64.5%. Order of TCZ: 1st biologics in 9 cases, 2nd biologics in 9 cases, 3rd biologics in 13 cases. Rates of symptomatic joints (pain or swelling): 45.1% in shoulders, 44.6% in elbows, 0.0% in hips, 51.9% in knees and 37.7% in ankles. Average CDAI was 23.3 at baseline, 6.8 at one year and 5.0 at two years. Average Δ mTSS was 8.1 at baseline, 2.7 from baseline to one year and 1.1 from one year to two years. Evaluation using ARASHI change score from baseline to two years was as followed [worsened, not changed, improved (%)]. Shoulders (51 joints) [9.8, 86.3, 3.9]. Elbows (56 joints) [12.5, 73.2, 14.3]. Hips (53 joints) [0, 94.3, 5.7]. Knees (52 joints) [9.6, 65.4, 25.0]. Ankles (53 joints) [3.8, 91.6, 5.7]. Joint surgery was not performed in evaluated joints during study periods. Influence of symptoms at baseline on large joint destruction: There was a significant difference between ARASHI change score in symptomatic knee joints and that in non-symptomatic joints (-0.5 vs. 0.1 , $p < 0.01$).

Abstract AB0477 – Figure 1. Evaluation of large joint destruction using ARASHI score during two-year tocilizumab treatment

Conclusions: Over 90% of large joints was not destructed during two-year TCZ treatment. Improvement was frequently observed in knees and elbows. Major reasons of improvement of joint destruction were stabilisation of joints by osteophyte formation and repair of bone erosions.

REFERENCES:

- [1] Drossaers-Bakker, et al. Rheumatology 2000.
- [2] Kaneko, et al. Mod Rheumatol 2013.

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Rheumatoid arthritis – non biologic treatment and small molecules

AB0478

MILD AND MODERATE HEPATIC IMPAIRMENT HAVE NO CLINICALLY RELEVANT IMPACT ON UPADACITINIB PHARMACOKINETICS: RESULTS FROM A DEDICATED PHASE 1 STUDY

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Background: Upadacitinib is a selective Janus kinase 1 (JAK1) inhibitor being developed for the treatment of several inflammatory diseases, including rheumatoid arthritis (RA). Upadacitinib efficacy was demonstrated in Phase 2 studies in RA, Crohn's disease, atopic dermatitis, in addition to three completed Phase 3 trials in RA. Upadacitinib is a non-sensitive substrate for hepatic metabolism by cytochrome P450 3A; however, 38% and 24% of upadacitinib immediate-release dose are eliminated unchanged in faeces and urine, respectively. Since, there is a potential for upadacitinib use in some patients with hepatic impairment, evaluation of impact of hepatic impairment on upadacitinib exposure is of key clinical relevance. Doses of 15 mg and 30 mg once daily (QD) using upadacitinib extended-release formulation have been evaluated in Phase 3 trials in RA.

Objectives: To evaluate the effect of mild and moderate hepatic impairment on the pharmacokinetics of upadacitinib.

Methods: This was a Phase 1, open-label study in subjects with mild ($n=6$) or moderate ($n=6$) hepatic impairment, according to the Child-Pugh classification, and demographically-matched healthy subjects ($n=6$). Subjects received a single 15 mg dose of upadacitinib extended-release formulation under fasting conditions. Blood samples for upadacitinib assay were collected over 120 hours after administration. Upadacitinib maximum observed plasma concentration (C_{max}), area under the plasma concentration curve (AUC), and terminal phase elimination half-life ($t_{1/2}$) were calculated using non-compartmental analyses. Analyses of covariance were conducted to estimate upadacitinib exposure in subjects with hepatic impairment relative to subjects with normal hepatic function.

Results: There was no statistically significant difference in upadacitinib C_{max} or AUC in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function. One subject with moderate hepatic impairment showed significantly lower upadacitinib exposures than subjects with normal hepatic functions and was excluded as an outlier to ensure a conservative estimate for effect of hepatic impairment on exposure. Upadacitinib exposure ratio central values [and 90% confidence intervals] in subjects with mild and moderate hepatic impairment were 1.28 [0.91–1.79] and 1.24 [0.87–1.76] for AUC and 1.04 [0.77–1.39] and 1.43 [1.05–1.95] for C_{max} , respectively, compared to subjects with normal hepatic function. Upadacitinib terminal elimination half-life (harmonic mean $\pm$ pseudo standard deviation) was 7.99 ± 4.60 and 4.14 ± 1.46 in subjects with mild and moderate hepatic impairment relative to 8.93 ± 4.87 in subjects with normal hepatic function. Upadacitinib was generally well tolerated by the subjects in the study.

Conclusions: Mild and moderate hepatic impairment result in only a very limited effect on upadacitinib plasma exposures ($<30\%$ increase in upadacitinib AUC). Therefore, in clinical trials, dose adjustments in subjects with mild or moderate hepatic impairment are not warranted.

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AB0479

CHARACTERISATION OF THE EFFECT OF RENAL IMPAIRMENT ON UPADACITINIB PHARMACOKINETICS

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Background: Upadacitinib is a selective inhibitor of Janus kinase 1 (JAK1) which is currently being evaluated for the treatment of several autoimmune disorders, including rheumatoid arthritis (RA). Although renal elimination plays a minor role in upadacitinib clearance ($<20\%$ of upadacitinib dose is eliminated unchanged in urine), a considerable number of RA patients have renal dysfunction. As such, characterisation of the effect of different degrees of renal impairment on upadacitinib plasma exposures is important for this patient population.

Objectives: The objective of this study was to assess the pharmacokinetics of upadacitinib in subjects with mild, moderate, and severe renal impairment compared to subjects with normal renal function.

Methods: This Phase 1 study was conducted in 24 adult subjects, who were assigned to one of four groups (six subjects per group) according to the estimated glomerular filtration rate (eGFR) as calculated by the Modification of Diet in Renal Disease (MDRD) equation: normal renal function (eGFR of ≥ 90 mL/min/1.73 m²), mild renal impairment (60–89 mL/min/1.73 m²), moderate renal impairment (30–59 mL/min/1.73 m²), and severe renal impairment (15–29 mL/min/1.73 m²). Subjects received a single 15 mg dose of upadacitinib extended-release formulation under fasting conditions. Blood samples for pharmacokinetic assessments were collected for 120 hours after dosing. The effect of renal impairment on upadacitinib plasma exposures was assessed through regression analysis as well as analysis of covariance across the renal impairment categories.

Results: The point estimates for upadacitinib plasma exposure ratios [90% confidence interval] in subjects with mild, moderate, and severe renal impairment were 1.18 [1.06–1.32], 1.33 [1.11–1.59], and 1.44 [1.14–1.82] for AUC and 1.06 [0.92–1.23], 1.11 [0.88–1.40], and 1.14 [0.84–1.56] for C_{max} , respectively, relative to subjects with normal renal function. In this analysis, one subject with moderate renal function showed exposures significantly lower than subjects with normal

renal function. This subject was excluded to ensure a conservative estimate of the impact of renal impairment on upadacitinib exposure. Results from the categorical analysis were consistent with the results from the primary regression analysis.

Conclusions: Renal impairment has only a limited effect on upadacitinib pharmacokinetics. Upadacitinib mean plasma exposures (AUC) in subjects with severe renal impairment are within 44% of mean exposures in subjects with normal renal function. This is in agreement with the known limited role of urinary excretion in upadacitinib elimination.

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AB0480 FOLIC ACID SUPPLEMENTATION DELAYS CLINICAL IMPROVEMENT IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH METHOTREXATE

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Background: Methotrexate (MTX) is the disease-modifying anti-rheumatic drug (DMARD) most commonly used in the treatment of rheumatoid arthritis (RA), and folic acid (FA) supplementation is usually employed to prevent MTX-related adverse effects.¹ However, the need of FA supplementation remains controversial, as it might influence the efficacy of MTX therapy.²

Objectives: The aim of this retrospective study was to evaluate the effects of FA supplementation on both efficacy and safety of low-dose MTX in the treatment of RA patients.

Methods: 120 RA patients (mean disease duration 11±30 months, mean age 61±13 SD years), according to ACR criteria,³ who started low-dose MTX treatment were retrospectively evaluated. Patients were not complaining of serious diseases other than RA. Two groups of patients were selected: patients supplemented with FA (#58) and patients not-supplemented with FA (#62). MTX dose, prednisone dose, disease activity (DAS28), and adverse event (AE) were recorded at 3, 6, 9, 12, 24, 36, and 48 months. At baseline, MTX mean dose was 8.3±1.9 and 8.1±1.4 mg/weekly, prednisone mean dose was 7.4±3.1 and 5.3±3.2 mg/daily, and mean DAS28 was 5.1±1.2 and 4.8±1.1, respectively for both groups. The patients were followed-up until MTX discontinuation, new DMARD/BiologicDMARD addition, need for FA supplementation, or after 48 months of therapy (mean follow-up 40±20 months). The maximum MTX dose administered during the follow-up was 15 mg/weekly. Statistical analysis was performed by non parametric tests.

Results: DAS28 decreased in both groups during the study. However, DAS28 was found significantly lower (p<0.04) in patients without FA supplementation, when compared with patients taking FA supplementation, at months 3, 6, 9, and 12. Patients without FA supplementation required significantly lower (p<0.01) doses of both prednisone and MTX during the follow-up. AEs were observed in 26% of patients with FA supplementation, as well as in 43% of patients without FA supplementation. The difference was statistically significant (p=0.049). No difference in AE type was observed between the groups (mainly, transaminase or mean red blood cell volume elevation, oral mucositis, urinary tract infections). AEs have been successfully managed in the majority of cases by either discontinuing MTX for two weeks or adding FA if required.

Conclusions: In RA patients taking low-dose MTX, FA supplementation decreases the efficacy of the treatment, delaying the clinical responsiveness. The lack of administration of FA increases the risk of AEs; however, by considering the benign type of AEs usually observed in this subset of patients, the treatment with low doses of MTX might be started without FA supplementation, and the FA administration deferred until AE appearance.

REFERENCES:

- [1] Shea B, et al. Cochrane Database Syst Rev. 2013 May 31;(5):CD000951.
- [2] Arabelovic S, et al. J Am Coll Nutr 2007;26:453–5.
- [3] Aletaha D, et al. Arthritis Rheum 2010;62:2569–81.

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AB0481 TRANSCUTANEOUS VAGUS NERVE STIMULATION IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid Arthritis is a prevalent, autoimmune disease causing joint destruction and severe physical disability. In various studies the vagal nerve has been postulated to play a role in modulation of systemic inflammation.

Objectives: Our aim was to investigate the effect of transcutaneous stimulation of the vagal nerve (t-VNS) in patients with rheumatoid arthritis. We hypothesised that stimulation of the vagal nerve and thereby enhanced parasympathetic tone would increase the activity of the vagal nerve and improve experienced clinical pain.

Methods: Sixteen patients with rheumatoid arthritis and flare (DAS28-CRP>3.2) and twenty without flare were recruited. Three bilateral electrical stimulations of the vagal nerve were done with a handheld device for 4 days. Cardiac vagal tone (CVT) was assessed with linear vagal scale (LVS) and DAS28-CRP were collected on the 1st, 2nd and 5th day.

Results: Cardiac vagal tone was significantly lower in patients with flare in comparison to patients without flare (3.2 vs. 4.9 LVS, p=0.03). t-VNS did not alter CVT in patients with flare, however decreased CVT in patients without flare (baseline: 4.9, 2nd day: 3.8 LVS, p=0.03). A decrease in DAS28-CRP in patients with flare was seen in response to t-VNS (baseline: 4.2, 5th day: 3.9, p=0.03), due to decrease in CRP (baseline: 8.2, 5th day: 6.0 mg/L, p=0.02) and number of swollen joints (baseline: 5.4, 5th day: 4.4, p=0.01) and tender joints (baseline: 3.7, 5th day: 2.8, p=0.02) in RA patients with flare. A negative association between baseline CVT and baseline DAS28-CRP was found in all RA patients, showing that lower CVT was associated to higher disease activity.

Conclusions: Baseline CVT was lower in RA patients with flare, possibly due to higher level of inflammation, and the observed decrease in DAS28-CRP was not associated to CVT modulation.

REFERENCE:

- [1] Rasmussen SE, et al. Vagal influences in rheumatoid arthritis. Scandinavian Journal of Rheumatology 2017.

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AB0482 SIMILAR EFFICACY OF TOFACITINIB ON DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS PATIENTS WITH AND WITHOUT PREVIOUS BIOLOGICALS; RESULTS FROM THE TURKBIO REGISTRY

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Background: The aim of this study was to investigate the drug survival, its efficacy and safety in patients with RA based on the database from the Turkish TURKBIO registry

Methods: A total of 180 patients were treated with TOFA for RA. Drug survival was assessed. In 118 patients with available data, treatment response was evaluated using the number of sensitive and swollen joints, VAS values, DAS28, HAQ and CRP at weeks 12, 24, 48 and 60

Results: At baseline, RA patients had a median (Q1-Q3) disease duration of 14 years. 75 patients had used ≥1 biologics previously. The other demographic and clinical features of the patients were shown in table 1. Median (Q1-Q3) followup period was 137 weeks. After 48 and 137 weeks, 75% and 48% of the patients respectively, maintained TOFA (figure 1). The most common reason for drug discontinuation was ineffectiveness of treatment (63%), followed by adverse events (23%). After 12 weeks, all disease activity parameters were reduced significantly compared to the baseline and most of them continued to be reduced until week 60. No difference was observed in disease activity parameters between the groups