**Oral Presentations**

**tsDMARD therapy of rheumatoid arthritis**

**OP0001 BARICITINIB, TOFACITINIB, UPADACITINIB, FILGOTINIB, AND CYTOKINE SIGNALING IN HUMAN LEUKOCYTE SUBPOPULATIONS: AN UPDATED EX-VIVO COMPARISON**

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**Background:** Several JAKi are now used for the treatment of RA; approved doses include baricitinib (bari) 2- and/or 4-mg QD, tofacitinib (tofa) 5-mg BID, upadacitinib (upa) 15-mg QD. The JAK selectivity these agents is proposed to vary across the class.

**Objectives:** In vitro cellular pharmacology of bari to tofa, upa, and filgotinib (filgo) were compared.

**Methods:** PBMCs from 6 healthy donors were incubated with the JAKis over a 7- to 8-point concentration range. Following cytokine stimulation, levels of pSTAT were measured and IC50 calculated in gated leukocyte subpopulations. Therapeutic dose relevance was assessed using calculated mean concentration-time (CT) profiles over 24 hours for bari 2- and 4-mg QD; tofa 5- and 10-mg BID; upa 15- and 30-mg QD; filgo 100- and 200-mg QD. Average daily % inhibition of pSTAT (%SI) was calculated for each JAKi, cytokine, and cell type; filgo %SI integrated parent drug + metabolite.

**Results:** The cytokines did not signal in all cell types (Figure 1). When signaling was detected, IC50 and %SI for a particular JAKi were generally similar across cell types, with dose-dependent inhibition (Figures 1 & 2). Based on IC50s, upa was most and filgo/metabolite least potent across JAK2/2 or JAK2/TYK2-dependent (IL-3, GM-CSF, G-CSF), JAK1/3-dependent (IL-2, 4, 15, 21), and JAK1/2/TYK2 dependent (IL-6 & 10, IFN-α & γ) signaling pathways. Incorporating CT profiles, no agent potently or continuously inhibited an individual cytokine signaling pathway throughout the dosing interval. Comparing bari 4-mg to tofa 5-mg BID, upa 15-mg QD, and filgo 100-mg QD, %SI of JAK2/2 or JAK2/TYK2-dependent cytokines was highest with bari 4-mg and upa. Inhibition of JAK1/2/TYK2 cytokines was highest with bari 4-mg. Inhibition of JAK2/2 or

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**Figure 1.** IC50 values (nM) for baricitinib, tofacitinib, upadacitinib, filgotinib (parent and metabolite) in cytokine-stimulated human PBMC preparations. *p<0.01, **p<0.001, ***p<0.0001 vs. bari.

**Figure 2.** Baricitinib, tofacitinib, upadacitinib, filgotinib: calculated average percent daily STAT inhibition for selected cytokines. −p<0.01, −−p<0.001, −−−p<0.0001 significantly lower compared to bari (vs. 2-mg if left of vertical line "|", vs. 4-mg if right of vertical line "|"). ++p<0.01, +++p<0.001, ++++p<0.0001 significantly higher compared to bari (vs. 2-mg if left of vertical line "|", vs. 4-mg if right of vertical line "|").

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Cardiovascular risk and management in IMIDS

OP0002

INCIDENCE OF FIRST CARDIOVASCULAR EVENT IN SPANISH PATIENTS WITH CHRONIC INFLAMMATORY RHEUMATIC DISEASES: PROSPECTIVE DATA FROM THE CARMA PROJECT AFTER 5 YEARS OF FOLLOW-UP

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Objectives: To determine the incidence and risk factors implicated in the development of first cardiovascular (CV) event (CVE) in patients with chronic inflammatory rheumatic diseases (CIRD) attending Spanish rheumatology clinics after 5 years of follow-up

Methods: Analysis of data of patients included in an observational prospective study (CARMA Database in rheumatology (CARMA) project) after 5 years of follow-up. The study includes a cohort of 2234 patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA), and another cohort of matched individuals (n=677) without CIRD from 67 hospitals in Spain. Cumulative incidence per 1000 patients of CVE was estimated in both cohorts at 5 years from the start. Weibull proportional hazard model was used to calculate the Hazard Ratio (HR) and 95% confidence intervals (CI) of the risk factors identified in the development of CV events. Losses to follow-up and their causes were also analyzed.

Results: The total number patient who completed the follow-up visit at 5 years was 2382 (81.9%). Fifteen patients died due to CVE and sixty due to non-CVE. The patients with CIRD showed higher cardiovascular cumulative incidence (40.5, 95% CI: 36.2-44.8) than controls (28.3, 95% CI: 21.8-34.8). The higher risk of developing a first CVE during the 5 years of follow-up was seen in patients with AS (HR: 4.60, 95% CI: 3.12-15.99; p=0.02), those with older age (HR:1.09, 95% CI: 1.05-1.13; p<0.001), higher systolic blood pressure (HR: 2.64; 95% CI: 1.32-5.25; p=0.006), and those with longer duration of the rheumatic disease (HR: 1.07; 95% CI: 1.03-1.12; p=0.002). In contrast, woman gender was a protective factor (HR: 0.45; 95% CI: 0.21-0.99; p=0.047).

Conclusion: Patients with AS prospectively followed-up at rheumatology outpatient clinic showed higher risk of developing a first CVE than those without CIRD. Besides traditional CV disease risk factors, a longer time course of the disease is a risk factor for the development of CV disease in patients with CIRD.

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Detection of type I interferon – Bridges into clinical applications

OP0003

EARLY AND SUSTAINED RESPONSES WITH ANIFROLUMAB TREATMENT IN PATIENTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) IN 2 PHASE 3 TRIALS

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Background: In the phase 3 TULIP-2 and TULIP-1 trials in SLE, treatment with the type I interferon receptor antibody anifrolumab resulted in higher percentages of patients with BICLA responses vs placebo at Week 52, with differences of 16.3% (primary endpoint; P=0.001, 95% CI 6.3–26.3) and 16.4% (secondary endpoint; P=0.002, 95% CI 6.3–26.3) vs placebo. This was supported by a higher percentage of patients with sustained responses with anifrolumab vs placebo at Week 52 (9.3% vs 3.1%, respectively; P=0.008). The percentage of patients who achieved remission (BICLA ≥ 50) with anifrolumab was also higher at Week 52 (16.3% vs 7.0%, respectively; P<0.001). However, the mechanism by which anifrolumab achieves these benefits is unknown.

Objectives: To better understand the time course of BICLA responses to anifrolumab, we examined responses over time compared with placebo in the TULIP-2 and TULIP-1, including those that were sustained from attainment to follow-up through Week 52.

Methods: The TULIP-2 and TULIP-1 randomized, double-blind, placebo-controlled trials evaluated the efficacy and safety of anifrolumab (300 mg Q4W) over 52 weeks in patients with moderately to severely active SLE who were receiving standard-of-care treatment. Time to onset of BICLA response that was sustained