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.

Disclosure of Interest: Y. Hirano Speakers bureau: Chugai pharma., K. Hattori: None declared, R. Yamada: None declared
DOI: 10.1136/annrheumdis-2018-eular.1863

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

M.-E.F. Mohamed, S. Coppola, T. Feng, A.P. Lacerda, A.A. Othman. *AbbVie, North Chicago, USA*

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.

Acknowledgements: The studies presented were funded by AbbVie. AbbVie contributed to the study design, research, and interpretation of data, reviewing, and approving the publication. All authors are employees and shareholders of AbbVie.

Disclosure of Interest: M.-E. Mohamed Shareholder of: AbbVie, Employee of: AbbVie, S. Coppola Shareholder of: AbbVie, Employee of: AbbVie, T. Feng Shareholder of: AbbVie, Employee of: AbbVie, A. P. Lacerda Shareholder of: AbbVie, Employee of: AbbVie, A. Othman Shareholder of: AbbVie, Employee of: AbbVie

DOI: 10.1136/annrheumdis-2018-eular.3530

AB0479 CHARACTERISATION OF THE EFFECT OF RENAL IMPAIRMENT ON UPADACITINIB PHARMACOKINETICS

M.-E.F. Mohamed, S. Coppola, T. Feng, J. Anderson, A.A. Othman. *AbbVie, North Chicago, USA*

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