SUPPLEMENTARY MATERIAL

Methotrexate, tofacitinib, and biologic disease-modifying antirheumatic drug safety and effectiveness among patients with rheumatoid arthritis in Japan: CorEvitas registry observational study

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Supplementary methods

Major adverse cardiovascular events included non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths, excluding fatal pulmonary embolism. Total cardiovascular disease was defined as hypertension requiring hospitalization, cardiac revascularization procedure (coronary artery bypass graft, stent, angioplasty), ventricular arrhythmia, cardiac arrest, myocardial infarction, acute coronary syndrome, unstable angina, congestive heart failure requiring hospitalization, stroke, transient ischemic attack, other serious cardiovascular event (specify), deep vein thrombosis, peripheral arterial thromboembolic event, urgent peripheral arterial revascularization, peripheral ischemia or gangrene (necrosis) and pulmonary embolism. Venous thromboembolism included deep vein thrombosis and pulmonary embolism. Serious infections were defined as infections meeting serious adverse event criteria or requiring treatment with intravenous antibiotics. Serious infection types collected in the registry are pneumonia, sepsis, joint/bursa, cellulitis/skin, sinusitis, diverticulitis, bronchitis, gastroenteritis, meningitis/encephalitis, urinary tract infection, upper respiratory infection, active tuberculosis, and other (free text) serious infections. Total herpes zoster (HZ) was defined as non-serious and serious HZ events. Total malignancy excluding non-melanoma skin cancer included the following malignancy types collected in the registry: lymphoma, lung cancer, breast cancer, skin cancer (melanoma), and other cancer.

Supplementary Table S1. Demographics and baseline characteristics of patients in MTX, tofacitinib, TNFi, and non-TNFi initiator groups (effectiveness cohort)

	MTX (*N*=276)	**Tofacitinib (*N*=205)**	**TNFi (*N*=603)**	**Non-TNFi (*N*=687)**
Demographics/socioeconomic characteristics				
Age (years), mean (SD)	59.6 (14.3)	61.3 (13.6)	60.4 (15.0)	65.8 (12.4)
Sex – female, *n* (%)	206 (74.6)	167 (81.9)	485 (80.6)	519 (75.5)
Race, *n* (%)				
Japanese	273 (99.3)	202 (99.0)	597 (99.5)	682 (99.9)
Other[a]	-	-	-	-
Education, *n* (%)				
No college	157 (58.8)	120 (60.0)	315 (54.3)	414 (63.2)
Some college/college graduate	110 (41.2)	80 (40.0)	265 (45.7)	241 (36.8)
Work status, *n* (%)				
Full-time	106 (38.4)	56 (27.3)	195 (32.3)	166 (24.2)
Other	170 (61.6)	149 (72.7)	408 (67.7)	521 (75.8)
Lifestyle characteristics				
Smoking status,[b] *n* (%)				
Non-smoker	193 (76.3)	168 (90.8)	506 (89.1)	575 (89.0)
Current smoker	60 (23.7)	17 (9.2)	62 (10.9)	71 (11.0)
Alcohol use in the past year, *n* (%)	151 (54.7)	91 (44.4)	267 (44.3)	247 (36.0)
Health measures				
Body height (m), mean (SD)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)
Body weight (kg), mean (SD)	55.4 (10.1)	56.5 (15.1)	57.2 (25.3)	55.4 (12.3)
BMI (kg/m^2), categorical, *n* (%)[c]				
BMI <25 (underweight/normal)	216 (86.4)	134 (77.0)	370 (81.0)	403 (77.4)

	MTX (*N*=276)	Tofacitinib (*N*=205)	TNFi (*N*=603)	Non-TNFi (*N*=687)
BMI 25–<30 (overweight)	28 (11.2)	29 (16.7)	69 (15.1)	96 (18.4)
BMI ≥30 (obese)	6 (2.4)	11 (6.3)	18 (3.9)	22 (4.2)
History of comorbidities, *n* (%)				
CVD[d]	24 (8.7)	22 (10.7)	53 (8.8)	91 (13.2)
Depression	2 (0.7)	7 (3.4)	5 (0.8)	8 (1.2)
Diabetes mellitus	25 (9.1)	19 (9.3)	45 (7.5)	93 (13.5)
GI perforation	0 (0.0)	3 (1.5)	4 (0.7)	6 (0.9)
Hyperlipidemia	41 (14.9)	38 (18.5)	84 (13.9)	141 (20.5)
Hypertension	87 (31.5)	57 (27.8)	170 (28.2)	270 (39.3)
HZ[e]	32 (11.6)	24 (11.7)	65 (10.8)	88 (12.8)
IBD	1 (0.4)	3 (1.5)	4 (0.7)	1 (0.1)
Malignancy[f]	19 (6.9)	12 (5.9)	41 (6.8)	102 (14.8)
Peptic ulcer	10 (3.6)	6 (2.9)	28 (4.6)	35 (5.1)
Serious infection[g]	22 (8.0)	28 (13.7)	54 (9.0)	97 (14.1)
Treatment characteristics				
Number of prior therapies				
csDMARDs, mean (SD)	0.2 (0.6)	1.8 (1.0)	1.6 (1.0)	1.7 (1.1)
bDMARDs, mean (SD)	0.0 (0.1)	1.4 (1.3)	0.5 (1.1)	0.8 (1.2)
tsDMARDs, mean (SD)	0.0 (0.0)	0.0 (0.2)	0.1 (0.3)	0.1 (0.4)
Prior prednisone/prednisolone use, *n* (%)	34 (12.3)	97 (47.3)	229 (38.0)	303 (44.1)
Concomitant therapy				
Prednisone/prednisolone, *n* (%)	47 (17.0)	58 (28.3)	185 (30.7)	229 (33.3)
Prednisone/prednisolone dose, mean (SD)	6.5 (4.6)	5.9 (7.1)	6.5 (6.7)	7.2 (10.4)
MTX, *n* (%)	0 (0.0)	146 (71.2)	444 (73.6)	345 (50.2)

	MTX (*N*=276)	Tofacitinib (*N*=205)	TNFi (*N*=603)	Non-TNFi (*N*=687)
MTX dose, categorical, *n* (%)				
<8 mg/week	132 (48.0)	25 (19.1)	70 (16.3)	74 (22.6)
≥ 8 mg/week	143 (52.0)	106 (80.9)	359 (83.7)	253 (77.4)
Other csDMARDs,[h] *n* (%)	33 (12.0)	37 (18.0)	174 (28.9)	250 (36.4)
Disease activity characteristics				
Duration of RA (years), mean (SD)	2.4 (5.9)	11.4 (10.9)	7.1 (9.4)	9.8 (11.0)
RF+ ever, *n* (%)	151 (58.1)	130 (71.8)	331 (59.0)	467 (74.4)
Anti-CCP+ ever, *n* (%)	124 (49.6)	101 (64.7)	274 (55.7)	389 (66.3)
Serum+ (RF+ and/or CCP+), *n* (%)	172 (63.7)	142 (77.2)	391 (67.3)	528 (78.9)
CDAI, mean (SD)	19.0 (11.5)	22.7 (12.9)	22.7 (13.1)	21.9 (12.2)
CDAI categorical, *n* (%)				
Remission (<2.8)	5 (1.9)	4 (2.0)	10 (1.7)	15 (2.3)
Low (2.8–≤10)	58 (21.6)	17 (8.6)	78 (13.4)	70 (10.5)
Moderate (>10–22)	113 (42.0)	93 (47.0)	231 (39.6)	301 (45.2)
High (>22)	93 (34.6)	84 (42.4)	264 (45.3)	280 (42.0)
Tender joints, mean (SD)	5.2 (5.2)	6.8 (6.5)	6.9 (6.6)	6.4 (5.8)
Swollen joints, mean (SD)	5.0 (4.5)	6.1 (5.4)	6.4 (5.5)	6.0 (5.0)
Physician Global Assessment, mean (SD)	44.4 (23.2)	45.0 (20.1)	44.9 (23.1)	44.0 (21.4)
DAS28-ESR, mean (SD)	4.6 (1.2)	4.9 (1.3)	4.9 (1.4)	5.0 (1.4)
PROs				
J-HAQ, mean (SD)	0.7 (0.7)	1.1 (0.8)	0.9 (0.8)	1.2 (0.8)
Morning stiffness, *n* (%)	209 (76.6)	140 (68.6)	435 (72.7)	513 (74.9)
Patient Global Assessment (VAS, 0–100), mean (SD)	42.9 (27.0)	52.6 (26.2)	49.1 (26.6)	51.1 (26.1)
Patient fatigue (VAS, 0–100), mean (SD)	39.4 (26.8)	49.5 (27.9)	43.6 (28.1)	45.7 (27.8)

	MTX (*N*=276)	Tofacitinib (*N*=205)	TNFi (*N*=603)	Non-TNFi (*N*=687)
Patient pain (VAS, 0–100), mean (SD)	46.3 (27.7)	53.4 (27.4)	50.3 (27.3)	51.7 (27.4)
EQ-5D-5L domains,[i] categorical, *n* (%)				
Mobility	42 (15.4)	52 (25.6)	152 (25.5)	231 (34.0)
Self-care	31 (11.4)	40 (19.5)	105 (17.7)	187 (27.5)
Usual activities	52 (19.1)	65 (31.9)	180 (30.2)	257 (37.7)
Pain and discomfort	128 (47.1)	113 (55.4)	318 (53.4)	417 (60.9)
Anxiety and depression	37 (13.7)	40 (19.5)	97 (16.4)	139 (20.4)

bDMARD biologic disease-modifying antirheumatic drug, *BMI* body mass index, *CCP* cyclic citrullinated peptide, *CDAI* Clinical Disease Activity Index, *CDC* Center for Disease Control and Prevention, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *CVD* cardiovascular disease, *DAS28-ESR* Disease Activity Score 28-joint count, *EQ-5D-5L* EuroQol 5-dimension 5-Level, *GI* gastrointestinal, *HZ* herpes zoster, *IBD* inflammatory bowel disease, *J-HAQ* Japanese version of the Health Assessment Questionnaire, *MTX* methotrexate, *N* number of patients, *n* number of patients with outcome, *PRO* patient-reported outcome, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *SD* standard deviation, *TNFi* tumor necrosis factor inhibitors, *tsDMARD* targeted synthetic disease-modifying antirheumatic drug, *VAS* Visual Analog Scale, *WHO* World Health Organization

N may vary for each outcome based on available data

Entries with *n*<5 and adjacent cells, denoted "–", are not displayed to avoid the potential risk of identifying individual patients

[a]Other included “Chinese,” “Korean,” or “Other”

[b]Data for past smokers are not available

[c]Based on the CDC and WHO cut-offs for normal/underweight (<25); overweight (25.0–<30.0); and obese (≥30.0)

[d]CVD includes baseline history of any of the following: cardiac revascularization procedure, ventricular arrhythmia, cardiac arrest, myocardial infarction, acute coronary syndrome, unstable angina, coronary artery disease, congestive heart failure; cerebrovascular disease includes baseline history of any of the following: stroke, transient ischemic attack, peripheral vascular disease, peripheral arterial disease

[e]Total HZ includes both non-serious and serious HZ

[f]Malignancy includes lymphoma, lung, breast, skin (basal cell, squamous cell, melanoma), and any other cancers

[g]Serious infections are defined as infections meeting serious adverse event criteria or requiring treatment with intravenous antibiotics. Serious infection types collected in the registry are joint/bursa, cellulitis/skin, sinusitis, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis/encephalitis, urinary tract infection, upper respiratory infection, active tuberculosis (regardless of seriousness), and other serious infections

[h]Other csDMARDs may have included bucillamine, iguratimod, leflunomide, sulfasalazine, tacrolimus, and other

[i]For each domain assessed in the EQ-5D-5L, patients indicate whether they have “no problems,” “slight problems,” “moderate problems,” “severe problems,” or “extreme problems/unable to do task.” The reported values in the table represent the number and percentage of patients reporting “moderate,” “severe,” or “extreme” problems in each of the domains

Supplementary Table S2. Mean change from baseline (95% CI) in PROs at month 6 (unadjusted effectiveness outcomes) in MTX, tofacitinib, TNFi, and non-TNFi initiator groups (effectiveness cohort)

	MTX (*N*=276)	**Tofacitinib (*N*=205)**	**TNFi (*N*=603)**	**Non-TNFi (*N*=687)**
Pain[a]	-21.7 (-25.1, -18.3)	-21.4 (-25.4, -17.5)	-17.6 (-19.9, -15.3)	-17.4 (-19.5, -15.2)
Fatigue[a]	-13.1 (-16.3, -9.9)	-15.5 (-19.2, -11.8)	-9.4 (-11.6, -7.2)	-10.7 (-12.8, -8.7)
Patient Global Assessment[a]	-18.5 (-21.8, -15.2)	-19.5 (-23.4, -15.7)	-16.8 (-19.1, -14.6)	-16.1 (-18.2, -14.0)
Morning stiffness[a,b]	-31.5 (-35.9, -27.1)	-19.7 (-24.7, -14.6)	-22.4 (-25.4, -19.5)	-17.9 (-20.6, -15.1)
J-HAQ[a]	-0.3 (-0.4, -0.2)	-0.3 (-0.4, -0.2)	-0.2 (-0.3, -0.2)	-0.3 (-0.3, -0.2)
EQ-5D-5L[c]				
Mobility	-10.2 (-14.0, -6.5)	-10.8 (-15.2, -6.4)	-6.8 (-9.4, -4.3)	-11.1 (-13.4, -8.7)
Self-care	-8.6 (-12.0, -5.2)	-9.0 (-12.9, -5.0)	-7.6 (-9.9, -5.3)	-12.2 (-14.3, -10.0)
Usual activities	-12.6 (-16.5, -8.7)	-14.8 (-19.3, -10.3)	-13.5 (-16.2, -10.8)	-14.5 (-17.0, -12.0)
Pain/discomfort	-31.2 (-35.9, -26.4)	-25.3 (-30.8, -19.8)	-24.6 (-27.9, -21.4)	-28.5 (-31.5, -25.5)
Depression/anxiety	-9.5 (-12.9, -6.0)	-4.2 (-8.2, -0.2)	-7.1 (-9.5, -4.7)	-9.5 (-11.7, -7.3)

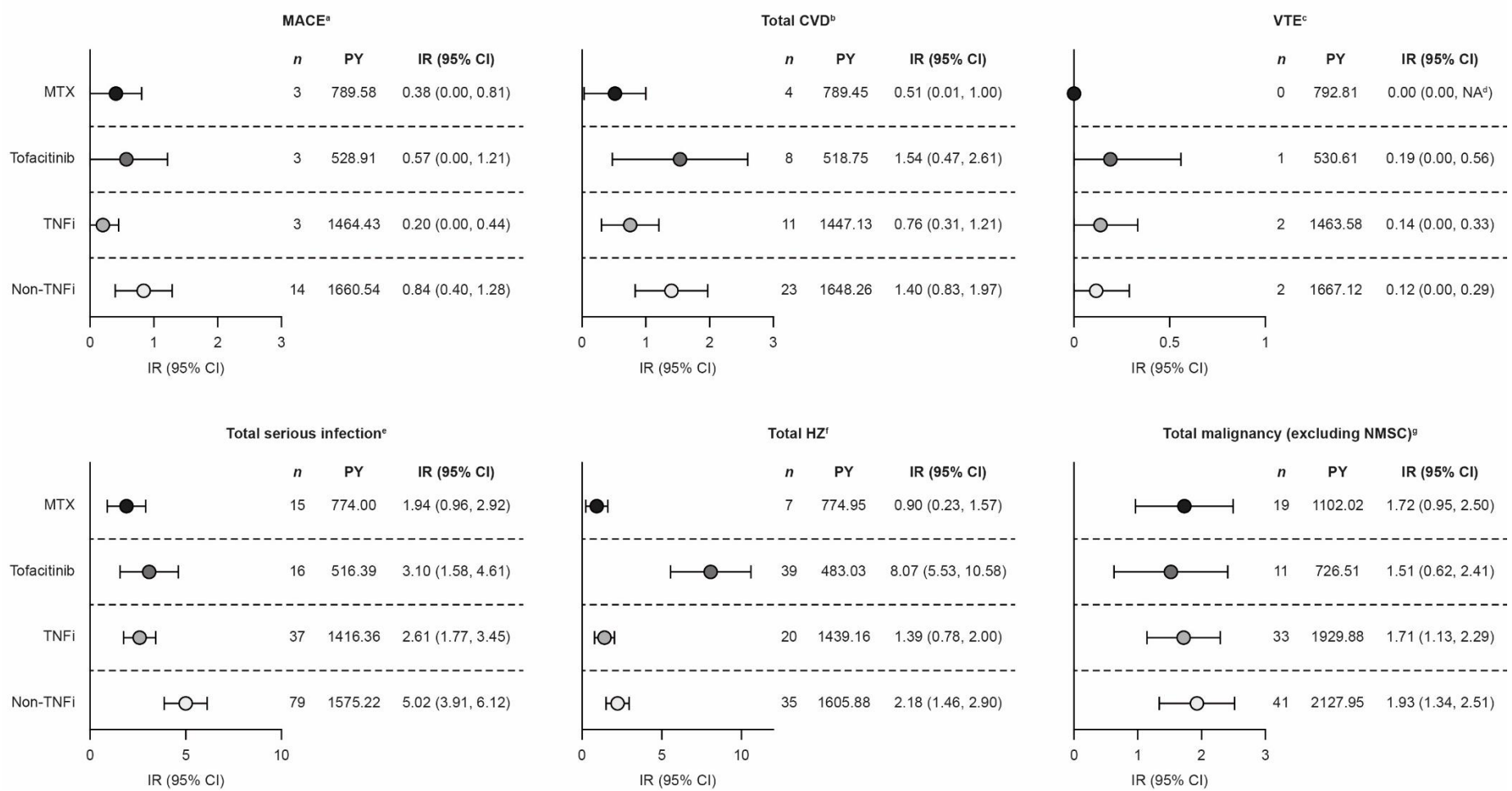
CI confidence interval, *EQ-5D-5L* EuroQol 5-Dimension 5-Level, *J-HAQ* Japanese version of the Health Assessment Questionnaire, *MTX* methotrexate, *N* number of patients, *PRO* patient-reported outcome, *TNFi* tumor necrosis factor inhibitors

[a]Continuous measures (pain, fatigue, Patient Global Assessment, morning stiffness, J-HAQ) represented as mean change from baseline to 6 months. Calculated by subtracting the baseline value from the 6-month value; a negative value indicates improvement

[b]Morning stiffness calculated as the mean change from baseline to 6 months in the percentage of patients reporting morning stiffness

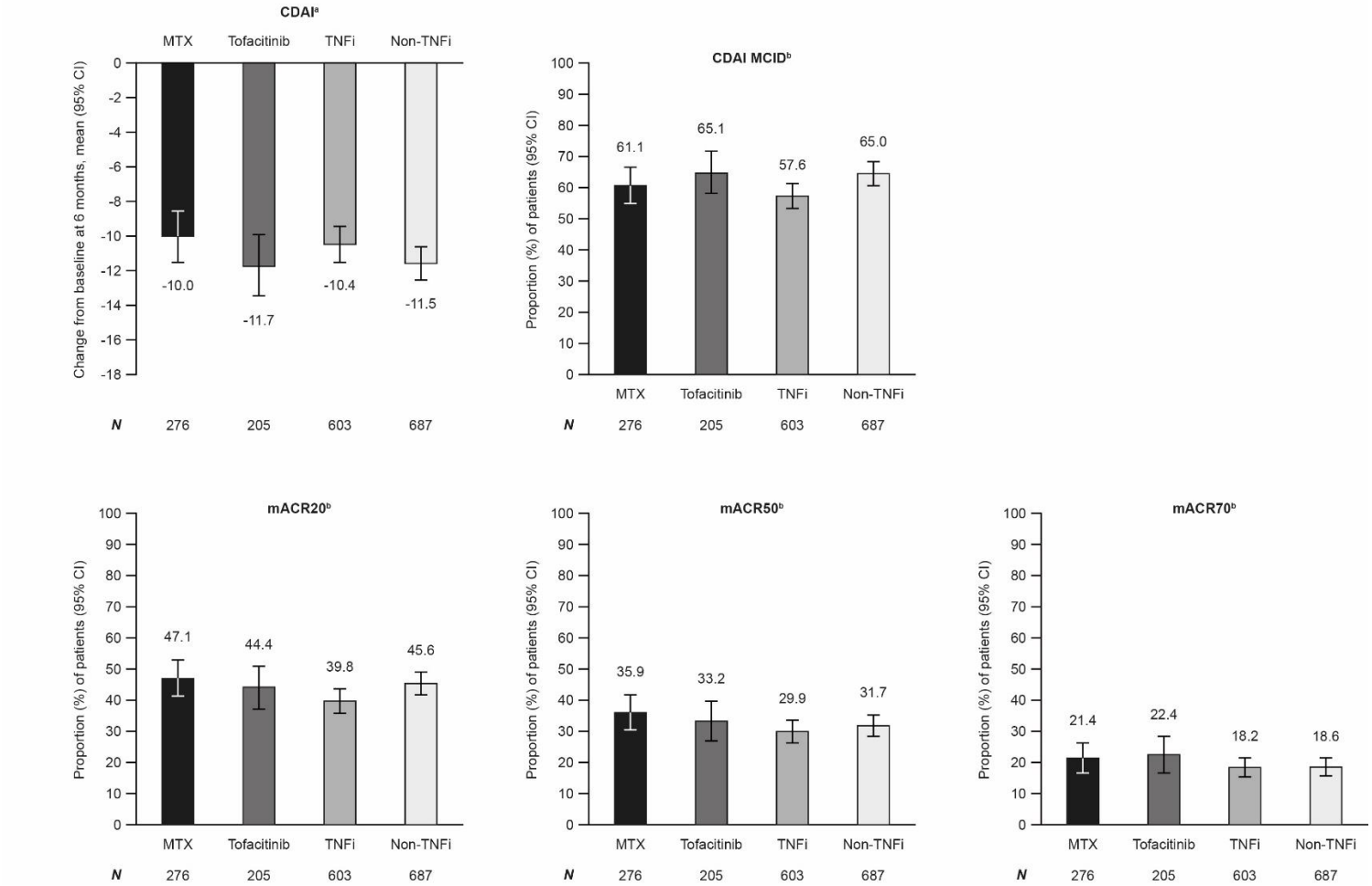
[c]For each domain assessed in the EQ-5D-5L, patients indicate whether they have "no problems," "slight problems," "moderate problems," "severe problems," or "extreme problems/unable to do task." The reported values represent the mean change in the percentage of patients reporting moderate/severe/extreme problems from baseline to 6 months. A negative value indicates improvement

Supplementary Fig. S1. Unadjusted IRs (patients with events per 100 PY) of safety events in MTX, tofacitinib, TNFi, and non-TNFi initiator groups (safety cohort)



[a]MACE includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths, excluding fatal pulmonary embolism. [b]Total CVD is defined as hypertension requiring hospitalization, cardiac revascularization procedure (coronary artery bypass graft, stent, angioplasty), ventricular arrhythmia, cardiac arrest, myocardial infarction, acute coronary syndrome, unstable angina, congestive heart failure requiring hospitalization, stroke, transient ischemic attack, other cardiovascular event (specify), deep vein thrombosis, peripheral arterial thromboembolic event, urgent peripheral arterial revascularization, peripheral ischemia or gangrene (necrosis) and pulmonary embolism. [c]VTE is defined as deep vein thrombosis, and pulmonary embolism. [d]CIs for events with zero counts are not computed. [e]Total serious infections are defined as infections meeting serious adverse event criteria or requiring treatment with intravenous antibiotics. Serious infection types collected in the registry are joint/bursa, cellulitis/skin, sinusitis, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis/encephalitis, urinary tract infection, upper respiratory infection, active tuberculosis (regardless of seriousness), and other serious infections. [f]Total HZ includes both non-serious and serious HZ. [g]Total malignancy excluding NMSC includes lymphoma, lung, breast, skin (melanoma), and other cancers. *CI* confidence interval, *CVD* cardiovascular disease, *HZ* herpes zoster, *IR* incidence rate, *MACE* major adverse cardiovascular events, *MTX* methotrexate, *n* number of patients with events, *NMSC* non-melanoma skin cancer, *PY* patient-years, *TNFi* tumor necrosis factor inhibitors, *VTE* venous thromboembolism

Supplementary Fig. S2. Marginal mean change from baseline in CDAI (95% CI) and proportion of patients achieving effectiveness outcomes (95% CI) at month 6 (unadjusted effectiveness outcomes) in MTX, tofacitinib, TNFi, and non-TNFi initiator groups (effectiveness cohort)



[a]CDAI represented as mean change from baseline to 6 months. Calculated by subtracting the baseline value from the 6-month value; a negative value indicates improvement.

[b]Binary outcomes represented as percent achieving the threshold (please see methods for details)

CDAI Clinical Disease Activity Index, *CI* confidence interval, *mACR* modified American College of Rheumatology, *MCID* minimum clinically important difference, *MTX* methotrexate, *N* number of patients, *TNFi* tumor necrosis factor inhibitors