Research Square

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Comparison between Janus Kinase Inhibitor Monotherapy and Combination Therapy with Methotrexate in Patients with Rheumatoid Arthritis: Insight from the National Database of Rheumatic Diseases in Japan (NinJa) Registry

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Abstract

Background:

Janus kinase inhibitors (JAKi) are effective for rheumatoid arthritis (RA) and can be used as monotherapy; however, the clinical benefit of concomitant methotrexate (MTX) and the optimal MTX dose in JAKi-treated patients remain unclear in real-world settings. In this study, we aimed to clarify the roles of MTX by comparing the patient profiles between JAKi monotherapy (Mono) and combination with MTX (Combi) using the National Database of Rheumatic Diseases in Japan (NinJa).

Methods:

Using the 2022 version of the NinJa database, we analyzed RA patients treated with JAKi. Patients were classified into Mono and Combi groups. Clinical characteristics, disease activity, remission rates, and hospitalization due to serious adverse events (SAEs) were compared. Multivariable logistic regression and propensity score (PS)-matched analyses were performed to adjust for confounding factors. Associations between MTX dose and disease activity were examined using correlation and multiple regression analyses.

Results:

Among the enrolled patients (n = 1315), 554 (42.1%) received Combi therapy. Patients in the Combi group were younger, had shorter disease duration, and showed lower DAS28 (ESR) and HAQ scores than those in the Mono group. DAS28 (ESR)–defined remission was achieved more frequently in the Combi group (50.0% vs. 38.1%, $p < 0.001$). Multivariable logistic regression demonstrated that MTX use was independently associated with clinical remission (odds ratio [OR], 1.47; 95% confidence interval [CI], 1.06–2.04). In PS-matched analyses, Combi therapy remained associated with lower DAS28 (ESR) values and higher remission rates. MTX dose was not associated with disease activity among patients receiving Combi therapy. Hospitalization due to SAEs occurred in 11.0% of JAKi-treated patients and was not independently associated with MTX use, whereas glucocorticoid use was a significant risk factor for several SAEs.

Conclusions:

In real-world clinical practice, Combi therapy with JAKi and MTX was associated with higher remission rates without increasing the risk of SAEs. However, MTX dose did not influence disease activity, suggesting that low-dose MTX may be sufficient when used in combination with JAKi. Although further studies are warranted to evaluate long-term outcomes, Combi therapy appears to be a favorable and well-tolerated option for RA management.

Background

Rheumatoid arthritis (RA) is characterized by erosive polyarthritis caused by a combination of genetic and environmental factors (1, 2). Unregulated autoimmune synovial inflammation leads to progress destruction of joint structures and subsequent impairment of joint functions. To modify the natural course of the disease, strict control of disease activity through the early initiation of disease-modifying anti-rheumatic drugs (DMARDs) is thought to be essential (1, 2). Methotrexate (MTX) is considered the anchor DMARD for RA, whereas some patients are intolerant to MTX due to adverse effects or comorbidities, such as chronic kidney diseases (3). Indeed, the recent rate of MTX use was reported to be less than 70% in the National Database of Rheumatic Diseases in Japan (NinJa) (4). Several randomized controlled trials (RCTs) have evaluated the efficacy of MTX-free regimens. For example, upadacitinib (UPA), a Janus kinase inhibitors (JAKi), demonstrated superior clinical and functional efficacy as monotherapy compared with MTX monotherapy in patients with active RA despite prior MTX treatment (5). Similarly, baricitinib (BAR), another JAKi, showed sufficient efficacy as monotherapy compared with MTX monotherapy in patients with prior DMARD-resistant RA (6). These findings suggest that JAKi monotherapy can provide sufficient efficacy even in MTX-resistant patients. However, few RCTs have directly compared JAKi monotherapy with combination therapy consisting JAKi and MTX.

The RA-BEAM study demonstrated that combination therapy with BAR and MTX exerted superior protective effects against joint destruction compared with BAR monotherapy, despite no significant difference in clinical efficacy (6). Although this result suggests a potential advantage of combination therapy, it remain unclear whether the combination with MTX consistently improves outcomes when used with other JAKi agents. For example, it remains unclear whether JAKi monotherapy or combination therapy with MTX provides superior clinical benefit in patients with prior DMARD resistance, including those with MTX-resistant disease. Consequently, evidence guiding the choice between JAKi monotherapy and combination therapy with MTX is limited. Furthermore, the optimal dose of MTX when used in combination therapy has not been established.

In addition, recent European League Against Rheumatism (EULAR) recommendation of RA management suggested dose reduction and discontinuation of DMARDs after achieving sustained remission (3). Importantly, a long-term extension study of BAR indicated the feasibility of successful dose reduction in patients who achieve clinical remission (7). Given that long-term and high-dose MTX use is associated with an increased risk of serious adverse events, such as MTX-associated lymphoproliferative disorders (8), MTX dose reduction or discontinuation is often considered, particularly in patients under clinical remission. However, the therapeutic contribution of MTX in patients receiving JAKi therapy remains controversial. Real-world data directly comparing JAKi monotherapy with combination therapy including MTX are still limited.

NinJa is one of the largest RA registries in Japan, collecting annual cross-sectional data on treatment regimens, disease activity, patient outcomes, and adverse events (4, 9–10). Previously, we reported glucocorticoid (GC) dose-sparing effects of JAKi using the NinJa database (11), suggesting that this

large-scale registry provides valuable real-world evidence for clinical practice. The present study aimed to clarify whether combination therapy with JAKi and MTX confers additional clinical benefit by comparing patients receiving JAKi monotherapy with those receiving combination therapy using the latest (2022) version of the NinJa database. Furthermore, we analyzed differences in clinical parameters according to MTX dose among patients treated with JAKi. This study provides clinically relevant insights to optimize the use of JAKi in patients with RA.

Methods

NinJa database

Data from the 2022 version of the NinJa was analyzed. The NinJa database is a national-wide prospective registry that annually collects cross-sectional clinical data from patients with RA across Japan, and its detailed explanation is provided in previous literatures (4, 9–10). All patients fulfilled the 2010 American College of Rheumatology (ACR)/EULAR classification criteria for RA (12). Among NinJa database, patients treated with JAKi, including tofacitinib (TOF), BAR, UPA, filgotinib (FIL), and peficitinib (PEF), were included in the study. Clinical and demographic information extracted from the database included age, sex, body mass index (BMI), smoking history (never/ever smoker), treatment, serum C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), seropositivity, Steinbrocker's class and stage (13), Health Assessment Questionnaire (HAQ) score, swollen joint count (SJC), tender joint count (TJC), patient's global assessment (PGA), evaluator's global assessment (EGA), and scores calculated by these measurements, including Disease Activity Score (DAS)28, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI). Seropositivity was defined as follows: serum rheumatoid factor (RF) more than 15 IU/mL and/or anti-cyclic citrullinated peptide (CCP)2 antibody more than 5 U/m. Additionally, hospitalization due to serious adverse events (SAEs) within the preceding year was recorded. SAEs were defined according to the Rheumatology Common Toxicity Criteria (RCTC) version 2.0 developed by the Outcome Measures in Rheumatology Drug Safety Working Group (14), with events classified as serious when hospitalization was required.

This study was approved by the ethics committees of all participating institutions. The NinJa study protocol was reviewed and approved by the ethics committee of the National Hospital Organization Sagamihara National Hospital (approval number: 2014031816) and the ethics committee of Tokyo Medical University Hospital (T2019-0154). Informed consent was obtained either in written form or through an opt-out approach, depending on the institution's policy. This study was conducted in accordance with the latest version of the Declaration of Helsinki.

Propensity score matching

To adjust for potential confounding factors between patients treated with and without MTX, propensity score (PS)-matching was performed (15, 16). PSs were generated using a multivariable logistic

regression model, with MTX use as the dependent variable. The independent variables were determined according to the prior literatures on clinical remission (17–19), and included age, sex, BMI, and seropositivity for calculating PSs. One-to-one matching without replacement was performed using the nearest neighbor matching method, within a caliper width of 0.1 standard deviations of the logit of the PS. For sensitivity analyses, conditional multiple logistic regression analyses were performed under both univariate and multivariate conditions.

Statistics

All statistical analyses were performed using R software (version 4.3.3). For comparisons between two groups, two-tailed unpaired t-tests were applied. Difference in frequencies were tested using Fisher's extract test. Pearson's correlation coefficients were calculated to evaluate correlations between variables. Multiple logistic regression analyses were conducted to identify factors associated with achieving clinical remission and hospitalization due to SAEs. Multiple linear regression analysis was performed with DAS28(ESR) as the dependent variable and age, sex, disease duration, seropositivity, MTX dose, and GC dose as independent variables. Receiver Operating Characteristic (ROC) curves analyses were performed using the pROC package (20). P-values less than 0.05 were considered statistically significant.

Results

Comparison between JAKi-treated RA patients with and without MTX

Among 17,503 cases registered in the 2022 version of the NinJa database, a total of 1,315 RA patients receiving JAKi were included in this study. The numbers of patients treated with each JAKi were as follows: TOF n = 302, BAR n = 433, UPA n = 305, FIL n = 186, PEF n = 89. The demographic and clinical characteristics of the patients were summarized in Table 1. The mean age (± standard deviation (SD)) was 69.0 (± 12.4) years old, and 81.1% of the patients was female. The mean disease duration (± SD) was 15.8 ± 11.7 years, and 80.8% of the patients was seropositive. Regarding MTX, 554 patients (42.1%) received combination therapy with JAKi and MTX (Combi) with a mean MTX dose (± SD) of 7.52 ± 3.01 mg/week.

Table 1
Summary of JAK inhibitor (JAKi)-treated patients in NinJa database.

Age (years)	**Total**	**Mono**	**Combi**	**p-value**
	(n = 1315)	**(n = 771)**	**(n = 554)**	
	69.0 ± 12.4	**71.4 ± 11.6**	**65.4 ± 12.7**	**< 0.001*** **
Disease duration (years)	15.8 ± 11.7	16.8 ± 12.1	14.7 ± 11.0	0.004**
Sex (female)	1066 (81.1%)	621 (80.5%)	445 (81.8%)	0.62
BMI	23.1 ± 4.0	23.3 ± 4.1	23.0 ± 3.8	0.25
Ever smoker	401(34.7%)	223 (33.0%)	178 (37.0%)	0.17
Class 1	176 (24.9%)	176 (24.9%)	158 (31.5%)	0.041*
2	368 (52.1%)	368 (52.1%)	252 (50.3%)	
3	145 (20.5%)	145 (20.5%)	80 (16.0%)	
4	18 (2.5%)	18 (2.5%)	11 (2.2%)	
Stage 1	169 (23.7%)	169 (23.7%)	134 (26.6%)	0.46
2	188 (26.3%)	188 (26.3%)	137 (27.2%)	
3	140 (19.6%)	140 (19.6%)	84 (16.7%)	
4	217 (30.4%)	217 (30.4%)	148 (29.4%)	
PtGA	2.48 ± 2.30	2.54 ± 2.34	2.40 ± 2.25	0.30
EGA	1.25 ± 1.35	1.24 ± 1.33	1.26 ± 1.37	0.79
SJC28	1.17 ± 2.80	1.17 ± 2.80	1.18 ± 2.79	0.97
TJC28	0.90 ± 2.18	1.00 ± 2.50	0.75 ± 1.60	0.039*
CRP (mg/dL)	2.97 ± 1.13	0.49 ± 1.28	0.40 ± 1.29	0.17
ESR (mm/h)	29.6 ± 23.7	33.6 ± 25.0	24.0 ± 20.4	< 0.001***
DAS28(ESR)	2.97 ± 1.13	3.08 ± 1.11	2.80 ± 1.13	< 0.001***
DAS28(CRP)	2.17 ± 0.98	2.20 ± 1.02	2.12 ± 0.93	0.16
SDAI	6.32 ± 6.63	6.48 ± 6.76	6.10 ± 6.43	0.32
CDAI	5.89 ± 6.30	6.04 ± 6.48	5.68 ± 6.04	0.33
Pain VAS	2.33 ± 2.25	2.35 ± 2.29	2.30 ± 2.20	0.68
Seropositivity	816 (80.8%)	498 (81.5%)	318 (79.7%)	0.51
RF titer (IU/mL)	168.3 ± 373.4	191.1 ± 420.8	133.6 ± 283.6	0.018*

Age (years)	Total (n = 1315)	Mono (n = 771)	Combi (n = 554)	p-value
	69.0 ± 12.4	**71.4 ± 11.6**	**65.4 ± 12.7**	**< 0.001*** **
Anti-CCP2 Ab titer (IU/mL)	250.9 ± 496.0	268.1 ± 496.9	225.2 ± 494.6	0.29
HAQ	0.47 ± 0.64	0.53 ± 0.68	0.38 ± 0.57	< 0.001***
Treatment				
GC user	369 (28.1%)	237 (30.7%)	132 (24.3%)	0.011*
mean dose in users (mg/day in PSL)	3.48 ± 2.37	3.47 ± 2.43	3.48 ± 2.28	0.96
NSAID user	466 (35.4%)	267 (34.6%)	199 (36.6%)	0.48

Table 1. Summary of JAK inhibitor (JAKi)-treated patients in NinJa database.

The demographic and clinical characteristics of the enrolled patients. The strategy of inclusion and exclusion is shown in Supplementary Figure S1. Data are presented as mean ± S.D., or as numbers with percentages. Abbreviations are referenced in the Methods section. The comparison between the patients with Mono and Combi groups were performed by Fisher's extract test and two-tailed unpaired t-tests were applied for statistical analysis. * p<0.05, ** p<0.01, *** p<0.001.

Compared with the patients receiving JAKi monotherapy (Mono), those receiving Combi therapy were significantly younger, and had a shorter disease duration, as well as lower DAS28(ESR) and HAQ scores (Table 1). With respect of remission, 210 patients (50.0%) in the Combi group achieved DAS28(ESR)-defined remission, compared with 235 patients (38.1%) in the Mono group (p < 0.001). Notably, ESR and serum RF titers were significantly lower in the Combi group than in Mono group (Table 1). In contrast, serum CRP or anti-CCP2 antibody titers did not differ between the two groups, and the proportion of seropositive patients was also comparable (Table 1). TJC was lower in the Combi group than those in the Mono group, whereas SJC, PtGA, or EGA were not different between two groups (Table 1). Consequently, composite disease activity indices, including SDAI, CDAI or DAS28(CRP), were comparable between two groups (Table 1). Sex, BMI, smoking status, and pain VAS scores also showed no significant difference between two groups (Table 1). Regarding GC use, the GC doses among GC-treated patients did not differ significantly between the patients, however, the proposition of patients receiving GC therapy was significantly lower in the Combi group than in the Mono group (Mono n = 237, 30.7%, Combi n = 142, 22.9%. p = 0.001) (Table 1).

Next, multivariate logistic regression analyses were conducted to identify factors associated with clinical remission in the patients treated with JAKi (Table 2). Based on the results shown in Table 1 and the previous literatures (17–19), age, sex, disease duration, smoking habit (ever smoker), HAQ score, seropositivity, GC use, and MTX use were included as covariates in the model. Several variables, namely

younger age, male sex, shorter disease duration, seronegative status, lower HAQ scores and absence of GC use, were significantly associated with achievement of DAS28(ESR)-defined clinical remission (Table 2). Notably, MTX use (i.e., Combi therapy) was independently associated with a higher likelihood of achieving DAS28(ESR)-defined remission (odds ratio (OR) 1.47, 95% confidence interval (CI) 1.06–2.04, p = 0.022).

Table 2
Multiple regression analysis for achievement of DAS28(ESR)-defined remission.

	Univariate		Multivariate	
	OR (95%CI)	**p-value**	**OR (95%CI)**	**p-value**
Age	0.97 (0.96–0.98)	< 0.001***	0.98 (0.97–0.99)	0.022*
Disease duration	0.95 (0.94–0.97)	< 0.001***	0.98 (0.97–0.99)	0.022*
Sex (male)	1.97 (1.44–2.69)	< 0.001***	1.56 (1.01–2.42)	< 0.001***
Ever smoker	1.52 (1.16–1.98)	0.0023**	1.10 (0.77–1.59)	0.59
Seropositivity	0.57 (0.41–0.80)	0.0010**	0.64 (0.43–0.96)	0.029*
HAQ score	0.18 (0.13–0.26)	< 0.001***	0.27 (0.19–0.41)	< 0.001***
GC use	0.33 (0.24–0.45)	< 0.001***	0.46 (0.31–0.67)	< 0.010**
MTX use (Combi therapy)	1.62 (1.26–2.08)	< 0.001***	1.47 (1.06–2.04)	0.022*

Table 2. Multiple regression analysis for achievement of DAS28(ESR)-defined remission.

The odds ratios (ORs) (95% CI) for achievement of DAS28(ESR)-defined remission were analyzed by logistic regression in univariable and multivariable analyses. In multivariable analyses, all the indicated parameters were included as variables. Abbreviations are referenced in the Methods section. * p<0.05, ** p<0.01, ***p<0.001

Given that multiple potential confounders other than MTX use were associated with disease activity, we additionally performed PS-matched comparison the patients receiving Mono and Combi therapies. After PS matching, there was no differences in baseline clinical characteristics, including age, sex, disease duration, BMI, HAQ, scores, seropositivity, or the proportion of GC use between the two groups (Table 3). In the PS-matched cohort, the patients receiving Combi therapy exhibited significantly lower DAS28(ESR) and a higher rate of DAS28(ESR)-defined remission compared with those receiving Mono therapy (DAS28(ESR) (mean ± SD): Mono 3.07 ± 1.09, Combi: 2.88 ± 1.09. p = 0.037. DAS28(ESR)-defined remission rate: Mono 39.1%, Combi 47.9%. p = 0.036) (Table 3). In addition, ESR levels were significantly lower in the Combi group than in the Mono group (Table 3). Conditional logistic regression analyses using the PS-matched data further demonstrated that Combi therapy was associated with a significantly higher likelihood of achieving DAS28 (ESR)–defined remission compared with Mono therapy (OR, 2.23; 95% CI, 1.22–4.08; p = 0.0089) (Supplementary Table 1). Taken together, the patients receiving Combi

therapy exhibited more favorable clinical characteristics, including younger age, shorter disease duration, lower DAS28(ESR) and HAQ scores, and less frequent GC use, compared with those receiving Mono therapy. Importantly, even after adjusting for multiple confounding factors, Combi therapy remained independently associated with achievement of DAS28(ESR)-defined remission.

Table 3
Propensity score (PS)-matched comparison between the patients with Mono and Combi therapies.

Age (years)	**Mono**	**Combi**	**P-value**
	(n = 324)	**(n = 324)**	
	67.5 ± 11.8	**67.2 ± 11.5**	**0.80**
Disease duration (years)	15.3 ± 11.0	15.4 ± 11.5	0.99
Sex (female)	272 (84.0%)	267 (82.4%)	0.68
BMI	22.8 ± 3.9	23.0 ± 3.9	0.37
Ever smoker	117 (37.3%)	119 (37.5%)	1.00
Class 1	84 (27.0%)	86 (27.6%)	1.00
2	164 (52.7%)	163 (52.2%)	
3	56 (18.0%)	57 (18.3%)	
4	7 (2.3%)	6 (1.9%)	
Stage 1	83 (26.4%)	83 (26.7%)	1.00
2	86 (27.4%)	85 (27.3%)	
3	48 (15.3%)	48 (15.4%)	
4	97 (30.9%)	95 (30.5%)	
PtGA	2.29 ± 2.26	2.46 ± 2.21	0.33
EGA	1.22 ± 1.24	1.30 ± 1.32	0.45
SJC28	1.28 ± 2.68	1.32 ± 3.08	0.89
TJC28	0.87 ± 2.14	0.78 ± 1.65	0.53
CRP (mg/dL)	0.44 ± 0.91	0.44 ± 1.56	0.99
ESR (mm/h)	32.5 ± 24.1	24.8 ± 20.3	< 0.001***
DAS28(ESR)	3.07 ± 1.09	2.88 ± 1.09	0.037*
DAS28(ESR)-defined remission	115 (39.1%)	135 (47.9%)	0.036*
DAS28(CRP)	2.17 ± 1.02	2.15 ± 0.97	0.77
SDAI	6.18 ± 6.40	6.39 ± 6.74	0.70
CDAI	5.74 ± 6.14	5.95 ± 6.24	0.68
Pain VAS	2.15 ± 2.20	2.38 ± 2.23	0.21

Age (years)	Mono (n = 324)	Combi (n = 324)	P-value
	67.5 ± 11.8	**67.2 ± 11.5**	**0.80**
Seropositivity	263 (81.2%)	259 (79.9%)	0.77
RF titer (IU/mL)	173.1 ± 350.6	128.7 ± 287.6	0.082
Anti-CCP2 Ab titer (IU/mL)	290.4 ± 558.4	232.7 ± 513.3	0.27
HAQ	0.43 ± 0.61	0.40 ± 0.56	0.51
Treatment			
GC user	91 (28.1%)	84 (25.9%)	0.60
mean dose in users (mg/day in PSL)	3.39 ± 2.11	3.43 ± 2.15	0.89
NSAID user	121 (37.3%)	195 (39.8%)	0.57

Table 3. Propensity score (PS)-matched comparison between the patients with Mono and Combi therapies.

Comparison between the patients with Mono and Combi therapies after propensity score (PS)-matching. PSs were generated using a multivariable logistic regression model, with MTX use as the dependent variable. The independent variables included age, sex, BMI and seropositivity. One-to-one matching without replacement was performed using the nearest neighbor matching method, within a caliper width of 0.1 standard deviations of the logit of the PS. Fisher's extract test and two-tailed unpaired t-tests were applied for statistical analysis. * $p<0.05$. *** $p<0.001$.

Association between MTX doses and disease activity in patients receiving Combi therapy

Next, we examined the association between MTX dose and clinical parameters in patients receiving Combi therapy. MTX dose was significantly correlated with age ($r = -0.27$, $p < 0.001$). In contrast, MTX dose was not significantly associated with DAS28(ESR) ($r = -0.028$, $p = 0.57$) (data not shown). Furthermore, a multiple linear regression analysis was performed to identify factors associated with DAS28(ESR) in patients receiving Combi therapy. Male sex ($\beta = -0.82$, $p = 0.035$) was independently associated with lower DAS28(ESR), whereas MTX dose was not was not significantly associated with DAS28 (ESR) ($\beta = 0.020$, $p = 0.68$) (Supplementary Table 2). These findings indicate that MTX dose did not independently influence disease activity as assessed by DAS28 (ESR). Taken together, MTX dose was not associated with DAS28(ESR) in the patients receiving Combi therapy with JAKi and MTX.

Frequencies of hospitalization due to SAEs in JAKi-treated patients

Finally, the incidence of hospitalization due to SAEs was compared between the patients receiving Mono and Combi therapies (Table 4). Overall, hospitalization due to SAEs occurred in 11.0% of all JAKi-treated patients and was significantly less frequent in the Combi group than in the Mono group (Combi, 7.2%, Mono,13.6%. $p < 0.001$) (Table 4). The incidence of individual SAEs was 3.3% for infection, 1.3% for insufficiency fracture, 1.1% for malignancy, and 0.2% for major adverse cardiovascular events (MACE), with no significant difference between the Mono and Combi groups (Table 4). Comparisons between the patients with and without hospitalization due to SAEs identifies several variables as potential confounders, including age, disease duration, disease activity indices, HAQ score, GC use, and MTX use (Supplementary Table 3). Subsequent multivariate logistic regression analyses demonstrated that GC use was significantly associated with an increased risk of several SAEs, including hospitalization due to SAEs (OR 2.20, 95%CI: 1.33–3.62, $p = 0.0020$), infection (OR 3.03, 95%CI: 1.24–7.41, $p = 0.015$), and insufficiency fracture (OR 5.35, 95%CI: 1.25–22.9, $p = 0.024$.) (Table 5). Although Combi therapy was associated with lower ORs for several SAE outcomes, MTX use was not independently associated with the incidence of SAEs in the adjusted analyses (Table 5). No clinical variables were significantly associated with the incidence of malignancy or MACE (data not shown). Taken together, GC use was identified as a major risk factor for the development of several SAEs, whereas the incidence of SAEs was comparable between patients receiving Mono and Combi therapies after adjustment for confounding factors.

Table 4
Frequency of hospitalization due to serious adverse events (SAEs) in JAK inhibitor-treated patients in NinJa database.

hospitalization due to SAEs	**Total (n = 1315)**	**Mono (n = 771)**	**Combi (n = 554)**	**p-value**
	144 (11.0%)	**105 (13.6%)**	**39 (7.2%)**	**< 0.001*** **
infection	44 (3.3%)	32 (4.2%)	12 (2.2%)	0.062
insufficiency fracture	17 (1.3%)	12 (1.6%)	5 (0.9%)	0.46
malignancy	14 (1.1%)	11 (1.4%)	3 (0.6%)	0.17
MACE	3 (0.2%)	1 (0.1%)	2 (0.4%)	0.57

Table 4. Frequency of hospitalization due to serious adverse events (SAEs) in JAK inhibitor-treated patients in NinJa database.

Frequencies of hospitalization due to SAEs, including all SAEs required for hospitalization, infection, insufficiency fracture, any malignancy, major adverse cardiovascular event (MACE) were compared between the patients with Mono and Combi therapies. Fisher's extract test was applied for statistical analysis. *** $p<0.001$.

Table 5
Multiple regression analysis for incidences of hospitalization due to serious adverse events (SAEs).

	hospitalization due to SAEs		infection		insufficiency fracture	
	OR (95%CI)	**p-value**	**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**
Age	1.02 (0.99–1.04)	0.08	1.00 (0.97–1.05)	0.82	1.06 (0.98–1.14)	0.13
Disease duration	1.01 (0.98–1.03)	0.61	1.03 (0.99–1.07)	0.10	0.99 (0.93–1.05)	0.70
Sex (male)	1.62 (0.86–3.05)	0.13	2.83 (1.02–7.88)	0.046*	0.00 (0.00-inf)	0.99
Ever smoker	0.94 (0.53–1.65)	0.83	1.34 (0.50–3.60)	0.56	1.58 (0.37–6.67)	0.53
Seropositivity	1.19 (0.63–2.25)	0.58	1.10 (0.35–3.45)	0.87	2.40 (0.29-20.0)	0.42
DAS28(ESR)	1.09 (0.86–1.38)	0.47	1.18 (0.77–1.80)	0.46	1.06 (0.55–2.04)	0.86
HAQ score	1.23 (0.82–1.85)	0.32	0.62 (0.26–1.44)	0.26	0.98 (0.34–2.83)	0.97
GC use	2.20 (1.33–3.62)	0.0020**	3.03 (1.24–7.41)	0.015*	5.35 (1.25–22.9)	0.024*
MTX use (Combi therapy)	0.61 (0.36–1.04)	0.068	0.74 (0.29–1.89)	0.53	0.59 (0.12–3.01)	0.53

Table 5. Multiple regression analysis for incidences of hospitalization due to serious adverse events (SAEs).

The odds ratios (ORs) (95% confidence interval (CI)) for hospitalization due to SAEs, including infection and insufficiency fracture, were analyzed by multivariate logistic regression analyses. In multivariable analysis, all the indicated parameters were included as variables. * p<0.05, ** p<0.01.

Discussion

In this large real-world study, we demonstrated the advantage of Combi therapy with JAKi and MTX. Combi therapy was associated with higher DAS28(ESR)-defined remission rates without an increased

risk of SAEs, including infections. Consistent with our findings, several previous studies have suggested potential benefit of Combi therapy. For example, a study of TOF showed that Mono therapy failed to demonstrate non-inferiority to Combi therapy in achieving ACR50 response (21). In comparison of BAR Mono and Combi therapies, less progression of structural damage was observed in Combi group despite comparable clinical efficacy (6). Additionally, a long-term extension study reported that the addition of MTX improved disease activity in the patients with insufficient response to BAR Mono therapy (22). Furthermore, a cohort study demonstrated that concomitant MTX use was associated with significant improvement in CDAI without compromising safety in JAKi-treated patients (23). Taken together, these reports support the potential advantage of Combi therapy in terms of both clinical efficacy and safety.

Our study adds further real-world evidence by characterizing patients receiving Combi therapy in routine clinical practice. Notably, PS-matched analyses demonstrated that Combi therapy was associated with lower DAS28(ESR). Particularly, ESR was significantly lower in the patients receiving Combi therapy than those receiving Mono therapy. ESR is influenced by persistent inflammation and serum immunoglobulin levels, and MTX has been reported to reduce transitional B cells and serum immunoglobulin levels (24). Therefore, the addition of MTX to JAKi may modulate B cell-related immune responses and contribute to reduced ESR. In contrast, other composite disease activity indices, including DAS28(CRP), SDAI and CDAI, did not differ significantly between the two groups. Thus, the clinical relevance of the observed reduction in DAS28(ESR) requires further evaluation through longitudinal analyses with longer follow-up.

Another important finding of this study is the lower frequency of GC use among the patients receiving Combi therapy. Although GC remains recommended as bridging therapy for RA (3, 25), its high risk of several AEs warrants caution use (26). Indeed, our analyses demonstrated that GC use was a significant risk factor for several SAEs, including infections and insufficient fractures. These finding suggest that one clinical advantage of Combi therapy may be its potential to reduce GC exposure. With respect to safety, although Combi therapy was associated with a lower crude incidence of hospitalization due to SAEs, MTX use was not independently associated with SAEs after adjustment, whereas GC use consistently emerged as a major risk factor. Therefore, Combi therapy may contribute indirectly to improve safety by facilitating GC sparing in the patients who can tolerate MTX. Importantly, MTX dose did not significantly influence disease activity among the patients receiving Combi therapy. This finding is consistent with a previous report showing that MTX dose did not affect the efficacy of TOF in Japanese RA patients (27). Although the optimal MTX dose in Combi therapy remains to be determined, our results suggest that even low-dose MTX may be sufficient to confer additional clinical benefit when used with JAKi.

Several limitations of this study should be acknowledged. First, the cross-sectional design precludes causal inference and limits the assessment of longitudinal outcomes, including radiographic progression and long-term safety. Second, residual confounding cannot be completely excluded despite multivariable adjustment and propensity score matching. In particular, renal function and comorbidities, which may influence both MTX use and clinical outcomes, could not be fully evaluated due to data limitations. Third, treatment selection for Mono or Combi therapy was entirely dependent on clinicians' decisions;

consequently, the Mono group likely included both MTX-intolerant patients and patients in whom MTX had been discontinued after achieving sustained remission. Finally, analyses of SAEs may have been underpowered for very rare events, such as malignancies and major adverse cardiovascular events.

Conclusions

In conclusion, this large real-world study demonstrates that Combi therapy with JAKi and MTX is associated with higher clinical remission rates compared with JAKi Mono therapy, without an increased risk of serious adverse events. Importantly, MTX dose did not influence disease activity among patients receiving Combi therapy, suggesting that low-dose MTX may be sufficient when used with JAKi. These findings provide clinically relevant evidence to support individualized treatment strategies aimed at optimizing concomitant MTX use in patients with RA treated with JAKi.

Abbreviations

RA
rheumatoid arthritis
DMARD
disease-modifying anti-rheumatic drugs
MTX
methotrexate
NinJa
National Database of Rheumatic Diseases in Japan (NinJa)
RCT
randomized controlled trial
UPA
upadacitinib
JAKi
Janus kinase inhibitors
BAR
baricitinib
EULAR
European League Against Rheumatism
GC
glucocorticoid (GC)
ACR
American College of Rheumatology
TOF
tofacitinib
FIL
filgotinib

PEF
peficitinib
BMI
body mass index
CRP
C-reactive protein (CRP)
ESR
erythrocyte sedimentation rate
HAQ
health assessment questionnaire
SJC
swollen joint count
TJC
tender joint count
PGA
patient’s global assessment
EGA
evaluator’s global assessment
DAS
disease activity score
SDAI
simplified disease activity index
CDAI
clinical disease activity index
RF
rheumatoid factor
CCP
cyclic citrullinated peptide (CCP)
SAE
serious adverse events
RCTC
Rheumatology Common Toxicity Criteria
PS
propensity score
ROC
Receiver Operating Characteristic
SD
standard deviation
Combi
combination therapy

Mono
monotherapy
CI
confidence interval.

Declarations

Ethical approval and consent to participate

This study was approved by the ethics committees of all participating institutions. The NinJa study protocol was reviewed and approved by the ethics committee of the National Hospital Organization Sagamihara National Hospital (approval number: 2014031816) and the ethics committee of Tokyo Medical University Hospital (T2019-0154). Informed consent was obtained either in written form or through an opt-out approach, depending on the institution's policy. This study was conducted in accordance with the latest version of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

Data can be available from the corresponding author on reasonable request.

Competing interests: The authors have declared no conflicts of interest.

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Authors' contributions

SY, HS and TM conceived and designed the study. SY, HS and YY performed main analyses and wrote the manuscript with help of TM and TS. TM, ST and TS supervised the project. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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