

SUPPLEMENTARY MATERIAL

Generation-Dependent Retention Rates and Reasons for Discontinuation of Molecular Targeted Therapies in Patients with Rheumatoid Arthritis: From FIRST Registry

Satoshi Kubo^{1,2}, Yusuke Miyazaki², Yasuyuki Todoroki^{1,2}, Atsushi Nagayasu²,
Ryuichiro Kanda², Takafumi Aritomi², Satsuki Matsunaga², Masanobu Ueno², Ippei
Miyagawa², Koshiro Sonomoto³, Kentaro Hanami², Shingo Nakayamada², Yoshiya
Tanaka²

¹ Department of Molecular Targeted Therapies, University of Occupational and
Environmental Health, Japan, Kitakyushu, Japan

² The First Department of Internal Medicine, University of Occupational and
Environmental Health, Japan, Kitakyushu, Japan

³ Department of Clinical Nursing, School of Health Sciences, University of
Occupational and Environmental Health, Japan, Kitakyushu, Japan

Address for Correspondence and reprint requests:

Prof. Yoshiya Tanaka, MD, PhD

The First Department of Internal Medicine,

School of Medicine, University of Occupational and Environmental Health, Japan,

1-1 Iseigaoka, Yahata-nishi-ku, Kitakyushu, Fukuoka, 807-8555, Japan

Tel. +81-93-603-1611 (ext. 2426); Fax +81-93-691-9334

Email: tanaka@med.uoeh-u.ac.jp

Supplementary Table 1. Patient characteristics of individuals aged below 65 years.

Variables	TNFi	Anti-IL-6R	CTLA-4 Ig	JAKi	P value
Age (years)	49.2 (10.9)	52.4 (10.5)	54.1 (9.3)	50.5 (9.7)	<0.0001
Gender, n (% female)	432 (86.4%)	240 (80.8%)	135 (87.1%)	164 (83.3%)	0.1443
Disease duration (month)	61.9 (75.3)	90 (104.4)	99.1 (100.7)	105.0 (100.7)	<0.0001
Steinbrocker's classification, %, I/II/III/IV	42/43/9/6	34/42/12/12	29/37/18/15	27/42/16/12	<0.0001
Treatment history					
Prior use of biologics	158 (31.6%)	148 (49.8%)	72 (46.5%)	137 (69.5%)	<0.0001
MTX use at baseline, n (%)	451 (90.2%)	176 (59.3%)	109 (70.3%)	152 (77.2%)	<0.0001
dose, mg/w	12.0 (3.5)	12.5 (3.5)	12.0 (3.8)	13.3 (3.0)	0.4641
Glucocorticoid use at baseline, n (%)	49 (9.8%)	79 (26.6%)	37 (23.9%)	33 (16.8%)	<0.0001
dose, mg/day	5.9 (8.4)	9.2 (11.5)	8.3 (10.9)	8.9 (12.4)	0.4085
28-tender joint count	8.5 (6.6)	8.5 (6.6)	7.3 (5.3)	8.5 (6.1)	0.2096
28-swollen joint count	6.7 (5.2)	7 (5.4)	6 (4.5)	6.6 (4.8)	0.2093
PGA, VAS 0-100 mm	48.3 (24.4)	52.8 (24.9)	49.5 (23.9)	49.7 (23.6)	0.0972
EGA, VAS 0-100 mm	40.4 (19.9)	44.1 (20.5)	37.9 (17.9)	43.2 (22.2)	0.0061
CDAI	48.3 (24.4)	52.8 (24.9)	49.5 (23.9)	49.7 (23.6)	0.0972
HAQ-DI	24.2 (13.1)	25 (12.7)	22 (9.7)	24.4 (12.1)	0.1178
CRP (mg/dl)	1.0 (0.7)	1.2 (0.8)	1.1 (0.7)	1.1 (0.7)	0.0011
ESR (mm/hr)	1.6 (3.0)	3.1 (4.3)	1.1 (2.1)	1.4 (2.8)	<0.0001
Rheumatoid factor (U/ml)	38.1 (28.5)	51 (31.9)	36.3 (26.6)	36.3 (28.6)	<0.0001
Anti-CCP antibody (U/ml)	320.2 (486.9)	347.8 (878.9)	393.3 (891.2)	232.1 (576.4)	0.1840
MMP-3 (ng/ml)	193.8 (305.7)	291.0 (332.2)	127.8 (140.9)	176.0 (258.5)	<0.0001

TNFi, tumor necrosis factor inhibitors; Anti IL-6R, Anti IL-6 receptor antibodies; CTLA-4 Ig, cytotoxic T-lymphocyte antigen 4 immunoglobulin; JAKi, Janus kinase inhibitors; MTX, methotrexate; PGA, patient's global assessment; EGA, evaluator's global assessment; DAS28, disease activity score 28 joint; ESR, erythrocyte sedimentation rate; CDAI, clinical disease activity index; HAQ, health assessment questionnaire; CRP, C reactive protein; CCP, cyclic citrullinated peptide ;MMP-3, matrix metalloproteinase-3.

Supplementary Table 2. Patient characteristics of individuals aged 65 to 74 years.

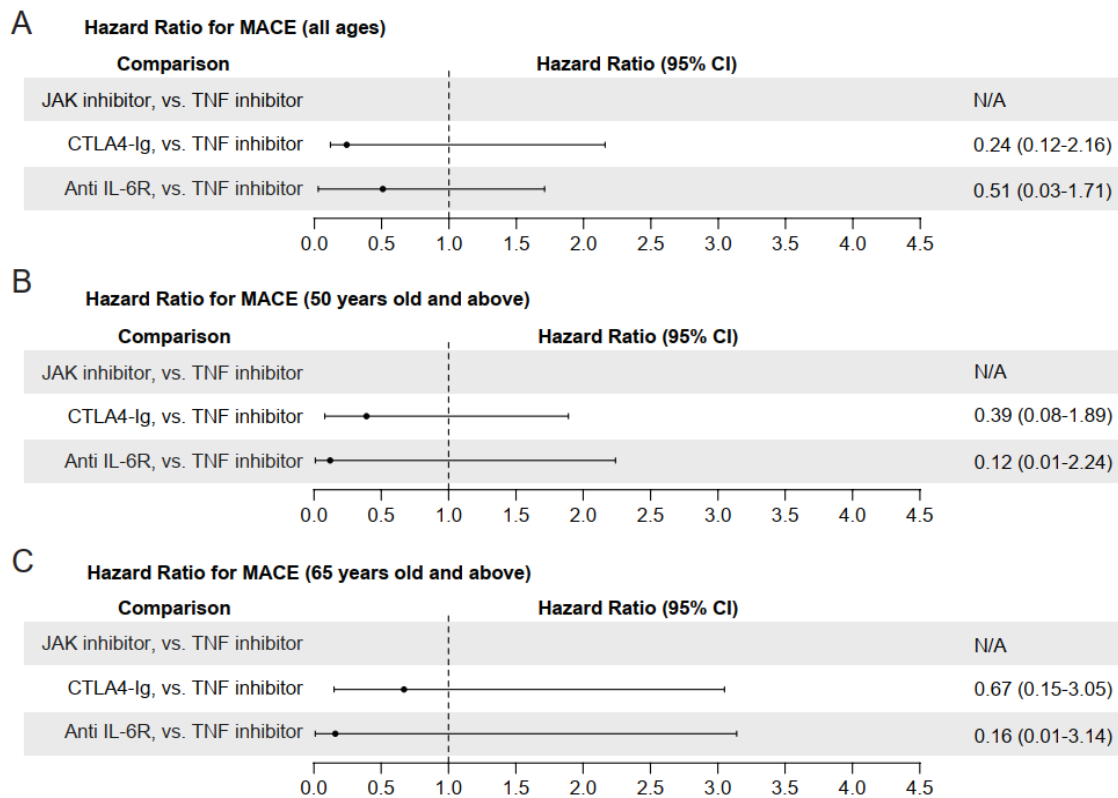
Variables	TNFi	Anti-IL-6R	CTLA-4 Ig	JAKi	P value
Age (years)	69.4 (2.7)	69.5 (2.5)	69.8 (2.8)	69.2 (2.4)	0.3350
Gender, n (% female)	145 (80.6%)	137 (81.1%)	145 (80.6%)	52 (66.7%)	0.0736
Disease duration (month)	112.9 (129.2)	130.5 (147.2)	146.7 (130.8)	170.4 (134.7)	0.0039
Steinbrocker's classification, %, I/II/III/IV	21/47/17/14	12/46/19/23	11/38/25/26	8/40/28/24	0.0009
Treatment history					
Prior use of biologics	106 (42.1%)	94 (55.6%)	83 (46.1%)	63 (80.8%)	<0.0001
MTX use at baseline, n (%)	219 (86.9%)	81 (47.9%)	86 (47.8%)	57 (73.1%)	<0.0001
dose, mg/w	12.0 (3.4)	10.8 (3.8)	11.4 (3.9)	12.6 (3.3)	0.0117
Glucocorticoid use at baseline, n (%)	33 (13.1%)	49 (29.0%)	57 (31.7%)	17 (21.8%)	<0.0001
dose, mg/day	6.4 (6.1)	8.9 (10.0)	13.6 (14.7)	13.0 (15.0)	0.0269
28-tender joint count	8.8 (6.3)	10.1 (7.2)	7.5 (6.1)	9.1 (6.1)	0.0017
28-swollen joint count	8 (5.4)	8.5 (5)	7.2 (5.2)	7.6 (5.6)	0.1434
PGA, VAS 0-100 mm	54.7 (24.5)	55 (26.1)	49.6 (25.3)	54.9 (24.6)	0.1265
EGA, VAS 0-100 mm	45.7 (19.2)	47.4 (20.9)	40.7 (19.7)	46.9 (22.7)	0.0092
CDAI	26.9 (12.7)	28.6 (13.3)	23.7 (12.2)	26.9 (13)	0.0030
HAQ-DI	1.4 (0.8)	1.5 (0.9)	1.3 (0.9)	1.5 (0.9)	0.1054
CRP (mg/dl)	2.4 (3.1)	3.8 (4.5)	1.4 (1.8)	2.0 (3.1)	<0.0001
ESR (mm/hr)	53.3 (30.0)	67.4 (28.6)	52.1 (28.0)	41.7 (30.1)	<0.0001
Rheumatoid factor (U/ml)	152.9 (326.2)	234.7 (422.8)	244.5 (433.7)	462.1 (815.5)	<0.0001
Anti-CCP antibody (U/ml)	398.6 (608.2)	617.8 (1471.5)	329.2 (424.4)	3904 (667.0)	0.0351
MMP-3 (ng/ml)	230.1 (252.8)	334.7 (319.8)	211.4 (235.6)	248.5 (297.9)	0.0003

TNFi, tumor necrosis factor inhibitors; Anti IL-6R, Anti IL-6 receptor antibodies; CTLA-4 Ig, cytotoxic T-lymphocyte antigen 4 immunoglobulin; JAKi, Janus kinase inhibitors; MTX, methotrexate; PGA, patient's global assessment; EGA, evaluator's global assessment; DAS28, disease activity score 28 joint; ESR, erythrocyte sedimentation rate; CDAI, clinical disease activity index; HAQ, health assessment questionnaire; CRP, C reactive protein; CCP, cyclic citrullinated peptide ;MMP-3, matrix metalloproteinase-3.

Supplementary Table 3. Patient characteristics of individuals aged 75 years and older.

Variables	TNFi	Anti-IL-6R	CTLA-4 Ig	JAKi	P value
Age (years)	79.3 (3.8)	79 (3.5)	79.9 (3.7)	77.5 (2)	0.0021
Gender, n (% female)	97 (75.8%)	90 (76.3%)	144 (79.1%)	29 (80.6%)	0.8517
Disease duration (month)	121.8 (131.3)	111.5 (141.6)	120.7 (134.9)	131.5 (129.5)	0.8626
Steinbrocker's classification, %, I/II/III/IV	15/45/26/15	11/60/14/14	13/48/21/18	6/53/22/19	0.3317
Treatment history					
Prior use of biologics	68 (53.1%)	49 (41.5%)	68 (37.4%)	29 (80.6%)	<0.0001
MTX use at baseline, n (%)	87 (68.0%)	43 (36.4%)	97 (53.3%)	20 (55.6%)	<0.0001
dose, mg/w	10.8 (4.0)	9.1 (4.1)	10.5 (4.3)	10.3 (3.1)	0.1614
Glucocorticoid use at baseline, n (%)	26 (20.3%)	41 (34.8%)	63 (34.6%)	4 (11.1%)	0.0010
dose, mg/day	5.2 (3.2)	11.1 (10.6)	10.5 (14.0)	5.3 (3.8)	0.1246
28-tender joint count	8.3 (6.3)	8.1 (6.3)	9.2 (6.1)	10.1 (5.6)	0.2170
28-swollen joint count	8 (5.7)	8 (6.3)	7.9 (5.3)	8 (3.6)	0.9989
PGA, VAS 0-100 mm	52.8 (24.8)	55.9 (26.9)	53.1 (23.6)	61.4 (23.9)	0.2246
EGA, VAS 0-100 mm	46.3 (20.6)	45.2 (21.2)	44.6 (20.8)	51.8 (20.3)	0.3021
CDAI	26.2 (12.1)	26.2 (14.6)	27 (12)	29.4 (9.1)	0.5341
HAQ-DI	1.5(0.9)	1.6 (0.9)	1.7 (0.9)	1.7(0.8)	0.4616
CRP (mg/dl)	2.4(3)	4.4(4.2)	2.4(3.1)	2.1(4.2)	<0.0001
ESR (mm/hr)	57.8(33.8)	70.1(29.9)	60.8(30.7)	50.5(36.3)	0.0024
Rheumatoid factor (U/ml)	218.3(475.5)	323.7(639.6)	372.3(1357.6)	194.6(417)	0.4874
Anti-CCP antibody (U/ml)	369.9 (509.8)	604.6 (993.4)	526.3 (1471.3)	533.1 (1167.5)	0.5351
MMP-3 (ng/ml)	287.2 (294.3)	387.5 (340.7)	254.8 (212.0)	325.1 (399.4)	0.0034

TNFi, tumor necrosis factor inhibitors; Anti IL-6R, Anti IL-6 receptor antibodies; CTLA-4 Ig, cytotoxic T-lymphocyte antigen 4 immunoglobulin; JAKi, Janus kinase inhibitors; MTX, methotrexate; PGA, patient's global assessment; EGA, evaluator's global assessment; DAS28, disease activity score 28 joint; ESR, erythrocyte sedimentation rate; CDAI, clinical disease activity index; HAQ, health assessment questionnaire; CRP, C reactive protein; CCP, cyclic citrullinated peptide ;MMP-3, matrix metalloproteinase-3.



Supplementary Figure S1. Hazard ratios for MACE. (a) Hazard ratios for MACE in all patients. (b) Hazard ratios for MACE in patients aged 50 and above. (c) Hazard ratios for MACE in patients aged 65 and above. MACE, major adverse cardiovascular events. TNF, tumor necrosis factor; Anti IL-6R, Anti IL-6 receptor antibodies; CTLA-4 Ig, cytotoxic T-lymphocyte antigen 4 immunoglobulin; JAK, Janus kinase.