although neutropenia was more frequent with sarilumab. Safety of sarilumab was generally comparable in monotherapy and combination studies; monotherapy was associated with fewer ALT elevations >3 × ULN compared with combination therapy: MONARCH, 3%; MOBILITY, 8%; TARGET, 4%.
Conclusions: Sarilumab 200 mg q2w + csDMARDs significantly reduced disease activity and improved physical function to a similar extent regardless of population (MTX-IR or TNF-IR) and as monotherapy. Safety profile of sarilumab was generally comparable across all 3 trials, with monotherapy resulting in fewer ALT elevations.
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SAT0181 LOW DOSE INTERLEUKIN-2 COMBINED WITH TOCILIZUMAB SELECTIVELY INCREASES REGULATORY T CELLS HELPING REFRACTORY RHEUMATOID ARTHRITIS PATIENTS ACHIEVE REMISSION MORE RAPIDLY

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Background: Rheumatoid arthritis (RA) is a prevalent chronic autoimmune inflammatory disease. Its pathogenesis is closely associated with a failure of endogenous immune tolerance that caused by the imbalance of pro-inflammatory T helper 17 (Th17) cells and anti-inflammatory regulatory T (Treg) cells. Low-dose Interleukin-2 (IL-2) has been showed to induce both Th17 and Treg cells' expansion and activation while IL-6 antagonist Tocilizumab suppresses the differentiation of Th17, which is expected to control the development of RA.
Objectives: To study the influence of the combination of IL-2 and Tocilizumab on T cells subgroups and its clinical efficacy and safety on refractory RA.
Methods: Total 50 RA patients with low Treg cells, who had been treated with glucocorticoids and DMARDs for over 6 months, were divided into three groups randomly. Patients in non-IL-2 group (n=15) were still given conventional glucocorticoids and DMARDs. Patients in IL-2 group (n=26) were not only given those treatments, but injected subcutaneously human IL-2 (aldesleukin) at 50 WIU per day for a 5 day course. Patients in IL-2 and Tocilizumab group (n=9) were not only received the treatment like IL-2 group, but also treated with Tocilizumab at the dosage of 160mg during the day 1 and day 3. The demographic features, clinical manifestations and laboratory indicators were compared before and after the treatment.
Results: There was no difference among all groups in gender, age and course of the disease (p >0.05). The ratios of Th1/Th2 and Th17/Treg were significant correlated with ESR, the number of tender or swollen joints and DAS28-ESR (p<0.05) in all three groups of patients. After treatment, the number of Th17 cells and Treg cells was significantly increased in IL-2 group (p<0.01). In IL-2/Tocilizumab group after the treatment, the number of Treg cells were also significantly increased (p<0.05), but not the Th17 cells (p>0.05), leading to a quickly decrease in their ratio (p<0.05). Before the treatment, there was no difference in clinical manifestations among all three groups (p>0.05), but compared with non-IL-2 group, there was a significantly decrease in the number of tender joints (p<0.01) or swollen joints (p<0.05) and DAS28-ESR (p<0.01) in IL-2 group and IL-2/Tocilizumab group after the treatment. Patients in IL-2/Tocilizumab group had better clinical manifestations' remission although no significant difference compared with IL-2 group (p>0.05). There was no difference in blood routine, liver and renal functions both before and after the treatment among all groups (p>0.05).
Conclusions: IL-2 can effectively increase the level of Treg cells as well as that of Th17 to some degree; while IL-2 combined with Tocilizumab only effectively expand Treg cell number without Th17 increasing, thereby quickly recovers the balance of Th17 and Treg cells. This combination selectively stimulate Treg Cells leading to induce autoimmune tolerance, and seems to help RA patients achieve remission in a rapid way without over-treatment and evaluated side effect, though the long term benefits of this therapy are required to further study in more patients.
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SAT0182 SIRUKUMAB LEADS TO SIGNIFICANT AND CLINICALLY MEANINGFUL IMPROVEMENTS IN HEALTH-RELATED QUALITY OF LIFE THAT MEET OR EXCEED NORMATIVE VALUES IN PATIENTS WITH RHEUMATOID ARTHRITIS REFRACTORY TO TNF INHIBITORS IN POST HOC ANALYSES OF A PHASE 3 TRIAL

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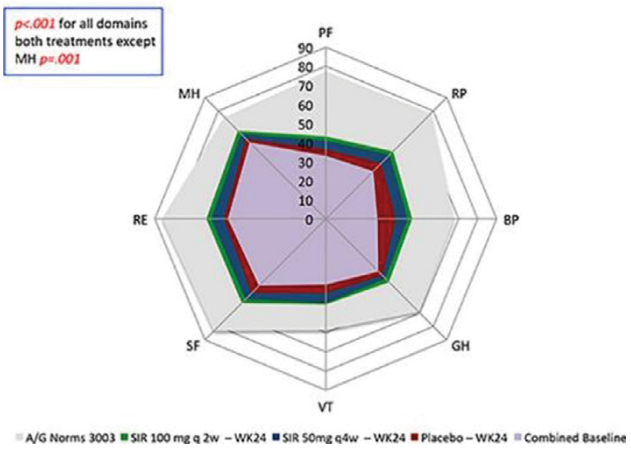
Background: Patients (pts) with rheumatoid arthritis (RA) experience reduced health-related quality of life (HRQoL). Sirukumab (SIR) is an anti–interleukin-6 (IL-6) monoclonal antibody.
Objectives: These post hoc analyses evaluated improvements over time in HRQoL relative to an age/gender-matched normative population in RA pts with inadequate responses to tumor necrosis factor inhibitors (TNF-IR) from the phase 3 SIRROUND-T trial.
Methods: 878 pts received SIR 50mg every 4 weeks (q4w), SIR 100mg every 2 weeks (q2w), or placebo (pbo) q2w. Health-related physical/emotional well-being were measured at baseline (BL) and Wk 24 by the 36-item Short Form Questionnaire (SF-36), fatigue by Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue (FACIT-F), and physical function by Health Assessment Questionnaire-Disability Index (HAQ-DI).
Results: SF-36 physical and mental component summary (PCS and MCS) mean scores at BL for pbo, SIR 50mg q4w, and 100mg q2w indicated substantial impairment (PCS: 33.2, 31.8, and 32.4; MCS: 41.9, 41.2, and 42.1). Significantly greater improvements from BL were reported at Wk 24 with SIR 50mg q4w and 100mg q2w vs pbo in PCS (4.8 and 5.1 vs 1.7) and MCS (3.9 and 4.0 vs 1.1) mean scores (all P<0.001), exceeding the minimum clinically important difference (MCID) of 2.5. Significantly greater least squares mean changes in the 8 SF-36 domain raw scores were reported with both doses of SIR vs pbo at Wk 24; all were >MCID of 5.0 (Table; Figure). More pts receiving SIR 50mg q4w or 100mg q2w reported SF-36 domain scores ≥normative values (ranges: 11–34% and 13–42%) vs pbo (range: 6–29%). For pbo, SIR 50mg q4w, and SIR 100mg q2w, BL FACIT-F scores were 26.0, 24.2, and 25.2; clinically meaningful improvements ≥MCID (4 points) were reported by 54.3 and 51.4% of pts receiving SIR 50mg q4w and 100mg q2w vs 33.7% with pbo (P<0.001). Numerically greater percentages of pts reported scores ≥normative values with both doses of SIR vs pbo (27 and 28% vs 16%). BL HAQ-DI scores were 1.57, 1.65, and 1.61 with pbo, SIR 50mg q4w, and 100mg q2w. Clinically meaningful improvements (change of ≤-0.22) were reported by significantly higher proportions of pts receiving SIR 50mg q4w (52.2%) or 100mg q2w (54.8%) vs pbo (37.4%; P<0.001). Numerically more pts reported HAQ-DI scores ≥normative values with SIR 50mg q4w and 100mg q2w vs pbo (13 and 16% vs 9%).

Table 1. Improvements in SF-36 Domain Scores at Wk 24 (all P<0.001)

Domain	LSM change SIR 50mg q4w	LSM change SIR 100mg q2w	LSM change pbo
Physical function	9.38	10.75	0.47
Role-physical	12.85	13.52	5.03
Bodily pain	17.66	17.51	7.46
General health	6.81	7.76	1.57
Vitality	10.10	9.68	4.14
Social function	12.40	11.75	3.68
Role-emotional	9.29	9.86	0.42
Mental health	6.73	7.96	2.10

LSM, least squares mean.

Figure. SF-36 domains at Wk 24 for SIR 50mg q4w and SIR 100mg q2w



Conclusions: In TNF-IR RA pts, SIR treatment resulted in greater and clinically meaningful improvements in HRQoL vs pbo that met or exceeded population normative values, with similar results for SIR 50mg q4w and 100mg q2w.
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Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Samsung, Sanofi and UCB, R. Ganguly Shareholder of: GlaxoSmithKline, Employee of: GlaxoSmithKline, N. Li Shareholder of: Janssen Research & Development, LLC, Employee of: Janssen Research & Development, LLC, K. McQuarrie Shareholder of: Janssen Research & Development, LLC, Employee of: Janssen Research & Development, LLC
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SAT0183 CLINICAL REMISSION IN SUBJECTS WITH RHEUMATOID ARTHRITIS TREATED WITH SUBCUTANEOUS TOCILIZUMAB AS MONOTHERAPY OR IN COMBINATION WITH METHOTREXATE OR OTHER SYNTHETIC DMARDS: A REAL-WORLD CLINICAL TRIAL (TOSPACE)

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Background: Subcutaneous tocilizumab (TCZ-SC) has demonstrated non-inferiority to TCZ-IV and superiority to placebo
Objectives: The primary objective of this study was to assess the 24-week efficacy and safety of subcutaneous (SC) tocilizumab (TCZ) 162 mg weekly (qw) as monotherapy or in combination with methotrexate (MTX) or other synthetic (s) DMARDs in patients with active rheumatoid arthritis (RA) in the real world setting
Methods: This multinational (Spain, Ireland, Portugal), multicenter, phase IIIb study. Subjects ≥18 years of age with active RA (DAS 28-ESR >3.2) who have had inadequate response or intolerance to sDMARDs or to a first anti-TNF drug. The study comprised a phase 1 with open-label design in which patients received TCZ-SC 162 mg qw (+/- oral/SC MTX or other sDMARDs) for 24-weeks and the main outcome was the percentage of patients achieving sustained clinical remission (DAS 28-ESR <2.6) at Week 20 and Week 24 (primary outcome of the study); and a phase 2 where patients achieving sustained clinical remission during the phase 1 were randomized to receive TCZ-SC 162 mg qw or TCZ-SC 162 mg q2w (+/- oral/SC MTX or other sDMARDs) for an additional 24 weeks; the main outcome of the phase 2 was the percentage of patients who maintained the remission at week 48 (i.e. DAS 28-ESR<2.6)
Results: 401 patients were included in the phase 1, 74 patients received TCZ-SC monotherapy and 327 patients received TCZ-SC in combination with oral/SC MTX or other sDMARDs. Sustained clinical remission rates were comparable between the mono- and combination-therapy groups at 24 week (48.4% vs. 52.9%, p=0.523). Of the 179 patients who achieved sustained clinical remission during the phase 1, 89 were randomly assigned to receive TCZ-SC 162 mg qw and 90 to receive TCZ-SC 162 mg q2w. At the end of phase 2, the percentage of patients who maintained the remission at week 48 was 91.5% with TCZ-SC qw and 73.9% with TCZ-SC q2w (p=0.002). Main efficacy outcomes for both phases of the study are presented in the table. Rates of serious adverse events (AEs) and rates of AEs leading to drug discontinuation were similar in patients treated with mono or combination therapy, and in patients treated with TCZ-SC qw or TCZ-SC q2w.

Phase 1 – Outcome	TCZ-SC monotherapy N=74	TCZ-SC Combination N=327	p-value
Sustained clinical remission, %	48.4	52.9	0.523
ACR20, %	79.7	83.3	0.495
ACR50, %	59.4	58.7	0.923
ACR70, %	40.6	37.7	0.666
ACR90, %	23.4	16.7	0.207
HAQ-DI (baseline/24 weeks), mean	1.49/0.85	1.36/0.82	NS
Phase 2 – Outcome	**TCZ-SC 162 mg qw N=89**	**TCZ-SC 162 mg q2w N=90**	**p-value**
Clinical remission, %	91.5	73.9	0.002
ACR20, %	96.4	88.8	0.056
ACR50, %	88.1	79.8	0.766
ACR70, %	71.4	65.2	0.377
ACR90, %	45.2	32.6	0.088
Mean change in DAS28	-0.02	0.35	0.037

Conclusions: In the real world setting, treatment with TCZ-SC 162 mg weekly in patients with active RA is associated with rate of sustained clinical remission of approximately 50% regardless it is administered as monotherapy or in combination with a sDMARD. The proportion of patients who remained in clinical remission at week 48 was significantly higher with TCZ-SC qw than with TCZ-SC q2w. The safety profile of TCZ-SC was consistent with previous studies of TCZ-SC and TCZ-IV
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SAT0184 THERAPEUTIC DRUG MONITORING ON RHEUMATOID ARTHRITIS PATIENTS WITH REDUCED DOSES OF INTRAVENOUS TOCILIZUMAB

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Background: Tocilizumab (TCZ) is an effective treatment for rheumatoid arthritis (RA). Literature suggests there is great variability in intravenous (iv) TCZ serum concentrations among individuals. Moreover, optimal drug dosage does not seem to be clear since Regulatory Agencies (FDA and EMA) approved the drug with a different initial posology. Empirical dose de-escalation strategies are being fostered in patients with disease remission.
Objectives: The purpose of the study was to examine TCZ serum concentrations at the different prescribed doses in RA. Secondary objectives were to evaluate the relationship between drug serum concentrations and laboratory parameters of disease activity.
Methods: Prospective, observational, single-center study conducted in a university tertiary hospital. Enrolled RA patients received iv TCZ at a dose range from 4 to 8 mg/kg every 28 days. Demographic characteristics and clinical laboratory data were obtained at study entry. Blood samples for drug concentration testing were collected from the third TCZ dose onwards, just before TZC infusion and, when possible, once a week until the next drug administration.
Results: 35 patients (88.6% women, 80% Caucasian) were included. Mean age ±SD was 54.1±12.3 and the median [range] of disease duration was 11.1 [2.9–48.5] years. Median treatment duration with iv TCZ was 36.5 [3–68] months. 54% of patients received the standard dose of 8mg/kg whereas the rest received reduced doses (23% were on 6mg/kg and 23% on 4mg/kg) due to persistent remission/low disease activity. 20 patients (57.1%) were being treated with low steroid dose and 24 (68.6%) were on concomitant DMARD, mainly methotrexate. Regarding drug concentration testing, a total of 109 samples were obtained. 19 patients participated to multiple drug sampling between two drug administrations and in the 17 remaining patients, a pre-dose sample was drawn. Mean TCZ concentrations are displayed in table 1 and showed in figure 1. No significant differences were observed in median pre-dose TCZ concentration values (54 samples) between patients on 8 and 6 mg/kg whereas significant lower drug levels were observed in those taking 4 mg/kg.
According to inflammatory parameters, mean C-reactive protein (CRP) concentration was significantly lower in those patients with trough TCZ concentrations >1μg/mL compared to those <1μg/mL (0.066mg/dL vs 0.689mg/dL, respectively; p<0.001). This difference was not observed with calprotectin serum concentrations (2.260μg/mL vs 2.143μg/mL).

Table 1. Mean (±sd) iv TCZ serum concentrations at different prescribed doses within time

Time (days)	TCZ 8 mg/kg	TCZ 6 mg/kg	TCZ 4 mg/kg
Pre-infusion (Ctrough)	8.9±6.1	5.7±9.1	0.8±1.2
T7	84.8±33.9	48.8±18.6	26.1±6.4
T14	46.4±19.8	31±11.4	15.2±5.6
T21	21.6±9.5	19.7±10.5	7.1±4.4
T28 (Ctrough)	10.6±7.3	10.3±10.8	1.3±2.3

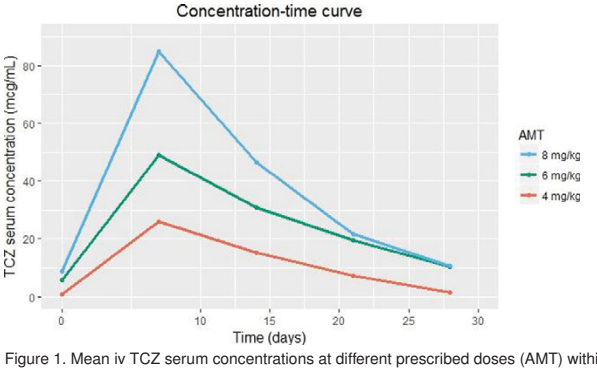

Figure 1. Mean iv TCZ serum concentrations at different prescribed doses (AMT) within time.

Conclusions: Trough TCZ serum concentrations do not differ between patients on an 8 and 6 mg/kg regimen. Therefore, according to the pharmacokinetics observed in our study, a maintenance dose of iv TCZ 6mg/kg would be appropriate for most RA patients. Although CRP levels are significantly higher in patients with trough iv TCZ concentrations <1μg/mL, serum calprotectin did not show the same tendency.
Disclosure of Interest: None declared
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