Background: Despite effective treatments, many patients (pts) with rheumatoid arthritis (RA) have inadequate responses to biologic DMARDs (bDMARD-IR), indicating an unmet need. It is unclear whether prior bDMARD use affects efficacy of the oral, selective JAK1 inhibitor filgotinib (FIL).

Objectives: To explore clinical response to FIL in bDMARD-IR pts stratified by mode of action (MOA) and number of prior bDMARDs.

Methods: The global, phase 3 FINCH-2 (NCT02873936) study treated 448 bDMARD-IR pts with active RA. Pts were randomised 1:1:1 to once-daily FIL 200 mg, FIL 100 mg, or placebo (PBO) for 24 weeks. Efficacy was assessed by percent of pts achieving low disease activity (LDA) or remission at week (W)24 as measured by CDAI and DAS28(CRP) stratified by number and MOA of prior bDMARDs. Comparisons were not adjusted for multiplicity. Nonresponder imputation was used.

Results: In total, 448 bDMARD-IR pts were included, 105 with prior experience with ≥3 bDMARDs (Table). At W24, pts receiving FIL were in LDA at a higher proportion vs PBO, irrespective of number of prior bDMARDs or MOA (Figure 1). For pts receiving FIL 200 mg vs PBO, DAS28(CRP) ≤2.6 was achieved at W24 by 52% vs 26%, 51% vs 22%, and 38% vs 9% of pts with 1, 2, or ≥3 prior bDMARDs, respectively, and 49% vs 21% and 50% vs 13% of pts exposed to TNF or IL-6 inhibitors; for all subgroups, rates were significantly higher vs PBO (Figure 1). Delta between FIL 200 mg and PBO was maintained irrespective of number or type of prior bDMARDs. At W24, pts receiving FIL achieved remission at a numerically higher rate vs PBO (Figure 2). For pts receiving FIL 200 mg vs PBO, DAS28(CRP) <2.6 was achieved at W24 by 36% vs 14%, 30% vs 14%, and 22% vs 6% of pts with 1, 2, and ≥3 prior bDMARDs, respectively, and 31% vs 14% and 29% vs 9% of pts exposed to TNF or IL-6 inhibitors (Figure 2). Delta between FIL 200 mg and PBO was maintained irrespective of number or type of prior bDMARDs. Treatment-emergent adverse events across subgroups were consistent with overall study population.

Conclusion: Treatment with FIL vs PBO led to higher rates of LDA and remission in pts with IR to IL-6 or TNF inhibition, or to 1, 2, or ≥3 prior bDMARDs, with a similar safety profile to the overall study population. A significantly higher proportion of pts overall receiving FIL 200 mg vs PBO were in LDA at W24. Improved efficacy of FIL vs PBO in pts who previously failed multiple bDMARDs indicates distinct benefits of selective JAK1 inhibition with FIL.

RESPONSE TO SMALL MOLECULES IS MOSTLY DRIVEN BY PATIENT GLOBAL ASSESSMENT OF DISEASE: A REAL WORLD OBSERVATION

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Background: Two Small molecules (Tofacitinib and Baricitinib) have been licensed in the UK for the use in rheumatoid arthritis. Their licensing came from several studies that showed good efficacy with baricitinib (1) study showed superior efficacy to adalimumab and tofacitinib showing non inferiority to TNF drugs (2). The response has also been shown in patient reported outcomes (find reference). Response when measure using the DAS score has two relatively subjective components (tender joints and patient global assessment) and two relatively objective components (Swollen joints and inflammatory markers)

Objectives: To determine in a real world setting if the response to small molecules is mostly due to a drop in subjective or objective components of the DAS score

Methods: A retrospective chart review was done on all new starters on small molecules in a district hospital in the North of England. Data were collected at baseline, three months and six months from October 2018 to date. Drop in the components of the DAS28 score was calculated and overall drop in DAS28 was modelled as the explanatory variable using linear regression modelling. This was the done Adjusting for age gender and duration of disease. Sensitivity of the model was examined using a logistic model of EULAR moderate/good response and using adjusted R squared estimates for linear model of improvement of the DAS28 score.

Results: 76 patients were included in the analysis from 85 starters on small molecules.61 (71.8 %) were on baricitinib and the baseline median DAS28 score was 2.42 (IQR 1.33,3.31), and at six months was 2.77 (IQR 2.01,3.83). There was numerical relative increased efficacy of baricitinib but this was not statistically significant (DAS drop at three months 2.54 IQR 1.73,3.09 vs 2.12 IQR 1.51,3.5). The relative contribution of the individual components of the DAS score to the drop ae in DAS are shown in table 1 below. Sensitivity analysis looking at predictors of a DAS drop of >0.6 confirmed this finding.

Conclusion: In this real world observational study, there was a good response to both small molecules with numerical better response to baricitinib. Tender joint count and patient global response accounted for more of the drop in DAS28 than swollen joints and inflammatory markers. At six months the biggest contributor to response was patient global assessment. This shows that JAK inhibitors might mediate their response initially mostly through pain modulation then by inflammation as exposure to drug continues.

References:

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SUSTAINABILITY OF RESPONSE TO UPADACITINIB AS MONOTHERAPY OR IN COMBINATION AMONG PATIENTS WITH RHEUMATOID ARTHRITIS AND PRIOR INADEQUATE RESPONSE TO CONVENTIONAL SYNTHETIC DMARDS

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Background: The presence of central sensitization (CS) significantly burdens the course of rheumatoid arthritis (RA). JAK inhibitors block intracellular signal pathways including the ones responsible for synthesis of mediators and cytokines causing pain and CS. The application of JAK inhibitors is supposed to relieve pain and reduce CS severity promptly.

Objectives: To evaluate JAK inhibitor effect on pain and signs of CS in patients with active RA 7 and 28 days after the start of therapy.

Methods: Study group included 39 patients with RA, their age was 50.9±11.79.5% of women, 89.7% of RF +; DAS28 5.8±0.6, receiving DMARDs (methotrexate 82.0% and leflunomide 18.0%), who were administered with tofacitinib 5mg 2 times a day due to inefficiency or intolerance of genetically engineered biological drugs. There were assessed the pain severity using Brief pain inventory (BPI) questionnaire, the presence of neuropathic pain component (NPC) using PainDETECT questionnaire and signs of CS using Central Sensitisation Inventory (CSI) questionnaire at early time after tofacitinib administration.

Results: Patients initially experienced a severe pain – 5.72±2.21 according to the visual analogue scale (VAS), 53.8% had signs of central sensitization (CSI ≥ 40), 17.9% had NPC (PainDETECT ≥18), 7 days after tofacitinib intake there was statistically reliable reduction of pain severity – up to 4.37±2.2 (p=0.01), pain decrease of 29.4±17.9% (BPI), NPC – PainDETECT from 12.9±5.5 to 10.6±5.6 (p=0.047) and CS – CSI from 43.1±12.8 to 35.9±11.2 (p=0.01). The effect had increased after 28 days: pain level (VAS) was 2.84±1.57 (p=0.000), pain decrease of 43.6±29.6% (BPI), PainDETECT 29.8±12.4 (p=0.000), CSI 26.4±13.9 (p=0.000).

During this period there were no serious adverse reactions.

Conclusion: The application of JAK inhibitor tofacitinib allows to reach a fast analgesic effect, also due to impact on CS and NPC.

Source: National Registry patients with RA

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