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THU0205 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 showing 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 .5.97 (IQR 5.35,6.55)The median drop at three months in the 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.

Table 1. Results of the adjusted linear regression models.

Component of DAS dropping at three months	Adjusted R squared at 3 months	Adjusted R squared at six months
Swollen Joints	0.12	0.05
Tender Joints	0.28	0.18
Patient global assessment	0.31	0.48
Erythrocyte sedimentation rate	0.04	0.17

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:
[1] N Engl J Med. 2017 Feb 16;376(7):652-662
[2] N Engl J Med. 2014 Jun 19;370(25):2377-86
Disclosure of Interests: : Clerin Joseph: None declared, Syed Mujtaba Bilgrami Speakers bureau: Pfizer, Lesley Ottewell: None declared, Leanne Gray: None declared, William Mitchell: None declared, Fiona Wood: None declared, Marco Massarotti: None declared, Marwan Bukhari Speakers bureau: Bristol-Myers Squib, UCB celltech, Roche/Chugai, Pfizer, Abbvie, Merck, Mennarini, Sanofi-aventis, Eli-Lilly, Janssen, Amgen and Novartis.
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THU0206 A VERY EARLY (7-28 DAYS) RESPONSE ON JAK INHIBITOR TOFACITINIB IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS: EFFECT ON PAIN AND CENTRAL SENSITIZATION.

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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±11.1, 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 5 mg 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), NCP – 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 NCP.
Source: National Registry patients with RA
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THU0207 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 primary treatment goal for patients (pts) with rheumatoid arthritis (RA) is a state of sustained clinical remission (REM) or low disease activity (LDA).[1,2]
Objectives: To assess the long-term sustainability of responses to upadacitinib (UPA), a JAK inhibitor, with or without background csDMARD(s) in pts with RA.
Methods: Data are from two phase 3 randomized, controlled trials of UPA in RA pts with roughly similar baseline disease characteristics: SELECT-NEXT enrolled pts with an inadequate response (IR) to csDMARD(s) on background stable csDMARD(s) receiving UPA 15 mg or 30 mg once daily or placebo for 12 weeks (wks);

SELECT-MONOTHERAPY enrolled methotrexate (MTX)-IR pts receiving UPA 15 mg or 30 mg monotherapy or blinded MTX for 14 wks. After 12/14 wks, pts could enter a blinded long-term extension and receive UPA 15 mg or 30 mg for up to 5 years. This post hoc analysis evaluated clinical REM (CDAI ≤2.8; SDAI ≤3.3), LDA (CDAI≤10; SDAI≤11), and DAS28(CRP) <2.6/≤3.2 at first occurrence before Wk 84; additionally, these measures were evaluated at 3, 6, and 12 months after the first occurrence for the total number of pts randomized to UPA 15 mg. Sustainability of response was evaluated by Kaplan-Meier only for those pts who achieved REM/LDA and was defined as time to the earliest date of losing response at two consecutive visits or discontinuation of study drug. The predictive ability of time to clinical REM/LDA was assessed using Harrell's concordance (c)-index (for reference, an index ~ 0.5, indicates no ability to predict; an index of 1 or -1 would be a perfect prediction). The last follow up dates were 22 March, 2018 (SELECT-NEXT) and 25 May, 2019 (SELECT-MONOTHERAPY), when all pts had reached the Wk 84 visit.

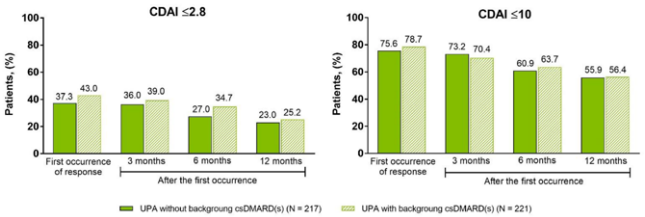
Results: Through Wk 84, the percent of treated pts achieving CDAI REM/LDA was 43%/79% for those receiving UPA 15 mg with background csDMARD(s) (SELECT-NEXT) and 37%/76% for those receiving UPA 15 mg without background csDMARD(s) (SELECT-MONOTHERAPY). 35%/25% of pts randomized to UPA 15 mg with background csDMARD(s) and 27%/23% of pts randomized to UPA 15 mg without background csDMARD(s) achieved sustained CDAI REM through 6/12 months after the first occurrence. 64%/56% of pts randomized to UPA 15 mg with background csDMARD(s) and 61%/56% of pts randomized to UPA 15 mg without background csDMARD(s) achieved sustained CDAI LDA through 6/12 months after the first occurrence (Figure 1). Time to initial clinical REM/LDA did not appear to be associated with sustained disease control. The c-indices (95%CI) for CDAI REM in the UPA 15 mg with background csDMARD(s) and UPA 15 mg without background csDMARD(s) groups were 0.541 (0.47, 0.62) and 0.568 (0.49, 0.65) and that of LDA were 0.521 (0.46, 0.58) and 0.498 (0.43, 0.56), respectively. Through last follow-up visit, 55% of pts receiving UPA 15 mg with background csDMARD(s) and 62% of pts receiving UPA 15 mg without background csDMARD(s) remained in CDAI REM while 72% and 70% of pts remained in CDAI LDA, respectively (Figure 2). Similar results were observed across other disease activity measures (SDAI REM/LDA and DAS28(CRP) <2.6/≤3.2).

Conclusion: More than a quarter and more than a half of pts with RA and prior IR to csDMARD(s) receiving UPA with or without background csDMARD therapy achieved sustained clinical REM and LDA, respectively, across disease activity measures. Sustainability of responses appeared comparable among pts receiving UPA with or without background csDMARDs through up to 84 wks.

References:

[1] EULAR: Smolen JS, et al. Ann Rheum Dis 2017;76:960–977.
[2]ACR: Singh et al. Arthritis & Rheumatology Vol. 68, No. 1, January 2016, pp 1–26.

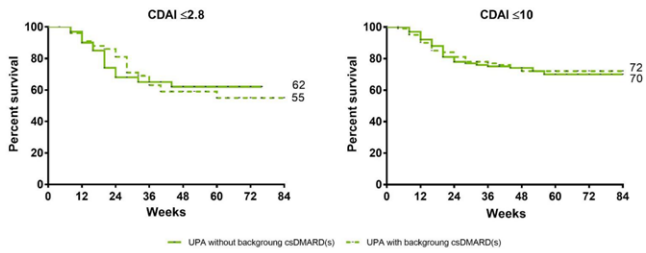
Figure 1. Proportion of patients sustaining CDAI remission or low disease activity at 3, 6, and 12 months after the first occurrence of response among the total randomized population



UPA, upadacitinib; csDMARD, conventional synthetic disease-modifying anti-rheumatic drugs; CDAI, Clinical Disease Activity Index; N, total number of patients randomized to UPA with or without background csDMARD(s).

Data for patients who maintained response through the cut-off (22 March, 2018 for SELECT-NEXT and 25 May, 2019 for SELECT-MONOTHERAPY, when all patients had reached Week 84 visit) were censored. Data are summarized, with no adjustments applied to account for between-study differences. Non-responder imputation was used for missing data.

Figure 2. Kaplan-Meier analysis of time to loss of CDAI remission or low disease activity after the first occurence of response



UPA, upadacitinib; csDMARD(s), conventional synthetic disease-modifying anti-rheumatic drugs; CDAI, Clinical Disease Activity Index; N, number of patients who had achieved CDAI remission or low disease activity.

Results are for patients who had achieved CDAI remission or low disease activity. UPA without backgroung csDMARD(s): CDAI ≤2.8: n = 81;CDAI ≤10: n = 164. UPA with backgroung csDMARD(s): CDAI ≤2.8: n = 95; CDAI ≤10: n = 174.

Data for patients who maintained response through the cut-off (22 March, 2018 for SELECT-NEXT and 25 May, 2019 for SELECT-MONOTHERAPY, when all patients had reached Week 84 visit) were censored. Data are summarized, with no adjustments applied to account for between-study differences. Non-responder imputation was used for missing data. Week 0 indicates the first occurrence of response.

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THU0208

AFFECTING COMMON BIOLOGICAL PROCESSES OR DISPARATE?: COMPARISON OF GENE-EXPRESSION MODIFICATION PROFILES AMONG TARGETING IL-6 AND TARGETING SPECIFIC JAK TREATMENTS.

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Background: After accumulation of evidences, it is recognized that inhibition of IL-6 signaling is one of the most established strategies for rheumatoid arthritis (RA) treatment. Tocilizumab (TCZ), an anti-IL6 receptor monoclonal antibody, is the pioneer which blocks IL-6 signaling by preventing IL-6 from binding to both membrane-bound and soluble receptors. Tofacitinib (TOF) inhibits Janus kinase (JAK) 1, JAK3 and, to a lesser extent, JAK2. Recently, Baricitinib (BAR), JAK 1 and JAK2 selective kinase inhibitor, were also approved to treat RA. These JAK inhibitors are known to inhibit cytokine signaling including interleukin (IL)-6. It is very important for clinicians to know whether these treatments affect common biological processes or disparate, because it will provide a rationale for switching each other if one of these treatments resulted in lack of efficacy.

Objectives: To compare the gene-expression modification profiles among TOF, BAR and TCZ treatments.

Methods: Total of 38 RA cases were analyzed, including TOF (n=15: 6-20mg/d), BAR (n=10: 2-4mg/d) and TCZ (n=13: 8mg/kg/4w or 163mg/2w) treatment groups. Peripheral blood was drawn at just before (pre) and 3 months after (post) these treatments. Total RNAs were then extracted with using PAXgene miRNA kit. After constructing single-stranded, strand-specific libraries, multiplex sequencing was done. After quantifying the expressions of transcripts, differentially expressed genes (DEGs) were selected by paired comparison (post vs. pre), setting thresholds at 2-fold change up/down and less than P=0.05 in paired T-test. And then, hierarchical clustering analysis and enrichment analysis using gene ontology (GO) terms were performed.

Results: From the comparison of post- vs. pre-treatment of TOF, BAR and TCZ, the 120 (up-regulated=25/down-regulated=95), 62 (up=20/down=42) and 193 (up=54/ down=139) genes were selected as DEGs respectively. It seems to be discrete depending on the treatment, because overlapped genes were only 1.0% in up-regulated and 5.7% in down-regulated genes. The hierarchical clustering with expression profiles of these DEGs showed major 4 clusters. 92.3% of TCZ and 70% of BAR cases were segregated into 1st and 3rd clusters respectively, while those of TOF cases fell into 2nd and 4th clusters. Disparate GO terms were enriched in each DEGs group. For example, genes relevant to viral defense including 'response to type I interferon (IFN)' were suppressed in TOF group. Meanwhile, down regulation of genes involved in phosphorylation process including 'IL-7 signaling' seemed to be significant in BAR group. It is noteworthy that terms related to wound healing such as 'platelet activation' were enriched in the down-regulated genes of TCZ group.