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/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/TYK2 cytokines was highest with bari 4-mg. Inhibition of JAK2/2 or TYK2-dependent cytokines was highest with bari 4-mg. Inhibition of JAK2/2 or TYK2-dependent cytokines was highest with bari 4-mg.
Cardiovascular risk and management in IMIDs

OP0002

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


References:

OP0003

EARLY AND SUSTAINED RESPONSES WITH ANIFROLUMAB TREATMENT IN PATIENTS WITH ACTIVATED 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; 95% CI 6.3–26.3) respectively.

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

Methods: Analysis of data of patients included in an observational prospective study (CARMA) in rheumatology centers (94) after 5 years of follow-up. The study included 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 implicated in the development of CVE events. Losses to follow-up and their causes were also analyzed.

Results: The total number of patients who completed the follow-up visit at 5 years was 2,382 (81.9%). Fifteen patients died due to CVE and six 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 in patients with AS (HR: 4.60, 95% CI: 1.32–15.99; p<0.02), with those 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 clinics 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

OP0004

ICY CYTOKINE MODULATION AMONG MEMBERS OF THE JAKi CLASS: IN VITRO MODULATORY EFFECTS ON CYTOKINE PROFILES, PHENOTYPES AND CELL FUNCTIONALITY

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Methods: In a recent study, we analyzed the overall cytokine modulatory potential of members of the JAKi class. JAKis display different in vitro pharmacologic profiles which, coupled to their in vivo pharmacokinetics, suggest they modulate distinct cytokine pathways to differing degrees and durations over 24 hours. Ex vivo whole cell assays seem distinct from cell free kinase inhibition assays in determining the overall cytokine modulatory potential of members of the JAKi class.

References: