cases occurred both early and lately during treatment courses, suggesting LTBI screening failures, treatment non-adherence or re-exposure. Current application and content of the protocol for screening and treatment of LTBI needs to be reviewed.

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SAT0124 MOLECULAR CHARACTERIZATION OF THE SERUM PROFILE ASSOCIATED TO THE INCREASED CARDIOVASCULAR RISK IN RHEUMATOID ARTHRITIS PATIENTS. EFFECTS OF BIOLOGICAL DRUGS.

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Background:

Objectives: 1- To characterize the serum molecular profile associated to the increased cardiovascular (CV) risk in Rheumatoid Arthritis (RA) patients. 2- To evaluate the *in vivo* and *in vitro* effects of biological drugs on the reestablishment of this altered molecular profile.

Methods: Serum samples of 280 RA patients and 100 healthy donors (HD) were studied. miRNomes were identified using next-generation sequencing miRNA assay (HTG EdgeSeq technology). The inflammatory profile, Netosis-derived products, and circulating biomolecules related to oxidative stress were quantified using commercial kits. The Cardiovascular Risk SCORE for RA patients was calculated following EULAR recommendations. Carotid intima-media thickness (CIMT) was evaluated as early atherosclerosis marker. The in vivo effects of biologic drugs such as Infliximab (IFX), Tocilizumab (TCZ) and Rituximab (RTX) were evaluated before and after 6 months of therapy in 45, 20 and 25 RA patients, respectively. Serum from RA patients with high and low CV risk scores -either before and after IFX, TCZ and RTX therapies-, were further added to HUVECs, monocytes, and neutrophils purified from HD, and activity profiles were evaluated.

Results: The miRNA whole transcriptome assay identified 104 circulating miRNAs altered in RA patients. Functional classification (IPA) established their involvement in inflammatory response, as well as in immunological and hematological diseases. Circulating biomolecules related to inflammation -interleukins, chemokines, adhesion molecules-, Netosis -cell-free nucleosomes, elastase and DNA- and oxidative stress -lipoperoxides, nitrated proteins, and total antioxidant capacity- were also found coordinately altered in the serum of RA patients. Multivariate analyses showed that levels of a number of those altered biomolecules and circulating microRNAs were predictors of a high Cardiovascular Risk SCORE and the presence of a pathologic CIMT in RA patients.

The in vivo treatments with IFX, TCZ and RTX for six months reduced disease activity and induced the re-establishment of normal levels in those altered biomolecules in RA patients. Mechanistic *in vitro* studies showed increased pro-inflammatory profiles of leukocytes subsets and HUVECSs after treatment with serum from high CV risk score-RA patients. These profiles were reversed by incubation with serum from those patients after biologic drugs treatment.

Conclusion: 1. Specific mediators of inflammation, oxidative damage and Netosis, along with the microRNAs modulating their expression, coordinately contribute to the higher CV risk score present in RA patients. 2. Biologic drugs such as IFX, TCZ and RTX, restore the normal levels of these altered biomolecules, reducing the CV risk in RA patients.

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SAT0125 LONG-TERM SAFETY WITH SARILUMAB PLUS CONVENTIONAL SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS AND SARILUMAB MONOTHERAPY IN RHEUMATOID ARTHRITIS: AN INTEGRATED ANALYSIS WITH 9,000 PATIENT-YEARS OF FOLLOW-UP

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Background: Sarilumab, a human IL-6R blocker approved for the treatment of RA, has shown efficacy as monotherapy and in combination with csDMARDs in Phase 3 trials.

Objectives: We assessed long-term safety from the sarilumab clinical development program in adult patients with RA who received subcutaneous (SC) sarilumab in eight clinical trials and their open-label extensions: MOBILITY (NCT01061736), TARGET (NCT01709578), ASCERTAIN (NCT01768572), EASY (NCT02057250), COMPARE (NCT01764997), ACT11575 (NCT01217814), MONARCH (NCT02332590), ONE (NCT02121210), and the open-label extension EXTEND (NCT01146652).

Methods: Data (cut-off Jan 15, 2018) were pooled from patients on sarilumab+csDMARD (N=2887) or sarilumab monotherapy (N=471). Patients had received sarilumab 200 mg or 150 mg q2w SC, except for 151 patients from MOBILITY Part A who received 100 mg qw, 150 mg qw, or 100 mg q2w. Treatment-emergent (TE) adverse events (AEs), AEs of special interest (AESIs), and discontinuations were assessed.

Results: Demographics were similar between combination and monotherapy pools (mean age 52 years; 81–83% female), and 38.7% and 8.5% of patients had received prior bDMARDs. Cumulative drug exposure was 7,985.5 and 798.7 patient-years (PY), with maximum duration 7.3 and 3.5 years. Exposure-adjusted rates of TEAEs, serious AEs, and TEAEs leading to discontinuations were similar (Table). Infections were the most common AESI. Rates of serious infection were 3.7 and 1.0/100 PY for combination and monotherapy, respectively, and were not associated with decreased absolute neutrophil counts (ANCs). Incidences of ALT >3× upper limit of normal and ANC <1.0 giga/L were 10.3% and 12.7% for combination, respectively, and 5.5% and 14.9% for monotherapy. Rates of confirmed GI perforation for combination and monotherapy were 0.1 and 0/100 PY. Analyzing data by 6-month intervals showed no increase in rate over time for serious infections, malignancy, major adverse cardiac events, or ANC <1.0 giga/L.

	Sarilumab+csDMARD (N=2887)	Sarilumab monotherapy (N=471)
Safety overview: n/Y_{FE} (IR/100 PY)[a]		
TEAEs	2489/1726 (144.2)	386/254 (151.8)
Serious TEAEs	685/7270 (9.4)	52/770 (6.7)
TEAEs leading to death	31/8187 (0.4)	5/812 (0.6)
TEAEs leading to discontinuation	705/8061 (8.7)	53/805 (6.6)
AESI: number of events (IR/100 PY)[b]	**PY=8187.7**	**PY=812.4**
Infections	4451 (54.4)	446 (54.9)
Serious infections	301 (3.7)	8 (1.0)
Opportunistic infections	76 (0.9)	6 (0.7)
Herpes zoster[c]	53 (0.6)	4 (0.5)
Tuberculosis[c]	4 (0.0)	1 (0.1)
Leukopenia[d]	1482 (18.1)	244 (30.0)
Thrombocytopenia[d]	147 (1.8)	8 (1.0)
Hepatic disorders	726 (8.9)	58 (7.1)
Confirmed GI perforations[e]	9 (0.1)	0
Elevation in lipids[d]	498 (6.1)	18 (2.2)
Major adverse cardiovascular events[f]	45 (0.5)	2 (0.2)
Hypersensitivity	444 (5.4)	48 (5.9)
Anaphylaxis	0	0
Injection site reactions	1934 (23.6)	279 (34.3)
Malignancy	56 (0.7)	5 (0.6)
Malignancy excluding NMSC	38 (0.5)	4 (0.5)
Lupus-like syndrome	5 (0.1)	0
Demyelinating disorders	0	1 (0.1)

n. number of patients; Y_{FE}, cumulative years at risk of first event; IR, incidence rate; GI, gastrointestinal; NMSC, non-melanoma skin cancer; PY, patient-years. [a]Exposure period is cumulative time at risk of first event; [b]AESI were investigator reported; exposure period is cumulative total TEAE period; [c]herpes zoster was reported as an opportunistic infection per protocol requirement; all cases of tuberculosis were reported as opportunistic infections; [d]individual events were reported and laboratory abnormalities were not necessarily persistent; [e]3 upper, 6 lower; [f]MACE includes cardiovascular death, myocardial infarction, stroke, hospitalization for either unstable angina and/or transient ischemic attack.

Conclusion: The long-term safety profile of sarilumab, either as monotherapy (observed for >3.5 years) or with csDMARD (observed for >7 years), remains stable and consistent with the anticipated profile of an IL-6R blocker.

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SAT0126

A PHASE 2 STUDY OF E6011, AN ANTI-FRACTALKINE MONOCLONAL ANTIBODY, IN PATIENTS WITH RHEUMATOID ARTHRITIS INADEQUATELY RESPONDING TO BIOLOGICS

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Background: Fractalkine (CX3CL1, designated as FKN hereafter) is the sole member of the CX3C-chemokine which leads to dual actions, chemotaxis and cell adhesion for leukocytes expressing the cognate receptor, CX3CR1, during their migration. We have conducted clinical trials of E6011, a novel humanized anti-FKN monoclonal antibody, for patients with rheumatoid arthritis (RA) in Japan[1]. This is the first report of a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study of E6011 in RA patients inadequately responding to biologics (NCT02960490).

Objectives: To evaluate efficacy and safety of E6011 compared with placebo.

Methods: During the 24-week double-blind period, patients with moderately to severely active RA of inadequate response to biologics were randomly assigned to E6011 400 mg or placebo groups at a 1:1 ratio. Patients who continued the study beyond Week 12 were further allocated to E6011 200 mg or 400 mg at a 1:1 ratio within the initially assigned group. Patients received either E6011 400 mg or placebo at Weeks 0, 1, 2, and every 2 weeks subsequently until Week 10 and then E6011 200 mg or 400 mg every 2 weeks between Weeks 12 and 22 in a double-blind manner. This abstract reports the results from the first 12-week placebo controlled period.

Results: A total of 64 subjects (33 in the placebo group and 31 in the E6011 400 mg group) received study drug. Of the 64 subjects, 55 completed and 9 discontinued study treatment prematurely during the 12-week placebo controlled double-blind period. The ACR20 response rate at Week 12 (non-responder imputation), the primary endpoint, was 27.3% (9/33 subjects) in the placebo group and 22.6% (7/31 subjects) in the E6011 group. ACR50 and ACR70 response rate at Week 12 were 3.0%, 0% in the placebo group and 9.7%, 3.2% in the E6011 group, respectively. Numerically greater improvement from baseline was found for some parameters of the ACR components in the E6011 group, however, no statistically significant differences were found in any of the ACR components between the placebo and E6011 groups. From the exploratory PK exposure analysis, there was a tendency that the effect of E6011 became clearer in the subjects who achieved higher serum trough E6011 concentration. Adverse events that occurred in at least 2 subjects in the E6011 group were stomatitis, injection site erythema, nasopharyngitis, and blood creatine phosphokinase increased. As a results, E6011 was well tolerated with no notable safety concerns at doses of 400 mg when administered subcutaneously for 12 weeks.

Conclusion: E6011 400 mg was well tolerated but did not show clear efficacy at Week 12 compared with placebo in RA patients with inadequately responding to biologics. Further investigation to seek an optimal clinical dose and evaluation period of E6011 are warranted.

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