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OP0027

EFFECT OF SHORT-TERM METHOTREXATE DISCONTINUATION ON THE DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS: POSTHOC-ANALYSIS OF TWO RANDOMIZED CLINICAL TRIALS

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Background: Patients with rheumatoid arthritis (RA) require a continuous, potentially life-long immune suppression with disease modifying antirheumatic drugs (DMARDs) including methotrexate (MTX). However, in special circumstances such as life-threatening infections, vaccinations or major surgeries, use of MTX should be minimized to restore the treatment-associated immune suppression. While a long-term or permanent discontinuation of MTX is associated with a disease flare or relapse, the effect of short-term discontinuation on disease activity has not been fully elucidated.
Objectives: To investigate the effect of short-term discontinuation of MTX on the disease activity in patients with RA on stable dose of MTX.
Methods: This is a posthoc analysis of 2 randomized controlled studies investigating effect of MTX discontinuation for 2 weeks or 4 weeks on vaccine response to seasonal influenza vaccination in patients with RA. In the 4-week discontinuation study, 54 patients continued MTX and 44 patients discontinued it for 4 weeks before vaccination with trivalent seasonal influenza vaccine. In the 2-week discontinuation study, 159 patients continued MTX and 161 patients held it for 2 weeks after a seasonal quadrivalent influenza vaccine. Disease activity (DAS28 change, DAS28 flare rate and flare-free survival) was compared between the patients who continued MTX and those held it. A RA flare was defined as an increase in DAS28 of >1.2 or >0.6 if the baseline DAS28 was $\geq$3.2.
Results: In the 4-week MTX-hold group, the mean DAS28 increased at the 4 weeks after MTX discontinuation by 0.38 ± 0.94 and then improved back to baseline after reintroduction of MTX, whereas the mean DAS28 in the MTX-continue group remained stable over time (Figure 1A). The overall flare-free survival during 20 weeks did not differ between the groups (log rank p=0.142) (Figure 1B). However, numerically more patients in the MTX-hold group experienced a flare than those in the MTX-continue group during the 4-weeks MTX discontinuation (20.5% vs. 7.4%, p=0.058). After resuming MTX, the flare rate did not differ between the groups up to 20 weeks of observations (Figure 1C). A temporary MTX discontinuation for 2 weeks was not associated with any clinically meaningful change in disease activity.

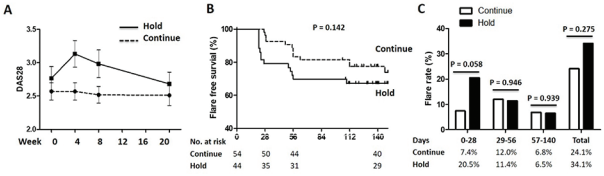

Figure 1. Changes in disease activity of rheumatoid arthritis after MTX discontinuation over time. (A) DAS28-CRP and (B) RA flare free survival in the MTX continue and the MTX hold group were depicted. (C) RA flare rates over time were shown. MTX, methotrexate.

Conclusion: A short-term MTX discontinuation for 2 weeks is safe without any change in disease activity. A 4-week MTX discontinuation is associated with transient increase in disease activity without affecting long-term outcomes.

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OP0028

POST-APPROVAL COMPARATIVE SAFETY STUDY OF TOFACITINIB AND BIOLOGIC DMARDS: FIVE–YEAR RESULTS FROM A US-BASED RHEUMATOID ARTHRITIS REGISTRY

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Background: Tofacitinib is an oral JAK inhibitor for the treatment of rheumatoid arthritis (RA). Real-world data (RWD) complement clinical trial data in assessing

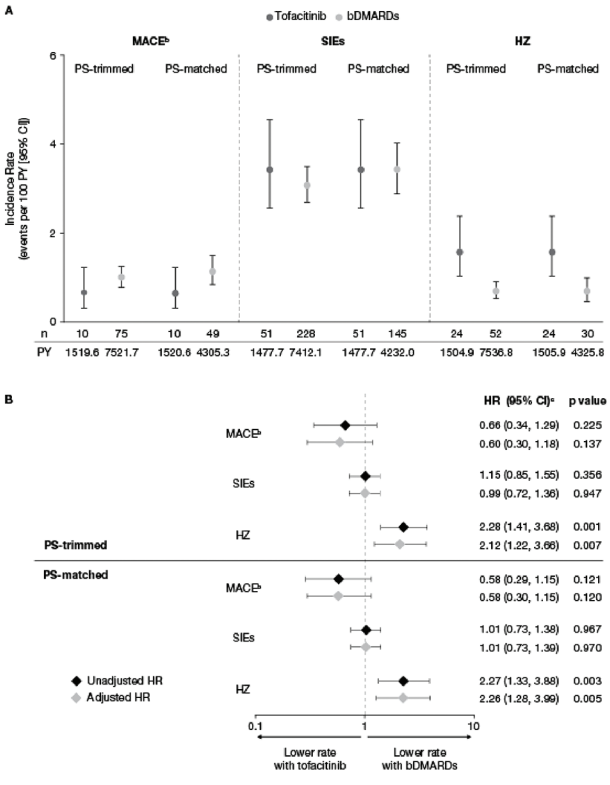
long-term safety. To our knowledge, this is the first long-term comparative RWD analysis of tofacitinib.

Objectives: To compare 5-year adverse event (AE) incidence rates (IRs) in patients (pts) starting tofacitinib vs biological (b)DMARDs using cohorts from the US Corrona RA registry.

Methods: This prospective, observational 5-year study embedded in the ongoing US Corrona RA registry routinely collected 9 categories of predefined AEs from participating physicians. Real-world safety event rates of major adverse cardiovascular events (MACE), serious infectious events (SIEs) and herpes zoster (HZ; serious and non-serious) were compared in pts with RA who started tofacitinib or a bDMARD regardless of dose/schedule between 6 Nov 2012 (US FDA approval) and 30 Jun 2017 (follow-up through 31 Dec 2017). Endpoints were selected *a priori* as having sufficient power to detect a 2-fold difference between cohorts at this datacut; there was insufficient power to assess malignancy. Baseline variables with a standardised difference >|0.10| between tofacitinib and bDMARD initiators, and *a priori* selected covariates (gender, age, line of therapy, history of AE of interest) were used to construct propensity scores (PS) to derive a PS-trimmed (primary) population and a PS–matched population for sensitivity analysis (ratio: max. 4 bDMARD:1 tofacitinib; calliper=0.05). Pts were followed from initiation until an AE of interest, discontinuation and/or start of a new therapy +90 days, death or end of follow-up, whichever came first. Crude IRs (events/100 pt–years [PY]) were estimated; multivariable-adjusted Cox regression was used to estimate hazard ratios (HRs) comparing rates of first events between cohorts.

Results: In total, 1544 tofacitinib (2138.2 PY) and 7083 bDMARD (9904.9 PY) initiators were included. PS–trimming resulted in 1117 tofacitinib and 5542 bDMARD initiators. Rates of MACE and SIEs were similar in both cohorts (Fig 1A); adjusted HRs (95% confidence intervals [CIs]) were: MACE 0.60 (0.30, 1.18); SIEs 0.99 (0.72, 1.36; Fig 1B). HZ IR was higher for tofacitinib vs bDMARDs (Fig 1A); HRs for HZ were significantly increased with tofacitinib vs bDMARDs (adjusted HR 2.12 [1.22, 3.66]; Fig 1B); all HZ events were non-serious with tofacitinib. Similar results were observed in PS-matched populations.

FIG 1: A. Crude incidence rates[a] for MACE, SIEs and HZ; and B. Hazard ratios for MACE, SIEs and HZ



[a]Incidence rates are events per 100 PY; [b]MACE is defined as any myocardial infarction, stroke/transient ischaemic attack or cardiovascular death; [c]bDMARD initiators were the reference population for calculation of HRs

bDMARD, biological disease-modifying antirheumatic drug; CI, confidence interval; HR, hazard ratio; HZ, herpes zoster; MACE, major adverse cardiovascular event; PS, propensity score; PY, patient-years; SIEs, serious infection events

Conclusion: This is the first comparative analysis of RWD for tofacitinib and bDMARDs to use PS-trimmed and PS-matched analyses to adjust for channelling/prescribing patterns for newly approved therapies. Pts starting tofacitinib or bDMARDs for RA had similar rates of MACE and SIEs. Tofacitinib initiators had higher HZ IRs vs bDMARD initiators. These results are consistent with long-term clinical trial findings.

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OP0029

SWITCHING BETWEEN THE JAK1-SELECTIVE INHIBITOR-UPADACITINIB AND ADALIMUMAB FOLLOWING INITIAL NON-RESPONSE: CLINICAL AND FUNCTIONAL OUTCOMES AMONG RHEUMATOID ARTHRITIS PATIENTS

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Background: Initiating advanced therapy for rheumatoid arthritis (RA) patients (pts) with a bDMARD or a Janus kinase (JAK) inhibitor is recommended if remission or low disease activity (LDA) is not achieved with csDMARDs.[1,2] While data show that pts are switched alternately between bDMARD and JAK treatments, there is lack of evidence for pts with inadequate response (IR) to a JAK inhibitor switching to a bDMARD. Recently, the JAK1-selective inhibitor-upadacitinib (UPA) demonstrated superior clinical and functional outcomes through 26 wks to the standard of care-adalimumab (ADA) with continued background methotrexate (MTX).[3]

Objectives: To describe outcomes associated with treatment switch from UPA to ADA and vice-versa among RA pts who do not achieve initial response.

Methods: This phase 3, double-blind, placebo (PBO)-controlled, head-to-head study of UPA 15 mg q.d. vs PBO or ADA 40 mg injection every other wk included MTX-IR patients; all pts continued stable background MTX through 26 wks. Pts without ≥20% improvements from bl in tender (68) and swollen (66) joint counts by wks 14, 18, or 22 were considered non-responders (NR) and switched without washout to either ADA (UPA group) or UPA (ADA group) in a bl fashion. Post-hoc analysis assessed clinical outcomes - DAS28 (CRP), CDAI, SDAI, and ACR responses (from baseline), and HAQ-DI at 3 and 6 mos (±2 wks) post-switch. Adverse events (infections) were summarized as n% (95% CI) through 6 mos post-switch (ps). Data were as observed.

	UPA 15 mg QD Non-responders Switched to ADA 40 mg eow (N=126)		ADA 40 mg eow Non-responders Switched to UPA 15 mg QD (N=77)	
n/N (%)	3 months post-switch	6 months post-switch	3 months post-switch	6 months post-switch
ACR20[a]	68/118 (58)	67/113 (59)	49/75 (65)	53/71 (75)
ACR50[a]	33/120 (28)	29/112 (26)	26/73 (36)	34/69 (49)
ACR70[a]	10/120 (8)	14/114 (12)	13/74 (18)	17/72 (24)
DAS28(CRP) ≤3.2	30/119 (25)	38/109 (35)	31/74 (42)	38/70 (54)
DAS28(CRP) <2.6	15/119 (13)	21/109 (19)	19/74 (26)	22/70 (31)
CDAI ≤10	33/120 (28)	41/114 (36)	24/72 (33)	33/70 (47)
CDAI ≤2.8	5/120 (4)	6/114 (5)	6/72 (8)	10/70 (14)
SDAI ≤11	32/119 (27)	41/109 (38)	26/71 (37)	33/69 (48)
SDAI ≤3.3	5/119 (4)	4/109 (4)	5/71 (7)	12/69 (17)
Mean change from baseline (95% CI)[b]				
HAQ-DI	-0.49 (-0.60, -0.38)	-0.52 (-0.64, -0.41)	-0.63 (-0.76, -0.50)	-0.67 (-0.81, -0.53)
DAS28(CRP)	-1.79 (-2.03, -1.55)	-2.10 (-2.36, -1.84)	-2.36 (-2.66, -2.06)	-2.56 (-2.90, -2.22)
CDAI	-20.87 (-23.62, -18.11)	-23.61 (-26.49, -20.73)	-22.45 (-25.79, -19.12)	-24.95 (-28.35, -21.55)
SDAI	-21.70 (-24.46, -18.94)	-24.52 (-27.47, -21.56)	-23.49 (-27.03, -19.95)	-26.07 (-29.55, -22.59)

[a]Responses are based on percent improvement in American College of Rheumatology criteria from baseline at randomization; [b]mean change from baseline at randomization.
UPA: upadacitinib; QD: once daily; ADA: adalimumab; eow: every other week; ACR: American College of Rheumatology; DAS28(CRP): 28-joint disease activity score based on C-reactive protein; CDAI: clinical disease activity index; SDAI: simplified disease activity index; CI: confidence interval; TJC68: tender joint count based on 68 joints; SJC66: swollen joint count based on 66 joints; HAQ-DI,: health assessment questionnaire disability index.