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FRI0247 MEDIAN TIME TO LOW DISEASE ACTIVITY IS SHORTER IN TOCILIZUMAB COMBINATION THERAPY WITH csDMARDS AS COMPARED TO MONOTHERAPY IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSES TO csDMARDS AND/OR TNF INHIBITORS: SUBANALYSIS OF THE SWISS AND AUSTRIAN PATIENTS FROM THE ACT-SURE STUDY

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Background: To analyze efficacy and safety of tocilizumab in patients with rheumatoid arthritis (RA) and an inadequate response to conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) and/or tumour necrosis factor (TNF) inhibitors of the Swiss and Austrian patients from the ACT-SURE study.

Objectives:

Methods: Sub-analysis of RA patients from Switzerland and Austria, who participated in the international phase IIIb, open-label, ACT-SURE study. Patients with an inadequate response to csDMARDs or TNF antagonists were included into the study receiving 8 mg/kg of IV tocilizumab every 4 weeks during a 24 week time period. Therapy with one or more csDMARDs could be continued as combination therapy with tocilizumab (Combo) or stopped, resulting in tocilizumab monotherapy (Mono), at the treating physician's discretion. These two patient groups were analyzed in separate and compared.

Results: Overall, 107 (22 on Mono vs 85 on Combo and) patients were treated with tocilizumab. The percentage of patients with at least one adverse event was significantly lower in the tocilizumab combination (58.8%) as compared to the monotherapy group (81.8%, $p=0.0458$). No differences in ACR20/50/70/90 response rates were observed between both treatment groups at week 24 (Mono: 63.6%, 40.9%, 22.7%, and 18.2% vs. Combo: 61.2%, 43.5%, 25.9%, and 10.6%). The median time to low disease activity (LDA) was significantly shorter in patients treated with tocilizumab combination therapy Mono: 9.1, Combo 7.9 weeks, Log Rank $p=0.038$).

Conclusions: In this post hoc regional sub-analysis of the ACT-SURE study no differences for disease activity were found comparing the two patient groups at week 24. However, median time to LDA was statistically shorter in patients treated with tocilizumab combination therapy as compared to tocilizumab monotherapy. Consequently, adding tocilizumab to csDMARD therapy rather than changing to tocilizumab monotherapy may be, in our opinion, the safest strategy to reach maximum effect in RA patients with active disease despite treatment with csDMARD. csDMARDs can be withdrawn either immediately due to adverse events or after at least low disease activity has been reached.

Disclosure of Interest: None declared

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FRI0248 INCIDENCE OF MELANOMA IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH TOCILIZUMAB

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Background: There have been conflicting reports whether patients with rheumatoid arthritis (RA) receiving conventional or biologic immunosuppressive therapies are at increased risk of specific malignancies. Melanoma is an aggressive malignancy with risk factors including sex, age, fair skin and elevated cumulative UV exposure. Interleukin-6 (IL-6) has a role in pro- and antitumorigenic pathways. Whether tocilizumab (TCZ), a biologic that alters IL-6 signaling, increases the risk of melanoma in patients with RA is unclear.

Objectives: This age- and sex-adjusted standardized incidence ratio (SIR) analysis compared the observed reports of melanoma in patients with RA treated with TCZ in clinical trial and postmarketing settings with the expected number of cases across geographic regions.

Methods: SIRs for melanoma were calculated from the TCZ clinical trials all-exposure population. Postmarketing rates were estimated from the TCZ Global Safety Database population. Both databases were searched cumulatively from 11 April 2005 to 10 October 2015. For clinical trials, observed reports of melanoma in patients with RA treated with TCZ were compared with expected number of cases in the general population based on the 2012 US Surveillance, Epidemiology, and End Results using an age- and sex-adjusted SIR. Postmarketing regional SIRs were calculated based on the estimated commercial exposure in each region and the incidence of melanoma as reported by Globocan by age and sex (2012).

Crude postmarketing rates were age- and sex-adjusted according to the clinical trial demographic profile to estimate the expected number of cases of melanoma in each region.

Results: In the clinical trial setting, 4 qualifying cases of melanoma were identified among 7093 patients with RA treated with TCZ (20,828 PY of exposure). The SIR estimate (0.71 [95% CI, 0.19–1.81]) for melanoma incidence in patients with RA treated with TCZ in clinical trials was comparable to that in the general population (Table 1). In the postmarketing setting, the number of observed reports of melanoma was comparable to the expected number of cases in Europe and Japan and fewer than expected in North America (Table 2). The exception is Australia, where SIR estimates indicated more than the expected number of cases in patients with RA receiving TCZ in Australia compared with the general population in that region (SIR 3.71 [95% CI: 2.16, 5.93]).

Table 1. Incidence of melanoma in patients with RA from TCZ clinical trials, stratified by sex

Sex	Observed cases ^a	Exposure (PY)	Expected cases ^b	SIR (95% CI)
Female	3	17,047	4.01	0.75 (0.15, 2.19)
Male	1	3781	1.66	0.60 (0.02, 3.35)
All	4	20,828	5.65	0.71 (0.19, 1.81)

^a The age range of patients in the study cases was 50–64.

^b Expected cases are based on Surveillance, Epidemiology, and End Results 2012 age-standardized incidence rates.

Table 2. Incidence of melanoma in patients with RA from TCZ postmarketing reports, stratified by region

Region	Observed cases	Region-Specific Exposure (PY) ^a	Expected cases ^d	SIR (95% CI)
Europe	30	126,683	26.6	1.13 (0.76, 1.61)
North America	17	131,546	36.9	0.46 (0.27, 0.74)
Japan	2	121,732	1.5	1.38 (0.17, 4.98)
Australia	17	6,480	4.6	3.71 (2.16, 5.93)

^c Combined exposure from Europe, North America, Japan and Australia accounts for 86% of the total cumulative postmarketing exposure and for all cases of melanoma at the data lock point of 10 October 2015.

^d Expected cases are based on region-specific incidence rates in the general population (Globocan 2012).

PY, patient years; SIR, standardized incidence ratio; TCZ, tocilizumab.

Conclusions: In clinical trials, no evidence was found to suggest there were more cases of melanoma than expected in patients with RA treated with TCZ compared with the general population. Consistent with this, no evidence was found to suggest that patients with RA treated with TCZ in Europe, North America or Japan had more cases of melanoma than expected compared with the general population in each region. In contrast, the estimated SIR of melanoma in patients with RA treated with TCZ in Australia indicated more than the expected number of cases in the general population. This finding is consistent with reports of elevated risk of melanoma in patients with RA in Australia (compared with the general population), where UV exposure is high and methotrexate is a common first-line therapy.^{1,2}

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FRI0249 CIRCULATING FOLLICULAR HELPER-LIKE T CELLS IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH ABATACEPT

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Background: Rheumatoid arthritis (RA) is characterized by synovial inflammation and, in most cases, by autoantibodies, including rheumatoid factor (RF) and anti-cyclic citrullinated peptide antigen (ACPA), whose presence is associated to a more severe disease. The capability of producing autoantibodies is acquired by B cells with the "help" of specialized T lymphocytes, known as Follicular helper T (TFH) cells, in the germinal centers (GC) of secondary lymphoid tissues. TFH express the inducible co-stimulator (ICOS), and are characterized by a high expression of CXC-chemokine receptor 5 (CXCR5), which mediate their migration into the GC, where its ligand CXCL13 is expressed. Here, TFH promote the GC development and B cell maturation. These cells are reported to exist in greater quantities in the peripheral blood (circulating TFH-like cells) of RA patients.

Abatacept (ABA) is a fusion protein, which through its CTLA4 portion can bind to CD80 and CD86 on antigen presenting cells, thereby inhibiting CD28 costimulation. Data from animal models and phenotypic analysis of circulating T cells in RA suggest that ABA may act in the secondary lymphoid organ, and not directly on the synovium (1,2). While experimental models show that ABA can block the generation of TFH (3), little is known on the effect of ABA on circulating TFH-like cells of RA patients (4).

Objectives: To analyze the effect of the blockade of costimulation performed by

ABA on the levels of circulating TFH-like cells of RA patients.

Methods: 25 RA patients (F/M=18/7; median age (25th-75th percentile): 57 (44–63) years; ACPA+: 16 (64%); RF+: 17 (68%)), treated for at least 6 consecutive months with ABA were evaluated. Circulating TFH-like cells were identified by flow-cytometry as CD4+ICOS+CXCR5+. The response to treatment was evaluated with the EULAR Criteria.

Results: After 6 months of therapy with ABA the percentage of circulating TFH-like cells among total CD4+ T-cells tended to decrease from a median of 1.8 (0.6–3.8) to 0.8 (0.1–2.3) (p:0.07; Wilcoxon signed rank test). The percentage of circulating TFH-like cells at baseline was higher among patient who did not respond to ABA (n:8; 2.6 (2.0–3.6)) than in those who achieved a moderate or good EULAR response (n:17; 1.0 (0.5–5.4)) (p<0.01; Mann-Whitney test), but their trend of reduction was similar in the two groups of patients. No difference in the levels of circulating TFH-like cells was found between ACPA+ and ACPA- RA patients.

Conclusions: ABA tends to reduce the number of circulating TFH-like cells in RA patients, suggesting the relevance of costimulation via CD28 in their generation. A higher percentage of these cells is present in patients not responding to ABA. While this observation suggests their possible use as predictors of clinical response to ABA, further studies are deserved to evaluate whether it reflects different localizations of TFH, or functional variability within this T-cell subset in patients with RA.

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FRI0250 SERIOUS ADVERSE EVENTS IN PATIENTS WITH RA TAKING ABATACEPT COMPARED WITH OTHER DMARDS BY LINE OF TREATMENT

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Background: Observational studies are critical in assessing medication safety and effectiveness in the real world. Nonrandom assignment can provide insight to how and when medications are prescribed. Since the US introduction of TNF inhibitors (TNFi) in 1998, several newer biologics with varying mechanisms of action are available to patients and physicians.

Objectives: To compare baseline characteristics and serious adverse events (serious infections (SI), malignancies) of patients who received abatacept (ABA) compared to those who received other comparison cohorts: conventional DMARDs (cD) and biologic DMARDs (bD) by line of treatment.

Methods: Participating patients from 2005–2015 with RA in the National Data Bank for Rheumatic Diseases (NDB) provided treatment and other characteristics through self-reported biannual questionnaires. Initiators of ABA were matched to patients initiating other DMARDs in a 1:3 ratio. All patient-reported outcomes were verified by medical record review. ITT (OT) analyses were performed for malignancies (SI). Incidence rates were calculated using Poisson regression (1000 patients-years (pt-yr)). Marginal structural models were used to estimate the effect of treatment on the outcome by an appropriate control for the effects of time-dependent confounders using stabilized weights and reported as hazard ratios (HR). Variables included sex, employment, smoking, education, income, BMI, insurance, comorbidity index, RA severity, and co-medications.

Results: Overall 1496 ABA patients with 2502 (4896) pt-yr of drug exposure (total follow-up time), 1520 cD treated patients with 4330 pt-yr of drug exposure (4816) and 3490 bD treated patients with 9658 pt-yr of drug exposure (11777) were studied (overall mean age 62 years (83% female)). At baseline, the distribution of first line patients in the several cohorts was: 15.2% ABA, for 23.4% bD and 33.8% cD. Switchers were more likely to have longer duration of RA (mean values (yrs): 11.4 for ABA, 8.3 cD; 14.7 bD first line vs. 17.6 ABA; 17.4 cD; 18.0 bD switchers), higher comorbidities, including prior cancer. ABA patients had worse disease compared to cD or bD, both used as first line or as switchers (mean HAQ any line for ABA 1.3 vs 1.0 (1.2) cD or 1.0 (1.3) bD as first line or as switchers).

Table 1. Incidence rates of malignancies and SI for 3 RA treatment cohorts by line of treatment

	ABA	cD	bD
All malignancies			
0	8.2 (1.7–23.9)	8.2 (4.8–13.1)	5.1 (2.8–8.5)
1	6.3 (2.3–13.7)	11.8 (4.3–25.7)	5.0 (2.2–9.8)
2+	8.3 (4.4–14.3)	4.5 (0.1–25.2)	4.7 (1.5–11.0)
SI			
0	3.0 (0.1–16.6)	15.3 (11.2–20.5)	15.1 (11.4–19.5)
1	17.9 (10.0–29.6)	27.2 (16.9–41.6)	18.6 (13.4–25.1)
2+	19.4 (12.0–29.7)	33.1 (16.5–59.2)	23.9 (16.6–33.2)

Excluding patients with prior events, incidence rates of malignancies tended to be uniform by line of treatment but SI seemed to increase with higher exposure of prior biologics, in all cohorts (Table). HR estimates by MSM did not show an increased risk for ABA in comparison with both cohorts, irrespectively of the line of treatment considered.

Conclusions: Differences in baseline characteristics revealed that channeling bias might be present when comparing ABA with other DMARDs and by line of treatment. After adjustment, no overall risk was found for increased risk of cancer and infections.

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FRI0251 SIRUKUMAB, AN ANTI-IL-6 CYTOKINE MONOCLONAL ANTIBODY, LEADS TO IMPROVEMENTS IN WORK PRODUCTIVITY AND GENERAL HEALTH STATUS IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS REFRACTORY TO ANTI-TNF THERAPY: RESULTS FROM THE PHASE 3 SIRROUND-T STUDY

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Background: Sirukumab is an anti-interleukin-6 (IL-6) monoclonal antibody that selectively binds to the cytokine with high affinity and is in development for rheumatoid arthritis (RA) and other diseases.

Objectives: This study evaluated the effects of sirukumab on work productivity/interference and health status in patients with active RA despite treatment with anti-tumor necrosis factor (TNF) therapy.

Methods: In this randomized, double-blind, phase 3 trial, 878 eligible patients with active RA who were intolerant/refractory to anti-TNFs were randomized 1:1:1 to sirukumab subcutaneous (SC) 50mg every 4 weeks (q4w; n=292), sirukumab SC 100mg every 2 weeks (q2w; n=292), or placebo SC q2w (n=294). At Week 18, placebo patients were re-randomized to 1 of the sirukumab doses if insufficient (<20%) improvement; at Week 24, all patients remaining on placebo crossed over to sirukumab. The Work Limitations Questionnaire (WLQ) evaluated health-related job limitations and productivity loss in 4 domains (mental-interpersonal, output, physical demands, time management); the 3-level EuroQol-5 Dimension (EQ-5D) questionnaire measured 5 dimensions of health status (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).

Results: At Week 24, mean total WLQ scores improved significantly from baseline for sirukumab 50mg q4w and 100mg q2w versus placebo (mean change, -2.2 and -2.3 vs 0.2, respectively; both p<0.001), as did all 4 mean WLQ domain scores (all p<0.01). Improvements from baseline in mean total WLQ and all 4 domain scores were maintained through Week 52 for both sirukumab doses. Mean EQ-5D index and health state visual analog scale (VAS) scores improved significantly from baseline at Week 24 for sirukumab 50mg q4w and 100mg q2w versus placebo (mean index change, 0.2 and 0.2 vs 0.0, respectively; mean VAS change, 13.9 and 15.4 vs 4.8, respectively; all p<0.001); improvements from baseline were maintained through Week 52 with both sirukumab doses.

Conclusions: Sirukumab treatment led to significant improvements in work-related productivity and general health status in patients with active RA despite anti-TNF therapy, consistent with demonstrated effects of sirukumab on RA disease improvement.

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