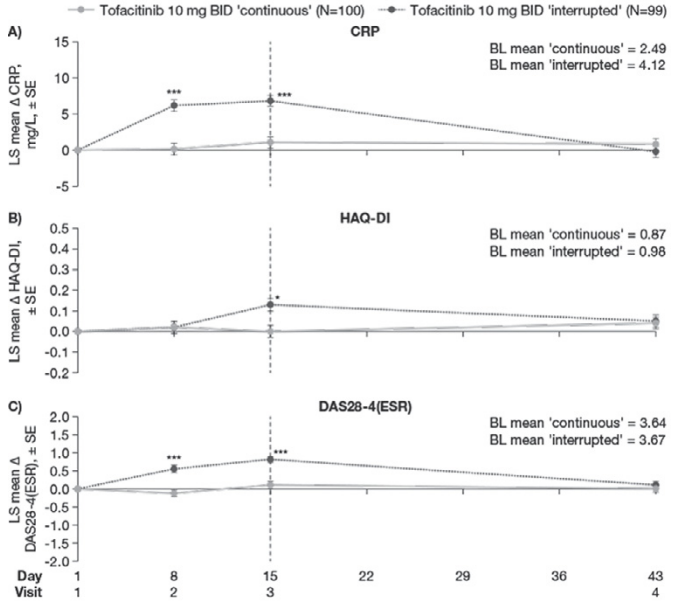
weeks post-randomisation [Day 1–Day 15; Visits 1–3], then tofacitinib 10 mg BID reinitiated as monotherapy or with MTX at Visit 3); randomisation was stratified by MTX use. Pneumococcal and influenza vaccines were administered to all pts on Day 8 (Visit 2; vaccine titers reported previously[1]). Blood samples were taken on Days 8, 15 (Visit 3) and 43 (Visit 4). Efficacy endpoints included change from baseline in C-reactive protein (CRP), Health Assessment Questionnaire Disability Index (HAQ-DI) and Disease Activity Score in 28 joints, erythrocyte sedimentation rate (DAS28-4[ESR]) at each visit. A mixed-effects model with repeated measures was used to evaluate treatment effect at each visit. Analyses for efficacy were exploratory, with no multiplicity adjustment for comparisons.

Results: Of the 199 pts in this analysis (continuous, n=100; interrupted, n=99), 117 received concomitant MTX. At LTE study baseline (BL) in the continuous and interrupted grps, respectively: 81.8/83.8% of pts were white, 84.8/86.9% were female and mean age was 55.0/53.9 years. BL (Day 1) values for CRP, HAQ-DI and DAS28-4(ESR) were generally similar between groups. At Day 8, mean CRP and DAS28-4(ESR) significantly increased from BL for interrupted vs continuous tx; HAQ-DI values were similar between grps (Figure). As expected at Day 15, mean CRP, HAQ-DI and DAS28-4(ESR) significantly increased from BL for interrupted vs continuous tx. After tofacitinib reinitiation for 28 days (Day 43), changes in CRP, HAQ-DI and DAS28-4(ESR) were similar between grps and approached BL levels. Adverse events (AEs) were experienced by 35.4% and 49.5% of pts receiving interrupted and continuous tx, respectively. The most frequent treatment-emergent AEs were bronchitis and upper respiratory tract infection (each AE: 6 pts) and vaccination-related immunisation reaction, myalgia and rash (each AE: 5 pts). Serious AEs occurred in 3 pts (3%) in each grp. In total, 1 pt (1%), in the interrupted tx grp, discontinued due to a study-drug related AE; no pts discontinued due to disease flare.

Figure. LS mean change from BL in RA efficacy endpoints over time from a vaccine sub-study with temporary tofacitinib dose interruption



*p<0.05, ***p<0.0001 for 'interrupted' vs 'continuous' tx
Dashed line indicates the end of the dose interruption period which began at BL
Δ, change from BL; BID twice daily; BL, baseline; CRP, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; LS, least squares; RA, rheumatoid arthritis; SE, standard error; tx, treatment

Conclusions: Efficacy of tofacitinib 10 mg BID can be reestablished following loss of efficacy during temporary (2 weeks) tx discontinuation in pts with RA. Pts receiving continuous tx maintained efficacy throughout the study. Further investigations are required.

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[1] Winthrop KL et al. Ann Rheum Dis 2016; 75: 687–695.

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THU0194 THE ROLE OF ENHANCED LIVER FIBROSIS (ELF) SCORE IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH METHOTREXATE

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Background: MTX is still a basic medicament used in treatment of patients with RA. One of its adverse reaction is its hepatoxicity. Previous studies have established high diagnostic accuracy of the ELF score to assess hepatic fibrosis in chronic viral hepatitis and fatty liver disease.

Objectives: The aim of the research was the evaluation of the usefulness of ELF markings, by patients treated with MTX, as an indicator which shows potential liver damage.

Methods: In the research were analyzed results of 96 patients with RA treated with MTX. Average age of patients was 60 (19–85 years old), median of body mass was 70 kg (46–140), median of BMI was 26 (16–46). Average time of taking MTX were 4 years and median of the accumulated dose was 3140 mg (12,5–27400mg). Disease activity in the moment of evaluation, evaluated by DAS 28, was 4,3 (0,98–8,42).

Achieved results ELF, PIIINP were correlated with body mass, BMI, dose of MTX, other illnesses (e.g. diabetes), taken nonsteroidal anti-inflammatory drugs and statins. In statistical analysis were used Pearson correlation and U Mann-Whitney test.

Results: The ELF values correlated with age, accumulated dose and DAS 28. Along with the increase of accumulated dose of MTX, disease activity and by older patients, were observed higher ELF values (the differences were statistically significant). The PIIINP values correlated with patients' body mass, accumulated dose of MTX and disease activity, evaluated by DAS 28. The differences were statistically significant. Along with the increase of body mass, accumulated dose and DAS 28, were observed higher values of PIIINP. Patients with diabetes had statistically higher values of PIINP (average: 11.13, median: 11,38), than patients without diabetes (average: 8.06, median: 7.15). There was observed no relationship between ELF and PIIINP results with taken nonsteroidal anti-inflammatory drugs and statins.

Conclusions: The ELF test, and one of its elements, PIIINP, may be useful in the evaluation of patients with higher probability of hepatotoxic effect of MTX. Special attention should be paid to older, obese patients, with diabetes, patients who take higher accumulated dose of MTX and with higher disease activity.

Disclosure of Interest: None declared

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THU0195 CONSISTENT EFFICACY AND SAFETY OF TOFACITINIB IN RHEUMATOID ARTHRITIS PATIENTS WITH INADEQUATE RESPONSE OR INTOLERANCE TO NON-MTX CSDMARDS

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Background: Tofacitinib is an oral JAK inhibitor for the treatment of RA. In clinical practice, a proportion of patients (pts) with RA may not be candidates for treatment with the conventional synthetic DMARD (csDMARD) methotrexate (MTX).[1]

Objectives: To evaluate tofacitinib 5 or 10 mg BID efficacy and safety using pooled data from 8 Phase (P) 2 and 6 P3 trials in RA pts who were (1) inadequate responders (IR)/intolerant to csDMARDs, but did not have an IR or intolerance to MTX or biologic DMARDs (ie, non-MTX csDMARD-IR population) or (2) pts with an IR/intolerance to any csDMARD including MTX but not bDMARD-IR (ie, 2nd-line population).

Methods: Month 3 efficacy outcomes included proportions of pts achieving ACR20/50/70 responses, and Disease Activity Score 28-4(ESR) (DAS28-4[ESR])<2.6 (remission), as well as change from baseline in DAS28-4(ESR) and Health Assessment Questionnaire-Disability Index (HAQ-DI) scores. No multiplicity adjustments were made. Crude incidence rates (CIR; unique pts with events/100 pt-years) based on adverse event (AE) reporting through Month 24 were calculated for treatment-emergent AEs (TEAEs), serious AEs (SAEs), discontinuations (DCs) due to AEs and AEs of special interest.

Results: In the P2/3 tofacitinib RA trials, prior csDMARDs received by the non-MTX csDMARD-IR and 2nd-line populations, respectively were: chloroquine (17.7% and 37.2%), hydroxychloroquine (13.7% and 22.7%), leflunomide (19.4% and 20.9%), MTX (7.3% and 93.3%), sulfasalazine (31.1% and 27.1%) and others (8.0% and 11.1%); pts may have received >1 prior csDMARD. The non-MTX csDMARD-IR population included 208, 247 and 82 pts receiving tofacitinib 5 and 10 mg BID or placebo (PBO), respectively; the 2nd-line population comprised 1206, 1266 and 856 pts, respectively. Baseline characteristics were generally similar between populations except for mean RA duration (5.2–7.2 years, non-MTX csDMARD-IR pts; 8.2–8.5 years, 2nd-line pts). Most pts were female (80.3–85.4%), mean age range was 49.7–52.5 years and mean DAS28-4(ESR)

score ranged from 6.2–6.5. Tofacitinib 5 and 10 mg BID achieved higher ACR responses and greater changes from baseline in DAS28-4(ESR) and HAQ-DI scores vs PBO at Month 3 in both populations (Table). Numerically higher proportions of non-MTX csDMARD-IR pts achieved efficacy outcomes vs 2nd-line population. CIRs for SAEs, DCs due to AEs and AEs of special interest were similar across groups; CIRs for TEAEs were higher with PBO vs tofacitinib. AE frequency was generally lower in the non-MTX csDMARD-IR population vs 2nd-line population.

Table. Efficacy outcomes at Month 3 and safety outcomes to Month 24

	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		PBO	
	Non-MTX csDMARD-IR	Second-line	Non-MTX csDMARD-IR	Second-line	Non-MTX csDMARD-IR	Second-line
% pts (95% CI) achieving efficacy outcome, FAS, NRI						
ACR20 response	69.3 (62.5–75.6)[a]	59.4 (56.1–62.5)[a]	74.0 (67.6–79.7)[a]	65.4 (62.3–68.4)[a]	25.0 (14.0–39.0)	27.1 (23.2–31.3)
ACR50 response	35.6 (29.1–42.7)[a]	30.7 (27.8–33.8)[a]	44.8 (38.1–51.6)[a]	35.0 (32.0–38.2)[a]	11.5 (4.4–23.4)	8.8 (6.5–11.7)
ACR70 response	16.3 (11.5–22.2)[b]	12.1 (10.1–14.4)[a]	23.3 (17.9–29.5)[a]	17.2 (14.8–19.8)[a]	5.8 (1.2–16.0)	2.7 (1.4–4.5)
DAS28-4(ESR)<2.6	9.2 (5.5–14.4)	6.5 (4.9–8.4)	16.9 (12.1–22.7)[a]	10.2 (8.2–12.5)	4.0 (0.5–13.7)	1.6 (0.7–3.3)
LSM (SE) change in score from baseline in efficacy outcome, FAS						
DAS28-4(ESR)	-2.1 (0.1)[a]	-1.9 (0.1)[a]	-2.5 (0.1)[a]	-2.1 (0.1)[a]	-1.0 (0.2)	-0.9 (0.1)
HAQ-DI	-0.5 (0.0)[a]	-0.5 (0.0)[a]	-0.6 (0)[a]	-0.5 (0.0)[a]	-0.2 (0.1)	-0.2 (0.0)
Safety outcomes, CIR (95% CI)						
TEAE	118.4 (99.9–139.2)	192.4 (179.8–205.8)	136.3 (116.8–158.1)	193.7 (181.3–206.9)	264.1 (183.9–367.3)	292.2 (265.8–320.5)
SAE	8.5 (5.2–12.9)	12.4 (10.3–14.8)	7.4 (4.6–11.3)	9.7 (7.9–11.8)	10.8 (1.3–39.1)	11.5 (7.6–16.8)
DC due to AE	7.1 (4.2–11.2)	9.7 (7.8–11.8)	7.2 (4.5–11.0)	10.4 (8.6–12.6)	10.8 (1.3–39.1)	11.9 (7.9–17.2)
SIE	2.8 (1.1–5.7)	3.4 (2.4–4.7)	1.4 (0.4–3.5)	3.4 (2.4–4.7)	5.4 (0.1–30.1)	1.7 (0.5–4.3)
OI, excluding TB	0.4 (0.0–2.2)	0.2 (0.0–0.7)	0.0 (0.0–1.3)	0.5 (0.2–1.1)	0.0 (0.0–19.9)	0.0 (0.0–1.6)
TB	0.0 (0.0–1.4)	0.0 (0.0–0.4)	0.3 (0.0–1.9)	0.7 (0.3–1.3)	0.0 (0.0–19.9)	0.0 (0.0–1.6)
Herpes zoster	1.2 (0.2–3.5)	3.9 (2.8–5.3)	3.5 (1.7–6.4)	4.8 (3.5–6.3)	0.0 (0.0–19.9)	2.6 (0.9–5.5)
MACE	0.8 (0.1–2.9)	0.4 (0.1–1.1)	0.7 (0.1–2.6)	0.6 (0.2–1.3)	0.0 (0.0–41.1)	0.6 (0.0–3.5)
Malignancies[#]	0.4 (0.0–2.2)	0.7 (0.3–1.4)	0.3 (0.0–1.9)	0.7 (0.3–1.5)	0.0 (0.0–19.9)	0.0 (0.0–1.6)

[a]p<0.001; [b]p<0.05 vs PBO; [#]excluding non-melanoma skin cancer; AE, adverse event; CI, confidence interval; CIR, crude incidence rate; csDMARD, conventional synthetic disease modifying antirheumatic drug; DAS28-4(ESR), disease activity score 28-4(ESR); DC, discontinuation; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; IR, inadequate response; LSM, least squares mean; MACE, major adverse cardiovascular events; MTX, methotrexate; NRI, non-responder imputation; OI, opportunistic infection; PBO, placebo; SAE, serious AE; SE, standard error; SIE, serious infection event; TB, tuberculosis; TEAE, treatment emergent adverse event

Conclusions: This analysis indicates that tofacitinib is associated with similar efficacy and safety outcomes between csDMARD-IR (including MTX-IR) pts and those who are csDMARD-IR but not MTX-IR. This suggests a favourable tofacitinib benefit/risk profile for RA pts who have a contraindication to or refuse treatment with MTX and failed other csDMARDs.

References:

[1] Lopez-Olivo MA et al. Cochrane Database Syst Rev 2014; CD000957.

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THU0196 SYSTEMATIC REVIEW AND META-ANALYSIS OF MALIGNANCIES, EXCLUDING NON-MELANOMA SKIN CANCER, IN PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH TOFACITINIB OR BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

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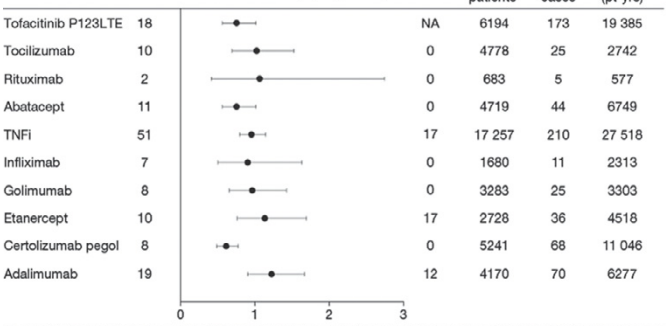
Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). The limited size of the control groups (placebo and active comparator) and limited duration of treatment within the tofacitinib RA clinical trial programme do not permit precise direct comparative assessments for adverse events of long latency, including malignancies, therefore a meta-analytic approach was taken.

Objectives: To compare the rate of malignancies in patients (pts) with moderately to severely active RA within the tofacitinib RA clinical trial programme with estimates from published trial data of approved biologic (b)DMARDS using meta-analytic methods.

Methods: Incidence rates (IR; pts with events per 100 pt-years [yrs] exposure) for tofacitinib were calculated using pooled data from randomised controlled trials (RCT) and long-term extension (LTE) studies. Two Phase (P) 1 studies, 9 P2 studies, 6 P3 studies and 2 LTE studies (one study ongoing; database unlocked at March 2015 data cut off) constituted the P123LTE dataset; pts received 1, 3, 5, 10, 15, 30 mg BID or 20 mg QD of tofacitinib. A systematic literature review of published RCT and LTE studies (through August 2014) of approved bDMARDs (abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab) was conducted. IRs for the endpoint of interest (all malignancies [excluding non-melanoma skin cancers (NMSC)]) were calculated for each bDMARD utilising a random-effects meta-analytic model with a restricted Maximum Likelihood Estimator for between-study variances. Estimates of Q statistic and I^2 were generated to determine the existence and degree of heterogeneity related to the study pool.

Results: The tofacitinib P123LTE dataset included 6194 pts with a total exposure of 19 385 pt-yrs. A total of 64 bDMARD articles were extracted for analysis, representing 58 unique studies and approximately 27 000 pts. Study populations were generally consistent across studies and treatments: mean pt age ranged from 51–54 yrs; mean percentage of pts who were female was 74–84%; and mean baseline C-reactive protein level was 20–31 mg/L. The IR (95% confidence interval [CI]) of malignancy for tofacitinib in the P123LTE dataset was 0.89 (0.76, 1.04) (Figure). Estimated IRs (95% CI) of malignancy were 0.75 (0.56, 1.01) for abatacept, 1.06 (0.41, 2.74) for rituximab, 1.02 (0.69, 1.52) for tocilizumab and 0.95 (0.79, 1.14) for tumour necrosis factor inhibitors (adalimumab, certolizumab, etanercept, golimumab and infliximab) (Figure).

Figure. Incidence rates for all malignancies (excluding NMSC) with biologic DMARDs and tofacitinib across RCTs and LTE studies



The results displayed include a continuity factor (r=0.05) to account for zero incidence rates. Tofacitinib data included through March 2015. Clinical trials for non-tofacitinib studies were conducted between 1997 and 2014.
CI, confidence interval; DMARD, disease-modifying antirheumatic drug; I^2, percent of total variability due to heterogeneity; LTE, long-term extension; NA, not applicable; NMSC, non-melanoma skin cancer; pt-yr, patient-year; RCT, randomised controlled trial; TNFi, tumour necrosis factor inhibitor

Conclusions: The results of this meta-analysis indicate that the tofacitinib IR for all malignancies (excluding NMSC) in pts with moderately to severely active RA is within a similar range to those reported in published interventional studies of similar RA populations treated with approved bDMARDs.

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THU0197 TOFACITINIB, AN ORAL JANUS KINASE INHIBITOR, IN THE TREATMENT OF RHEUMATOID ARTHRITIS: SAFETY AND EFFICACY IN OPEN-LABEL, LONG-TERM EXTENSION STUDIES OVER 8 YEARS

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Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA).

Objectives: The objective of this analysis was to report tofacitinib safety, tolerability and clinical efficacy in long-term extension (LTE) studies with up to 105 months of observation.

Methods: Data were pooled from two open-label studies (NCT00413699 [ongoing; database not locked at January 2016 data-cut] and NCT00661661) of patients with RA who had participated in Phase 1/2/3 tofacitinib studies. Patients received tofacitinib 5 or 10 mg twice daily (BID) as monotherapy or with background disease-