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.

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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

from attainment through Week 52 was evaluated using a Cox proportional hazards model. For TULIP-1, BICLA response rate and time to onset of BICLA response were analyzed using the amended restricted medication rules.²

Results: Overall, 180 patients each in TULIP-2 and TULIP-1 received anifrolumab compared with 182 and 184 patients in the placebo arms, respectively. At the first 3 assessments in TULIP-2 (Weeks 4, 8, and 12), numerically greater percentages of patients treated with anifrolumab (26.8%, 35.3%, and 42.9%, respectively) were classified as having a BICLA response compared with placebo (21.3%, 21.6%, and 31.8%). A similar trend was observed in TULIP-1 with anifrolumab (23.3%, 34.2%, and 36.5%) vs placebo (18.3%, 23.2%, and 27.5%). The time to onset of BICLA response sustained from onset through Week 52 favored anifrolumab in both TULIP-2 (HR 1.55, 95% CI 1.11–2.18) and TULIP-1 (HR 1.93, 95% CI 1.38–2.73) (**Figure**). In TULIP-2, 86 (47.8%) patients treated with anifrolumab had BICLA responses that were sustained from time of onset through Week 52 compared with 57 (31.3%) patients in the placebo group. In TULIP-1, 85 (47.2%) patients in the anifrolumab treatment arm had BICLA responses that were sustained from time of onset through Week 52 compared with 55 (29.9%) patients in the placebo group.

Conclusion: In 2 Phase 3 studies, a greater proportion of patients achieved BICLA responses sustained from onset through Week 52 with anifrolumab treatment compared with placebo. Anifrolumab resulted in numerically favorable differences in time to onset of BICLA responses maintained through Week 52 across the TULIP studies. These data support the sustainability of clinical benefit derived from anifrolumab treatment of patients with active SLE.

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Figure. Time to Onset of BICLA Response That Was Sustained From Attainment Through Week 52 in TULIP-2 and TULIP-1

BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment.
 Note: Evaluated using a Cox proportional hazards model; time course of sustained BICLA response is not multiplicatively adjusted.
 Patients without a BICLA response sustained up to Week 52 are censored at the date of study treatment discontinuation or Week 52, whichever occurred earlier. Points on graph show censored patients. Data were analyzed for TULIP-1 data using the amended restricted medication rules.²

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OP0004

THE EXPRESSION OF INTERFERON-STIMULATED GENES IN PERIPHERAL BLOOD OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) ASSOCIATES WITH AFRICAN ANCESTRY

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Background: Type I Interferons (IFNs), and especially IFN- α , play a crucial role in the pathogenesis of SLE. Interferon-stimulated genes (ISGs) are generally up-regulated in SLE patients. Their pattern of up-regulation is often termed as an IFN signature. Even though composite IFN-scores are already used to

express the up-regulation of the IFN-system, e.g. in studies testing therapeutic anti-IFN-antibodies, we are still lacking an in-depth understanding of the IFN signature.

Objectives: To summarize the available data on the expression of ISGs in peripheral blood of patients with SLE compared to healthy controls; to assess which ISGs are most up-regulated in SLE patients; and to analyse if up-regulations of 6 ISGs typically used in IFN-scores [1,2] are associated with SLE disease activity and ethnicity.

Methods: The electronic databases PubMed and EMBASE were searched using the terms “interferon signature”, “SLE”, “interferon-stimulated genes”, “microarray” and “gene expression” with inception date until Jan. 28, 2020. Original case-control studies containing quantitative data of ISG expression were included. Exclusion criteria were studies with animal models, clinical trials of drug treatment and studies with *ex vivo* stimulation of cells prior to gene-expression analysis. Fold changes (FCs) (ISG expression in SLE/ISG expression in healthy controls) for the ISGs analysed in each study were extracted. FCs were plotted gene-wise on a heatmap for studies analysing ≥ 7 genes and for genes that were analysed in ≥ 5 studies. Cluster analysis using principle component analysis (PCA) and association analyses using generalized linear modelling (GLM) were performed for 6 ISGs (IFI27, IFI44, IFI44L, RSAD2, PRKR and IFIT1) as well as disease activity and ethnicity (SPSS).

Results: 16 case-control studies comprising a total of 851 SLE patients were included in the analyses, see Tab. 1. 24 ISGs had an average FC of ≥ 4 . IFI27, RSAD2, IFI44L, IFI44, HERC5 and IFIT5 had an average FC > 6 . The heatmap showed great variation in the expression of ISGs within the individual studies but also gene-wise between the studies, see Fig. 1. The inter-study variation was statistically explored for the selected 6 ISGs. PCA showed that PRKR, RSAD2, IFIT1, IFI44 and IFI44L clustered with African ancestry, see Fig. 2. Subsequent GLM confirmed that RSAD2 and PRKR were positively associated with African ancestry. However, none of the 6 ISGs were positively correlated with disease activity.

Figure 1. Heatmap of ISG up-regulation.