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.

JAK2/2- or JAK2/Tyk2

stimulus	response	population	Upadacitinib	Baricitinib	Tofacitinib	Filgotinib	Filgotinib metabolite
G-CSF	STAT3	Monocytes	91.9	25.9	189.0 ***	2,176.3 ***	32,833.3 ***
G-CSF	STAT3	Monocytes	137.3 ***	25.8	134.3 ***	2,319.7 ***	25,454.3 ***
G-CSF	STAT3	B Cells	137.3 ***	197.1	786.8 ***	8,359.3 ***	67,499.3 ***
G-CSF	STAT3	Monocytes	36.8 **	39.7	231.9 ***	4,708.5 ***	62,456.3 ***

JAK1/JAK2/Tyk2

stimulus	response	population	Upadacitinib	Baricitinib	Tofacitinib	Filgotinib	Filgotinib metabolite
IFN-α	STAT1	B Cells	77.4	93.9	244.7 ***	2,176.3 ***	32,833.3 ***
IFN-α	STAT1	CD4+ T Cells	43.1 **	43.3	157.8 ***	1,478.9 ***	24,523.3 ***
IFN-α	STAT1	CD8+ T Cells	49.3	66.1	172.9 ***	1,957.2 ***	24,589.3 ***
IFN-α	STAT1	Monocytes	48.8 ***	93.6	242.7 ***	2,389.6 ***	36,647.3 ***
IFN-α	STAT1	NK Cells	79.4	74.8	189.3 ***	1,469.9 ***	24,647.3 ***
IFN-α	STAT3	B Cells	18.6	16.8	65.8 ***	4,887.3 ***	67,499.3 ***
IFN-α	STAT3	CD4+ T Cells	13.0 **	29.2	68.8 ***	4,738.3 ***	67,499.3 ***
IFN-α	STAT3	CD8+ T Cells	11.4	29.8	93.8 ***	4,887.3 ***	67,499.3 ***
IFN-α	STAT3	Monocytes	9.7 ***	11.8	27.5 ***	345.7 **	3,897.3 ***
IFN-α	STAT3	NK Cells	13.9	11.9	38.8 ***	471.3 ***	5,181.3 ***
IFN-γ	STAT1	B Cells	39.7	39.7	126.7 ***	2,271.6 ***	32,861.3 ***
IFN-γ	STAT1	Monocytes	49.4	34.7	111.8 ***	859.9 ***	7,738.3 ***
G-CSF	STAT3	CD4+ T Cells	49.4	34.7	111.8 ***	859.9 ***	7,738.3 ***
G-CSF	STAT3	Monocytes	39.8	29.8	78.6 ***	859.9 ***	12,942.3 ***
G-CSF	STAT3	B Cells	39.8	49.3	144.9 ***	1,837.4 ***	21,778.3 ***
G-CSF	STAT3	CD4+ T Cells	47.8	48.8	133.2 ***	1,874.3 ***	22,345.3 ***
G-CSF	STAT3	CD8+ T Cells	47.8 ***	58.2	133.2 ***	1,126.8 ***	22,097.3 ***
G-CSF	STAT3	Monocytes	39.8 ***	48.7	178.3 ***	2,483.4 ***	32,097.3 ***
G-CSF	STAT3	NK Cells	189.8 ***	62.3	174.9 ***	1,189.5 ***	22,097.3 ***

JAK1/JAK3

stimulus	response	population	Upadacitinib	Baricitinib	Tofacitinib	Filgotinib	Filgotinib metabolite
G-CSF	STAT3	CD4+ T Cells	11.3 ***	23.3	29.5	489.1 ***	12,365.3 ***
G-CSF	STAT3	CD8+ T Cells	11.3 ***	11.3	23.3 **	555.0 ***	8,979.3 ***
G-CSF	STAT3	NK Cells	29.8	29.8	93.6 ***	732.3 ***	8,979.3 ***
G-CSF	STAT3	B Cells	33.8 ***	45.8	93.6	2,878.2 ***	36,647.3 ***
G-CSF	STAT3	CD4+ T Cells	12.9 ***	25.3	32.3	786.9 ***	18,510.3 ***
G-CSF	STAT3	CD8+ T Cells	16.9 ***	21.3	28.6	714.2 ***	8,979.3 ***
G-CSF	STAT3	Monocytes	16.9 ***	21.3	61.8 ***	817.1 ***	22,097.3 ***
G-CSF	STAT3	NK Cells	11.8 **	23.3	27.9	555.0 ***	12,365.3 ***
G-CSF	STAT3	CD4+ T Cells	15.9 ***	25.8	31.3	864.2 ***	12,310.3 ***
G-CSF	STAT3	CD8+ T Cells	24.5 ***	34.9	44.5	1,184.4 ***	18,557.3 ***
G-CSF	STAT3	NK Cells	27.1	33.8	65.7 **	1,827.7 ***	18,529.3 ***
G-CSF	STAT1	B Cells	9.3 ***	24.8	21.2	927.9 ***	8,989.3 ***
G-CSF	STAT1	CD4+ T Cells	9.3 ***	24.8	29.6	738.8 ***	8,147.3 ***
G-CSF	STAT1	CD8+ T Cells	18.0 ***	33.3	39.6	792.0 ***	7,489.3 ***
G-CSF	STAT1	NK Cells	14.0 ***	24.8	22.2	815.3 ***	8,437.3 ***
G-CSF	STAT3	B Cells	19.8 ***	27.9	30.8	1,339.8 ***	22,097.3 ***
G-CSF	STAT3	CD4+ T Cells	19.8 ***	42.8	30.8	1,374.2 ***	21,653.3 ***
G-CSF	STAT3	CD8+ T Cells	29.7 ***	42.8	51.4	1,283.0 ***	28,782.3 ***
G-CSF	STAT3	NK Cells	33.3 ***	44.3	51.4	1,286.8 ***	28,389.3 ***
G-CSF	STAT3	CD4+ T Cells	1.8 ***	16.8	21.3	552.5 ***	8,981.3 ***
G-CSF	STAT3	CD8+ T Cells	9.8 ***	18.8	22.3	553.1 ***	7,128.3 ***

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.

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 potentially 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

JAK2/2- or JAK2/Tyk2

stimulus	response	population	Bari 2mg QD	Bari 4mg QD	Filgo combined 100mg QD	Filgo combined 200mg QD	Tofa 5mg BID	Tofa 10mg BID	Upa 15mg QD	Upa 30mg QD
G-CSF	STAT3	Monocytes	29.84	28.40	1.12	15.56	27.25	24.17	25.22	27.42
G-CSF	STAT3	Monocytes	29.54	44.78	6.47	17.25	25.95	22.84	24.46	24.78
G-CSF	STAT3	B Cells	11.94	18.19	9.86	14.54	11.85	7.12	12.85	22.04
G-CSF	STAT3	Monocytes	15.54	28.89	2.81	17.25	25.95	22.84	24.46	24.78

JAK1/JAK2/Tyk

stimulus	response	population	Bari 2mg QD	Bari 4mg QD	Filgo combined 100mg QD	Filgo combined 200mg QD	Tofa 5mg BID	Tofa 10mg BID	Upa 15mg QD	Upa 30mg QD
IFN-α	STAT1	B Cells	18.88	18.74	9.99	14.56	19.20	19.88	14.76	23.98
IFN-α	STAT1	CD4+ T Cells	18.83	29.10	15.32	24.58	28.15	18.15	28.14	31.46
IFN-α	STAT1	CD8+ T Cells	18.91	27.79	15.32	24.58	28.15	18.15	28.14	31.46
IFN-α	STAT1	Monocytes	19.34	24.19	15.32	24.58	28.15	18.15	28.14	31.46
IFN-α	STAT1	NK Cells	18.81	24.40	15.32	24.58	28.15	18.15	28.14	31.46
IFN-α	STAT3	B Cells	48.34	54.29	44.89	47.15	45.84	38.11	52.54	58.46
IFN-α	STAT3	CD4+ T Cells	36.41	52.89	36.49	55.01	52.77	36.71	52.85	64.52
IFN-α	STAT3	CD8+ T Cells	34.49	47.80	36.41	55.01	52.77	36.71	52.85	64.52
IFN-α	STAT3	Monocytes	49.41	47.19	39.80	59.14	45.82	48.82	72.45	89.77
IFN-γ	STAT1	B Cells	49.27	48.45	38.86	45.18	34.79	44.14	50.33	55.77
IFN-γ	STAT1	Monocytes	26.55	41.74	2.89	19.21	28.87	38.38	38.16	52.23
G-CSF	STAT3	CD4+ T Cells	27.97	44.90	29.56	45.18	44.91	33.21	54.16	59.25
G-CSF	STAT3	Monocytes	28.51	44.29	29.56	45.18	44.91	33.21	54.16	59.25
G-CSF	STAT3	B Cells	22.84	34.09	15.89	31.17	29.72	18.91	22.28	24.31
G-CSF	STAT3	CD4+ T Cells	22.84	34.09	15.89	31.17	29.72	18.91	22.28	24.31
G-CSF	STAT3	CD8+ T Cells	18.40	34.40	15.89	31.17	29.72	18.91	22.28	24.31
G-CSF	STAT3	Monocytes	14.42	29.29	15.89	31.17	29.72	18.91	22.28	24.31
G-CSF	STAT3	NK Cells	18.86	39.04	15.89	31.17	29.72	18.91	22.28	24.31

JAK1/3 group

stimulus	response	population	Bari 2mg QD	Bari 4mg QD	Filgo combined 100mg QD	Filgo combined 200mg QD	Tofa 5mg BID	Tofa 10mg BID	Upa 15mg QD	Upa 30mg QD
G-CSF	STAT3	CD4+ T Cells	22.12	47.25	61.49	57.12	44.52	47.11	53.29	76.96
G-CSF	STAT3	CD8+ T Cells	29.44	54.12	61.49	57.12	44.52	47.11	53.29	76.96
G-CSF	STAT3	NK Cells	29.10	44.76	29.85	45.19	40.12	42.53	43.45	57.06
G-CSF	STAT3	B Cells	26.90	25.82	29.85	45.19	40.12	42.53	43.45	57.06
G-CSF	STAT3	CD4+ T Cells	26.79	47.19	29.85	45.19	40.12	42.53	43.45	57.06
G-CSF	STAT3	CD8+ T Cells	26.69	51.30	29.85	45.19	40.12	42.53	43.45	57.06
G-CSF	STAT3	Monocytes	22.39	51.80	16.94	39.10	44.29	38.53	43.28	67.13
G-CSF	STAT3	NK Cells	29.27	50.81	29.85	45.19	40.12	42.53	43.45	57.06
G-CSF	STAT3	CD4+ T Cells	29.81	44.73	29.85	45.19	40.12	42.53	43.45	57.06
G-CSF	STAT3	CD8+ T Cells	29.73	29.79	29.85	45.19	40.12	42.53	43.45	57.06
G-CSF	STAT3	NK Cells	22.39	29.24	16.94	39.10	44.29	38.53	43.28	67.13
G-CSF	STAT1	B Cells	46.38	44.40	29.72	48.41	43.49	40.93	59.24	73.28
G-CSF	STAT1	CD4+ T Cells	22.97	41.27	31.91	50.84	44.90	48.12	59.10	73.28
G-CSF	STAT1	CD8+ T Cells	22.29	47.51	30.38	49.18	45.43	48.28	57.25	73.76
G-CSF	STAT1	NK Cells	21.31	44.46	38.51	49.45	42.57	44.24	49.12	69.41
G-CSF	STAT3	B Cells	28.11	27.29	22.31	29.98	44.71	39.18	48.57	60.86
G-CSF	STAT3	CD4+ T Cells	20.81	39.00	14.99	26.17	31.14	34.00	43.24	59.42
G-CSF	STAT3	CD8+ T Cells	21.50	29.38	14.99	26.17	31.14	34.00	43.24	59.42
G-CSF	STAT3	NK Cells	20.80	33.93	15.16	27.42	49.42	33.07	38.71	54.74
G-CSF	STAT3	CD4+ T Cells	48.44	34.87	29.53	59.14	45.82	48.82	63.52	77.85
G-CSF	STAT3	CD8+ T Cells	39.41	34.40	29.94	53.99	44.29	52.81	54.79	72.90

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 "I", vs. 4-mg if right of vertical line "I"). -p<0.01, ++p<0.001, +++p<0.0001 significantly higher compared to bari (vs. 2-mg if left of vertical line "I", vs. 4-mg if right of vertical line "I").

JAK2/TYK2, and of JAK1/3-dependent cytokines was lowest for filgo 100-mg QD. For bari 2-mg QD vs. these other JAKi doses, %SI of JAK2/2 or JAK2/TYK2 was highest with upa followed by bari 2-mg. The highest inhibitors of the JAK1/2/TYK2-dependent cytokines varied by cytokine / cell type though consistently included upa. Inhibition of JAK1/3 was highest for upa and tofa. Across comparisons, filgo 100-mg QD showed the least %SI of JAK2/2 or JAK2/TYK2-dependent, and of JAK1/3-dependent cytokines. Filgo reached the highest levels of %SI among agents only for 200-mg QD vs. lower doses of the other JAKi (for selected JAK1/2/TYK2-dependent cytokines).

Conclusion: 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:

[1] McInnes IB, et al. *Arthritis Res Ther*. 2019 Aug 2;21(1):183

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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 [CARDiovascular 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 involved 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 2.382 (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: 1.32-15.99; 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 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

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; 95% CI 6.7–26.2), respectively.1,2

Objectives: 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 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