20.7±2.5mm (p=0.008) and Ranawat value 15.4±1.6 and 15.9±1.5mm (p=0.073). The respective changes in cervical lesion parameters after 1 year were as follows: ADI: 0.21±0.53 and 0.25±0.44 mm (p=0.327); SAC: –0.16±0.44 and –0.17±0.38 mm (p=0.653); and Ranawat value: –0.13±0.34 and –0.11±0.32 mm (p=0.773). The respective changes in cervical lesion parameters after 2 years were as follows: ADI: 0.32±0.70 and 0.52±0.67 mm (p=0.045); SAC: –0.24±0.49 and –0.45±0.63 mm (p=0.067); and Ranawat value: −0.24±0.49 and –0.35±0.56 mm (p=0.270) in the patients receiving TCZ and MTX (Fig.1). The numbers of patients who did not showed progression in ADI, SAC and Ranawat value were each 30 (79%) and 41 (58%) cases (p=0.035); 30 (79%) and 44 (62%) cases (p=0.087) and 30 (79%) and 49 (69%) cases (p=0.367) after 2 years. Also the number who was able to suppress progression in all three parameters were each 29 cases (76%) receiving TCZ and 41 cases (58%) receiving MTX (p=0.062) after 2 years (Fig.2).

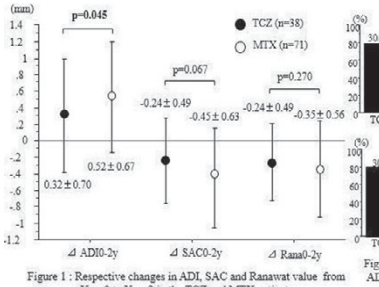

Figure 1 : Respective changes in ADI, SAC and Ranawat value from Year 0 to Year 2 in the TCZ and MTX patients

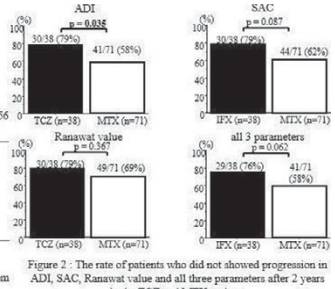

Figure 2 : The rate of patients who did not showed progression in ADI, SAC, Ranawat value and all three parameters after 2 years in the TCZ and MTX patients

Conclusions: This study suggested that TCZ treatment can be used to suppress the progression of RA cervical lesions more than MTX treatment.

Disclosure of Interest: None declared

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FRIDAY, 16 JUNE 2017

SLE, Sjögren's and APS - clinical aspects (other than treatment)

FRI0255 PATTERNS OF DISEASE ACTIVITY IMPACT ON ORGAN DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by fluctuating disease activity in which adverse long-term outcomes remain a major challenge. In the face of extreme individual unpredictability of the disease course over time, four different patterns can be defined, as elsewhere described [1], using SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index-2K) excluding serology in order to focus on clinical activity. The patterns are clinical quiescent disease (CQD), chronic active disease (CAD), relapsing-remitting disease (RRD) and minimal disease activity (MDA).

Objectives: The aim of our study was to assess the association between different disease activity patterns and damage accrual in SLE patients.

Methods: Patients with SLE registered at our Lupus Clinic at the Rheumatology Unit, between 1 January 2013 and 1 October 2016, were included. Demographic and clinical variables included age, gender, age at SLE onset, major organ involvement. SDI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index) was categorized as absent (SDI=0) or present (SDI ≥1), Disease activity patterns (CQD, MDA, RRD, CAD) were retrospectively assessed. Drugs used in the treatment of SLE, including hydroxychloroquine, cumulative dose of glucocorticoid (prednisone equivalent >10 g) and other immunosuppressive drugs, were also collected.
Multivariate logistic regression analyses were performed to identify disease patterns associated with damage accrual. Results are presented as odds ratio (OR) and 95% confidence intervals (CI).

Results: A total of 473 Caucasian patients were observed, mainly female (89.4% F, 10.6% M), mean age 52.6 years (± 14.9 SD). In our cohort, the disease activity pattern distribution was as follows: 65.4% CQD (290 pts), 21.5% RRD (91 pts), 6.1% MDA (28 pts) and CAD in 19.1% of the cases (64 pts). Damage was significantly more frequent in CAD subset (81.2%, 52/64 pts) versus 54.5% in CQD (158/290 pts), 50% in MDA (14/28 pts) and 58.2% in RRD (53/91 pts). Compared to a CQD course, CAD pattern was independently associated with overall damage after controlling for factors including gender, disease duration, cumulative glucocorticoid dosage, major individual organ involvement (neuropsychiatric and renal), positive antiphospholipid antibody profile, exposures to cyclophosphamide and hydroxychloroquine (Table 1).

Table1. Logistic regression analysis of independent factors associated with damage in SLE patients

Factors	Crude odds ratio (95% CI)	*P value*	Adjusted* Odds ratio (95% CI)	*P value*
Disease Activity Pattern				
Clinical quiescent disease	**Reference category**		**Reference category**	
Minimal disease activity	0.84 (0.38 - 1.81)	0.650	0.77 (0.33 - 1.80)	0.541
Relapsing-remitting disease	1.16 (0.73 - 1.87)	0.529	1.03 (0.62 - 1.72)	0.900
Chronic active disease	**3.62 (1.86 - 7.07)**	**<0.0001**	**3.07 (1.49 - 6.34)**	**0.002**
Gender (M)	1.23 (0.68 - 2.22)	0.489	1.29 (0.68 - 2.43)	0.434
Disease duration(yr)	1.05 (1.03 - 1.07)	<0.0001	1.03 (1.01 - 1.06)	0.033
NP involvement	2.86 (1.65 - 4.94)	<0.0001	2.11 (1.17 - 3.80)	0.013
Renal involvement	1.35 (0.76 - 2.41)	0.301	0.95 (0.49 - 1.84)	0.877
aPL positivity	1.68 (1.16 - 2.44)	0.006	1.64 (1.09 - 2.47)	0.017
Cumulative dosage of CS (>10g PDN)	2.50 (1.69 - 3.71)	<0.0001	1.64 (1.03 - 2.61)	0.038
HCQ	0.37 (0.24 - 0.57)	<0.0001	0.41 (0.26 - 0.66)	<0.0001
CYC	2.46 (0.97 - 6.25)	0.058	1.89 (0.66 - 5.46)	0.236

* adjusted for: age, gender, disease duration, NP and renal involvement, cumulative dosage of CS; aPL positivity, HCQ, CYC (*NP, neuropsychiatric; aPL, antiphosphlipid; CYC, cyclophosphamide; HCQ, hydroxychloroquine; M,male; CS,corticosteroid; PDN, prednisone*)