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Long-term effectiveness and safety of methotrexate-tacrolimus combination therapy versus methotrexate monotherapy in reducing rheumatoid arthritis flares after TNF inhibitor discontinuation: a retrospective cohort study

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Abstract

Background This study evaluates the long-term effectiveness and safety of methotrexate-tacrolimus combination therapy compared to methotrexate monotherapy in maintaining successful tumor necrosis factor (TNF) inhibitor discontinuation in rheumatoid arthritis (RA) patients.

Methods We retrospectively analyzed consecutive RA patients who discontinued TNF inhibitors after achieving disease control by October 2022 and received either methotrexate monotherapy or methotrexate-tacrolimus combination therapy for up to 10 years. Per-observation time-to-event analyses assessed treatment failure, treatment intensification, first disease flare, and irreversible functional deterioration. Mixed-effects Cox models, time-dependent Cox models without random effects, and Kaplan-Meier estimates with inverse probability weighting were applied. Safety assessment included treatment-limiting adverse events and renal function trends.

Results A total of 147 treatment lines (96 methotrexate monotherapy and 51 combination therapy) in 116 patients were analyzed. The combination therapy significantly reduced treatment failure (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.24–0.72), treatment intensification with the index drugs (HR, 0.38; 95% CI, 0.22–0.67) and with biologics or Janus kinase inhibitors (HR, 0.39; 95% CI, 0.22–0.71), and first flare (HR, 0.55; 95%CI 0.36–0.84), with consistent findings across models. The benefit was most pronounced in patients with prior flares during methotrexate monotherapy after TNF inhibitor discontinuation, with HRs as low as 0.04–0.12 across outcomes. No significant differences in treatment-limiting adverse events were observed. The annual increase in serum creatinine for tacrolimus users was 0.0032 mg/dL, suggesting minimal long-term renal impact.

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Conclusions Methotrexate-tacrolimus combination therapy significantly reduces relapse risk following TNF inhibitor discontinuation without compromising safety, offering a potentially sustainable treatment alternative after achieving remission with TNF inhibitor therapy.

Keywords Biological therapy, Clinical remission, Recurrence, Rheumatoid arthritis, Withdrawing treatment

Background

The use of immunomodulatory therapies, encompassing synthetic and biological disease-modifying antirheumatic drugs (DMARDs), play a pivotal role in managing rheumatoid arthritis (RA), aiding in inflammation control over patients' lifetimes [1, 2]. Recent advances with biological DMARDs (bDMARDs) and Janus kinase (JAK) inhibitors increase RA patients in remission [3–13].

Long-term bDMARD use has shown effectiveness and safety, with emerging evidence indicating that reduced doses or extended dosing intervals may be preferable to discontinuation, even when considering cost-effectiveness [1, 14, 15].

With the recent introduction of biosimilar formulations, the cost of tumor necrosis factor (TNF) inhibitor therapy has decreased. However, some patients who continue to receive TNF inhibitors at reduced doses and do not experience disease activity may prefer remission maintenance therapy with oral agents. Switching to JAK inhibitors is an option, but currently, the high cost of these drugs makes them unacceptable in many cases.

Utilizing conventional synthetic DMARD (csDMARD) combination therapy as maintenance therapy following bDMARD discontinuation has shown promise in reducing relapse risk [16]. Exploring more effective csDMARD combinations post-bDMARD discontinuation may offer alternative maintenance treatment options.

Tacrolimus, a calcineurin inhibitor approved in Japan for rheumatoid arthritis treatment in 2005, has since found clinical applications in other various autoimmune conditions, serving as a commonly used csDMARD across Asia-Pacific regions [17, 18]. Its combination with methotrexate has demonstrated superior clinical efficacy in active RA compared to methotrexate monotherapy [19, 20]. Our previous small-scale observational study demonstrated that adding tacrolimus to methotrexate after discontinuing TNF inhibitors significantly prolonged remission duration compared to methotrexate alone. Notably, among six patients enrolled, only one required TNF inhibitor reintroduction, suggesting that tacrolimus may help sustain TNF inhibitor-free remission in RA patients who previously relapsed [21]. Additionally, a recent 24-week prospective comparative study provided controlled evidence that replacing TNF inhibitors with tacrolimus in RA patients with low disease activity maintained remission in most cases for at least 24 weeks. Although adverse events were slightly more frequent in the tacrolimus group, they were generally well tolerated, supporting its feasibility as a maintenance therapy [22]. These findings suggest that concomitant tacrolimus use may provide a viable alternative for sustaining remission after TNF inhibitor discontinuation, warranting further investigation in a larger and long-term observational cohort.

Using real-world clinical data, we investigated the long-term effectiveness and safety of methotrexate and tacrolimus combination therapy versus methotrexate monotherapy as post-TNF inhibitor discontinuation maintenance treatment.

Methods

Study design and setting

This retrospective observational study included consecutive RA patients from the arthritis clinics at Nagoya City University Hospital and Takeuchi Orthopedics and Internal Medicine Clinic, who were prescribed TNF inhibitors due to an inadequate response to methotrexate and thereafter discontinued TNF inhibitors by October 2020 after achieving sustained low disease activity, defined by Disease Activity Score in 28 Joints (DAS28) < 3.2 [23] or Simplified Disease Activity Index (SDAI) ≤ 11 [24] on consecutive evaluations over at least three months, without glucocorticoid use. All patients met the 1987 American Rheumatology Association [25] or the 2010 American College of Rheumatology/European League Against Rheumatism [26] criteria, and those with concomitant active systemic rheumatic diseases other than secondary Sjögren's syndrome were excluded. Follow-up data were collected up to 10 years after TNF inhibitor discontinuation or until October 2022.

In our clinics, disease activity and physical function were routinely assessed every three months during the first year following TNF inhibitor discontinuation and every six months thereafter. These assessments were systematically recorded in pre-developed standardized templates. Tacrolimus dosing was maintained at or below the approved dose of 3 mg/day, aiming for a target blood trough concentration of 3–5 ng/mL. Methotrexate doses were titrated down from one year after TNF inhibitor discontinuation if no flares had been confirmed.

Dataset

The dataset included all eligible post-TNF inhibitor maintenance treatment periods. Patients with two or more TNF inhibitor discontinuations deemed eligible for this study contributed multiple observations. The baseline for TNF inhibitor discontinuation was defined as the next scheduled

administration date if treatment were to continue. Maintenance therapies were classified as methotrexate monotherapy (Mono) or methotrexate plus tacrolimus combination therapy (Combi) based on medications used at baseline.

Each observation included patient-specific data (e.g., gender, baseline parameters) and observation-specific data (e.g., parameters at TNF inhibitor discontinuation). Measures of sustained disease activity before TNF inhibitor discontinuation included days in DAS28 and SDAI remission and mean DAS28 and SDAI values calculated from at least two evaluations between the baseline and the most recent evaluation date at least 12 weeks prior.

A separate dataset assessed serum creatinine changes, categorizing patients by tacrolimus use. Data were collected from the earliest available serum creatinine measurement before tacrolimus initiation for users and before TNF inhibitor initiation for non-users.

Clinical outcome variables

The primary clinical outcome was treatment failure, defined as all-cause death, permanent discontinuation of methotrexate or tacrolimus due to adverse events, or initiation of the index agents, which included oral glucocorticoids, bDMARDs, JAK inhibitors, other csDMARDs classified as immunosuppressants, such as leflunomide, mizoribine, and cyclosporine, and other investigational agents. In the Mono group, the addition of tacrolimus was considered an index drug initiation event. Discontinuation of methotrexate for the intention to conceive was censored.

Secondary clinical outcomes included times to treatment with the index agents or bDMARDs/JAK inhibitors, first disease flare (either DAS28-ESR ≥ 3.2 or DAS28-CRP ≥ 2.7, with an increase of > 0.6 from the baseline [27] and one or more swollen joints; or treatment intensification with the index agents), and occurrence of irreversible physical function which was defined by Health Assessment Questionnaire-Disability Index (HAQ-DI) [28] greater than baseline that persists until last observation. Methotrexate doses during treatment failure-free periods years were also compared.

Safety assessments included adverse events leading to discontinuation of maintenance treatment and estimated annual change in serum creatinine levels based on a slope of change from baseline.

Statistical analyses

We used Fisher's exact and Mann-Whitney U tests for relevant comparisons, handling missing values through pairwise deletion.

To account for repeated measures, we employed mixed-effects Cox proportional hazards models with patient ID as a random effect in the primary analysis. Potential confounders were selected based on clinical relevance, prior evidence [29–31], findings from our overlapping cohort [32], associations between covariates and primary outcomes based on univariate mixed-effects Cox models and Akaike Information Criterion, and multicollinearity considerations. Given the sample size and number of events, eight variables, including the treatment variable, were included in the final multivariable models.

We systematically evaluated covariate combinations using a structured selection approach. Age, sex, smoking status, and mean DAS28 values before TNF inhibitor discontinuation were pre-specified as key covariates and included in all models. One of two disease duration-related variables (symptom duration or prior methotrexate duration) was selected. Two additional covariates were chosen from five markers of disease severity and treatment factors: anti-CCP seropositivity, DAS28 at TNF inhibitor initiation, prednisolone dose at TNF inhibitor initiation, rheumatoid factor titers at TNF inhibitor discontinuation, and HAQ-DI at TNF inhibitor discontinuation. The effect of Combi treatment on Mono treatment was assessed using a multivariate mixed-effects Cox regression model across 20 sets of covariates, considering all possible combinations of these selected variables.

As sensitivity analyses, we performed time-dependent Cox proportional hazards models in which the treatment variable was included as a time-varying covariate, without incorporating random effects for patient ID, to explicitly account for the potential influence of treatment sequence on effectiveness. Additionally, unadjusted and inverse probability weighting (IPW)-adjusted Kaplan-Meier estimates were generated using data from each patient's earliest maintenance treatment period in the Mono and Combi groups [33, 34]. The log-rank test or IPW log-rank test was used for time-to-event analyses between groups. P-values for pairwise comparisons were adjusted using the Bonferroni method. Details of these primary and sensitivity analytic methods are provided in Supplementary Data.

Changes over time in methotrexate dose and serum creatinine levels in both groups were compared using mixed-effects models. Fixed effects of concomitant tacrolimus were adjusted for covariates such as sex, age, response variables at baseline, and body weight, while patient ID and years from baseline were treated as random effects.

All statistical tests were exploratory, conducted at a significance level of 5%, and implemented in R version 4.2.2.

Results

Patient characteristics

A total of 156 maintenance treatment episodes following TNF inhibitor discontinuation were identified in 123 patients. After excluding ineligible cases, 147 treatment lines (96 Mono and 51 Combi) in 116 patients were analyzed (Fig. 1). Most patients discontinued TNF inhibitors due to the reduced disease burden, high costs, and

Fig. 1 Longitudinal Trend of Post-TNF Inhibitor Maintenance Treatment Lines: Mono vs. Combination Therapy. Each square matrix is vertically arranged in chronological order of maintenance therapy lines after tumor necrosis factor (TNF) inhibitor discontinuation and horizontally by individual maintenance therapy regimen, with color coding. Blue is methotrexate monotherapy; orange is methotrexate and tacrolimus combination therapy. The numbers of TNF inhibitor discontinuations per subsequent maintenance therapy regimen in the square matrices and those of subsequent relapses requiring resumption of biological disease-modifying antirheumatic drugs (bDMARD) or Janus kinase inhibitors (JAKi) in the black parallelograms are displayed

inconvenience of injectable medications. In all cases, TNF inhibitors were tapered to the lowest available vial, syringe, or pen dose and discontinued after confirming stable disease at the most extended dosing interval recommended in the package insert.

Patient characteristics at the first TNF inhibitor initiation, divided into 44 who had ever and 72 who had never received Combi treatment, are shown in Table 1. Variables with missing values and their numbers are shown in the Table's footnotes. Since DAS28 values at TNF inhibitor initiation were unavailable for patients referred after starting therapy, eight observations (three Mono, five Combi), accounting for 5.4% of the dataset, were excluded from Cox regression models incorporating this variable.

At the time of first TNF inhibitor initiation, patients who had ever received Combi treatment had significantly longer symptom duration, higher RA disease activity, and greater prednisolone use compared to those who had never received Combi treatment. Additionally, infliximab was more commonly the first TNF inhibitor in the Combi group, while adalimumab was more common in the Mono group. The mean tacrolimus dose in Combi-treated patients was 1.72 ± 0.56 mg/day.

Clinical characteristics at TNF inhibitor discontinuation per observations

Baseline characteristics for the 96 Mono and 51 Combi treatment lines are summarized in Table 2. Both groups achieved high SDAI remission rates (>85%), with no significant difference in the median duration of remission (329 days in Mono vs. 280 days in Combi).

The Combi group had significantly more previous TNF inhibitor discontinuations, lower tender joint count in 68 joints (mean 0.04 vs. 0.21), lower rate for no tender and no swollen joint in the full joints, and lower methotrexate dose (mean 11.8 vs. 12.9 mg/week). Although trends suggested fewer swollen joints and shorter DAS28 remission durations in the Combi group, these differences were not statistically significant.

Impact of methotrexate-tacrolimus combination therapy on events

Among 147 maintenance treatment episodes, 142 (96.6%) were observed until treatment failure or for at least two years. Over a median follow-up of 5.7 years (range: 3.0–8.5), there were 87 treatment failures, 80 index drug initiations, 71 bDMARD or JAK inhibitor initiations, 108 first disease flares, and 26 occurrences of irreversible HAQ-DI worsening.

The Combi group had consistently lower risks across all univariable and multivariable mixed-effects Cox models. In the multivariable model with the lowest Bayesian Information Criterion and no missing values, Combi treatment was associated with a significantly reduced risk of treatment failure (hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.24–0.75), treatment intensification with index drugs (HR, 0.40; 95% CI, 0.23–0.69), bDMARD/JAK inhibitor initiation (HR, 0.41; 95% CI, 0.23–0.75), first disease flare (HR, 0.56; 95% CI, 0.37–0.86), and irreversible HAQ-DI worsening (HR, 0.23; 95% CI, 0.08–0.68). Pooled hazard ratio estimates confirmed the significant protective effect of Combi treatment across all outcomes. The only

Table 1 Clinical characteristics at starting the initial TNF inhibitor classified by tacrolimus use (per patient)

Factor	Patients never received tacrolimus combination (n = 72)	Patients ever received tacrolimus combination (n = 44)	*P*-value
Age	59.3 [48.3, 65.3]	57.5 [49.9, 64.8]	0.72
Female gender	56 (77.8)	39 (88.6)	0.21
Height (cm)	158 [153, 163]	158 [154, 162]	0.58
Weight (kg)	53.5 [48.0, 58.0]	49.9 [46.5, 56.1]	0.09
Smoking status at starting TNF inhibitor			
Current	12 (16.7)	6 (13.6)	0.88
Previous	11 (15.3)	8 (18.2)	
Never	49 (68.1)	30 (68.2)	
Symptom duration (weeks)	107 [45, 258]	264 [96, 423]	**0.02**
Duration of prior methotrexate treatment (weeks)	30 [17, 107]	26 [12, 99]	0.36
Previous bDMARD use	8 (11.1)	3 (6.8)	0.53
Tender joint count (0–28)	5 [2, 8]	7 [4, 10]	**0.01**
Tender joint count (0–68)	9 [5, 13]	13 [6, 20]	**0.04**
Swollen joint count (0–28)	6 [3, 10]	8 [5, 13]	**0.03**
Swollen joint count (0–66)	9 [5, 13]	12 [6, 17]	0.07
PtGA (0–100)	50 [27, 68]	49 [30, 69]	0.94
PhGA (0–100)	35 [27, 48]	45 [33, 58]	**0.02**
C-reactive protein (mg/dL)	0.65 [0.22, 1.49]	1.40 [0.48, 3.08]	**0.04**
Erythrocyte sedimentation rate (mm/hr)	28 [16, 57]	39 [22, 65]	0.05
Matrix Metalloproteinase-3 (ng/mL)	110.7 [54.5, 202.9]	156.8 [70.0, 303.8]	0.18
Rheumatoid factor positivity	65 (90.3)	38 (86.4)	0.55
Rheumatoid factor titer (U/mL)	81 [35, 224]	98 [28, 252]	0.84
Anti-CCP antibody positivity	65 (90.3)	37 (84.1)	0.38
DAS28	5.07 [4.06, 5.65]	5.50 [4.54, 6.30]	**0.01**
SDAI	20.48 [14.44, 27.88]	26.30 [17.25, 38.33]	**0.02**
HAQ-DI (0–3)	0.62 [0.25, 1.50]	0.88 [0.34, 1.69]	0.15
Sharp/van der Heijde score	4 [1, 17]	9 [1, 27]	0.19
Erosion score	2 [0, 7]	2 [0, 12]	0.71
Joint space narrowing score	2 [0, 10]	6 [0, 17]	0.05
Methotrexate dose (mg/week)	13 [12, 16]	12 [10, 14]	0.13
Patients on tacrolimus	0 (0.0)	3 (6.8)	0.05
Patients on other csDMARDs	1 (1.4)	1 (2.3)	1
Patients on oral glucocorticoids	33 (45.8)	24 (54.5)	0.45
Prednisolone dose (mg/day)	0.0 [0.0, 3.0]	3.3 [0.0, 5.0]	**0.04**
TNF inhibitor, initially used in the study sites			
Infliximab	24 (33.3)	23 (52.3)	**0.04**
Etanercept	21 (29.2)	15 (34.1)	
Adalimumab	20 (27.8)	3 (6.8)	
Certolizumab pegol	4 (5.6)	1 (2.3)	
Golimumab	3 (4.2)	2 (4.5)	

Data are presented as median [interquartile range] or number (%). P values were calculated using Mann-Whitney U and Fisher's exact tests. Bold values for P-values denote statistical significance at the $p < 0.05$ level. The numbers of missing values for each variable in patients who never received methotrexate-tacrolimus combination and those who ever received it are as follows: number of tender or swollen in 28 joints, 1 and 4; numbers of tender or swollen in 66/68 joints, 3 and 6; patient general assessment, 1 and 5; physician general assessment, 2 and 5; laboratory values other than anti-CCP antibodies, 1 and 4; DAS28, 1 and 4; SDAI, 2 and 5; HAQ-DI, 1 and 8, respectively

Abbreviations: bDMARD, biological disease-modifying antirheumatic drugs; CCP, cyclic citrullinated peptide; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; DAS28, Disease Activity Score in 28 joints; HAQ-DI, Health Assessment Questionnaire-Disability Index; PtGA, patient's global assessment for disease activity; PhGA, physician's global assessment for disease activity; SDAI, Simplified Disease Activity Index; TNF, tumor necrosis factor

exception was irreversible HAQ-DI worsening, which did not reach statistical significance in the univariable analysis (Fig. 2, Supplementary Tables 1 and 2). Sensitivity analyses using time-dependent multivariable Cox models without random effects showed similar directional effects in point estimates, though some associations did not reach statistical significance (Supplementary Table 1).

Table 2 Clinical characteristics at TNF inhibitor discontinuation by maintenance therapy (per observation)

Factor	Mono (n = 96)		Combi (n = 51)		*P*-value
Age	62.0	[52.0, 67.4]	66.2	[54.1, 69.7]	0.17
With previous TNF inhibitor discontinuation (%)	5	(5.2)	26	(51.0)	**<0.001**
Duration of the TNF inhibitor treatment (week)	101	[67, 134]	115	[50, 160]	0.94
Multiple TNF inhibitor use in the prior treatment (%)	10	(10.4)	8	(15.7)	0.43
Tender joint count (0–28)	0	[0, 0]	0	[0, 0]	0.31
Swollen joint count (0–28)	0	[0, 0]	0	[0, 0]	0.31
Tender joint count (0–68)	0	[0, 0]	0	[0, 0]	**0.03**
Swollen joint count (0–66)	0	[0, 0]	0	[0, 0]	0.09
NTSJ in 28 joints (%)	83	(86.5)	48	(94.1)	0.18
NTSJ in 68 and 66 joints (%)	76	(79.2)	48	(94.1)	**0.02**
PtGA (0–100)	3	[0, 14]	4	[1, 12]	0.70
PhGA (0–100)	0	[0, 1]	0	[0, 0]	0.18
C-reactive protein (mg/dL)	0.10	[0.04, 0.15]	0.08	[0.03, 0.15]	0.56
Erythrocyte sedimentation rate (mm/hr)	11	[7, 18]	13	[8, 21]	0.25
Matrix Metalloproteinase-3 (ng/mL)	35.0	[25.2, 47.4]	38.2	[22.5, 48.9]	0.66
Rheumatoid factor titer (U/mL)	38	[15, 96]	31	[15, 78]	0.77
DAS28	1.88	[1.50, 2.38]	1.92	[1.57, 2.40]	0.60
Mean DAS28 before TNF inhibitor discontinuation	1.87	[1.47, 2.38]	2.04	[1.67, 2.35]	0.38
Days for sustained DAS28 ≤ 2.6	357	[198, 560]	199	[74, 497]	0.07
SDAI	0.78	[0.27, 2.15]	0.60	[0.32, 1.61]	0.79
Mean SDAI before TNF inhibitor discontinuation	1.01	[0.36, 2.11]	0.78	[0.46, 2.38]	0.70
SDAI ≤ 3.3 (%)	84	(87.5)	45	(88.2)	1.00
Days for sustained SDAI ≤ 3.3 (days)	329	[174, 459]	280	[116, 494]	0.73
Boolean remission (PtGA ≤ 1) (%)	63	(65.6)	35	(68.6)	0.85
Boolean remission (PtGA ≤ 2) (%)	76	(79.2)	39	(76.5)	0.83
HAQ-DI (0–3)	0.00	[0.00, 0.12]	0.00	[0.00, 0.12]	0.80
Methotrexate dose (mg/week)	12.0	[11.5, 15.3]	12.0	[10.0, 14.0]	**0.03**
Enrollment in the latter half of the study period (%)	46	(47.9)	27	(52.9)	0.61

Clinical characteristics at the time of TNF inhibitor discontinuation per observation are shown. Data are presented as median [interquartile range] or number (%). The mean DAS28 and SDAI values before TNF inhibitor discontinuation were calculated using data from two or more consecutive evaluation dates between the baseline and the latest evaluation date at least 12 weeks prior to baseline. Missing values were only one for matrix metalloproteinase-3 in the Mono group

Abbreviations: NTSJ, no tender and no swollen joints. Otherwise, refer to the footnotes in Table 1

Pooled hazard ratios from multivariable mixed-effects Cox regression models identified prolonged methotrexate use and higher prednisolone doses at TNF inhibitor initiation as risk factors for worse outcomes. Older age at TNF inhibitor discontinuation was associated with an increased risk of irreversible HAQ-DI worsening and disease flares but not other outcomes (Supplementary Table 2).

IPW-adjusted Kaplan-Meier analyses, based on data from each patient's first treatment line (Mono: n = 91; Combi: n = 44), confirmed the superiority of the Combi group in reducing outcome event rates (Fig. 3). In the unadjusted model, the 2-year treatment failure-free rates were 0.75 (95% CI, 0.59–0.85) for the Combi group and 0.52 (95% CI, 0.41–0.62) for the Mono group. In the IPW-adjusted model, these rates were 0.75 (95% CI, 0.56–0.86) and 0.51 (95% CI, 0.40–0.61), respectively, indicating significantly better outcomes in the Combi group.

While IPW adjustment left imbalances greater than the assumed acceptable threshold of 0.25 [32] in the standardized mean differences for some covariates (e.g., prednisolone dosage, DAS28 score) (Supplementary Figure 1), none of these factors were negatively correlated with adverse outcomes; instead, the prednisolone dose at TNF inhibitor initiation, which was significantly higher in the Combi group, was positively correlated with most adverse outcomes, thus did not bias in favor of the Combi group in its effectiveness in preventing events.

To assess the effectiveness of Combi treatment in different clinical contexts, we stratified the earliest maintenance treatment lines in the Combi group into two categories: those initiated after the first TNF inhibitor discontinuation (n = 25, referred to as the "initial Combi" group) and those initiated after the second or subsequent TNF inhibitor discontinuations (n = 19, referred to as the "subsequent Combi" group). These were compared with the Mono group (n = 44) (Fig. 4).

The subsequent Combi group showed numerically better outcomes in terms of treatment failure, treatment intensification, and disease flare event rates early in the maintenance period compared to both the initial Combi group and the Mono group, with a trend toward significantly lower event risks than the Mono group. In contrast, the first Combi group was comparable to the Mono group in treatment failure, intensification, and disease flare event rates during the first year after TNF inhibitor discontinuation. Still, it demonstrated a numerical advantage in reducing treatment failure and intensification risks in the later periods. However, none of these differences reached statistical significance.

We also performed a within-patient analysis to compare outcomes between Mono and Combi treatments in patients who received both regimens after multiple TNF inhibitor discontinuations. In this subset, Combi

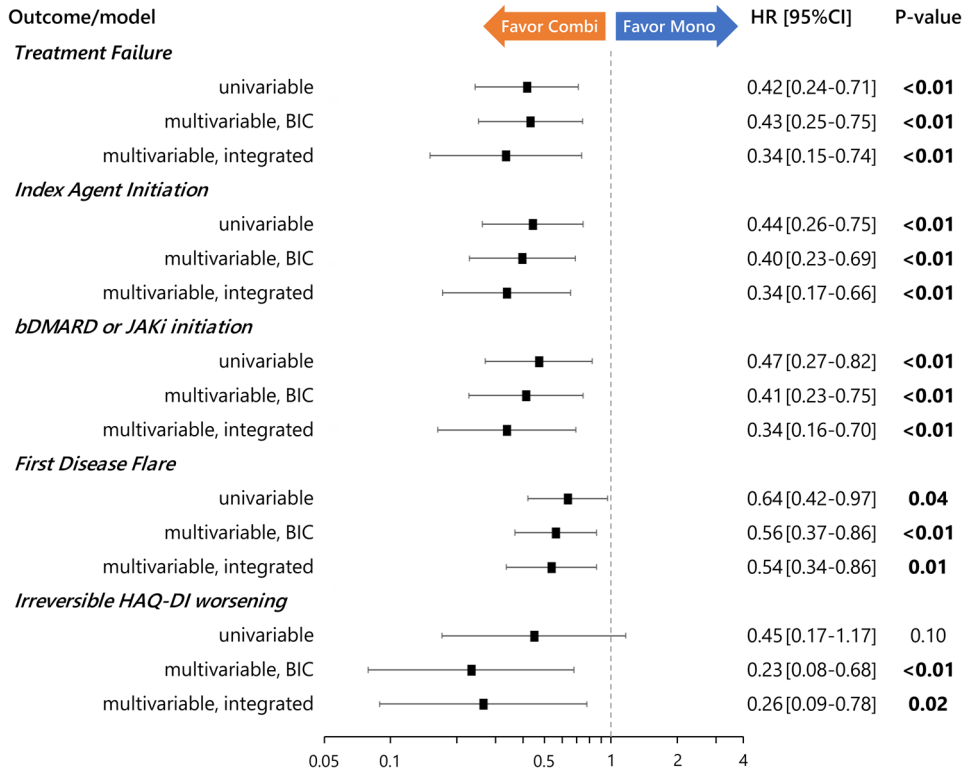

Fig. 2 Impact of Combi Treatment Relative to Mono Treatment on Outcome Events. Hazard ratios for each outcome event in the Combi group relative to the Mono group according to the univariable and multivariable mixed-effects Cox proportional hazards model using all treatment lines (Mono 96, Combi 51). The multivariate results include hazard ratios calculated from the model with the lowest Bayesian Information Criterion (BIC) and no missing values, with treatment failure as the dependent variable. Additionally, pooled hazard ratios are shown by combining results from all models. Abbreviations: CI, confidence interval; DAS28, Disease Activity Score in 28 Joints; HAQ-DI, Health Assessment Questionnaire-Disability Index; JAKi, Janus kinase inhibitors; TNF, tumor necrosis factor

treatment was associated with a statistically significant reduction in all evaluated outcome events compared to Mono treatment, with the difference being most pronounced compared to other supersets (Fig. 5). In this subset, hazard ratios [95% confidence interval] for each outcome of Combi treatment over Mono treatment in univariable mixed-effects Cox proportional hazards models are as follows. Treatment failure (0.04 [0.01–0.12]), treatment intensification with the index drugs (0.05 [0.02–0.17]) and with bDMARD or JAK inhibitors (0.04 [0.01–0.15]), first relapse (0.12 [0.05–0.30]). Univariable time-dependent Cox proportional hazards models without random effects showed similar results: treatment failure (0.01–0.15), treatment intensification with the index drugs (0.11 [0.03–0.40]), treatment intensification with bDMARDs or JAK inhibitors (0.07 [0.01–0.32]), and first relapse (0.22 [0.07–0.67]).

The primary cause of treatment failure in both groups was RA relapse, leading predominantly to the TNF inhibitor resumption. Adverse event frequencies leading to treatment discontinuation were comparable between groups (Table 3).

Methotrexate dose and renal function over time

Methotrexate doses declined over time in both groups, but the reduction was significantly greater in the Combi group. By the final observation, a higher proportion of Combi patients received 6 mg/week or less methotrexate ($p = 0.01$, Fig. 6). The estimated annual reduction in methotrexate dose was 0.28 mg/week greater in the Combi group.

For renal function analysis, observations were consolidated for treatment periods involving continuous tacrolimus use: 44 treatment lines with tacrolimus (median follow-up: 8.6 years; interquartile range: 5.6–10.4 years; total data points: 1,847) and 91 treatment lines without prior or current tacrolimus use (median follow-up: 7.5 years; interquartile range: 4.8–10.3 years; total data points: 3,985).

We assessed models incorporating covariates such as gender, body weight at each assessment, age and serum creatinine levels at baseline, and random effects for both intercept and slope. The yearly incremental slope of serum creatinine with tacrolimus use was estimated at 0.0032 mg/dL (standard error: 0.0017), with a

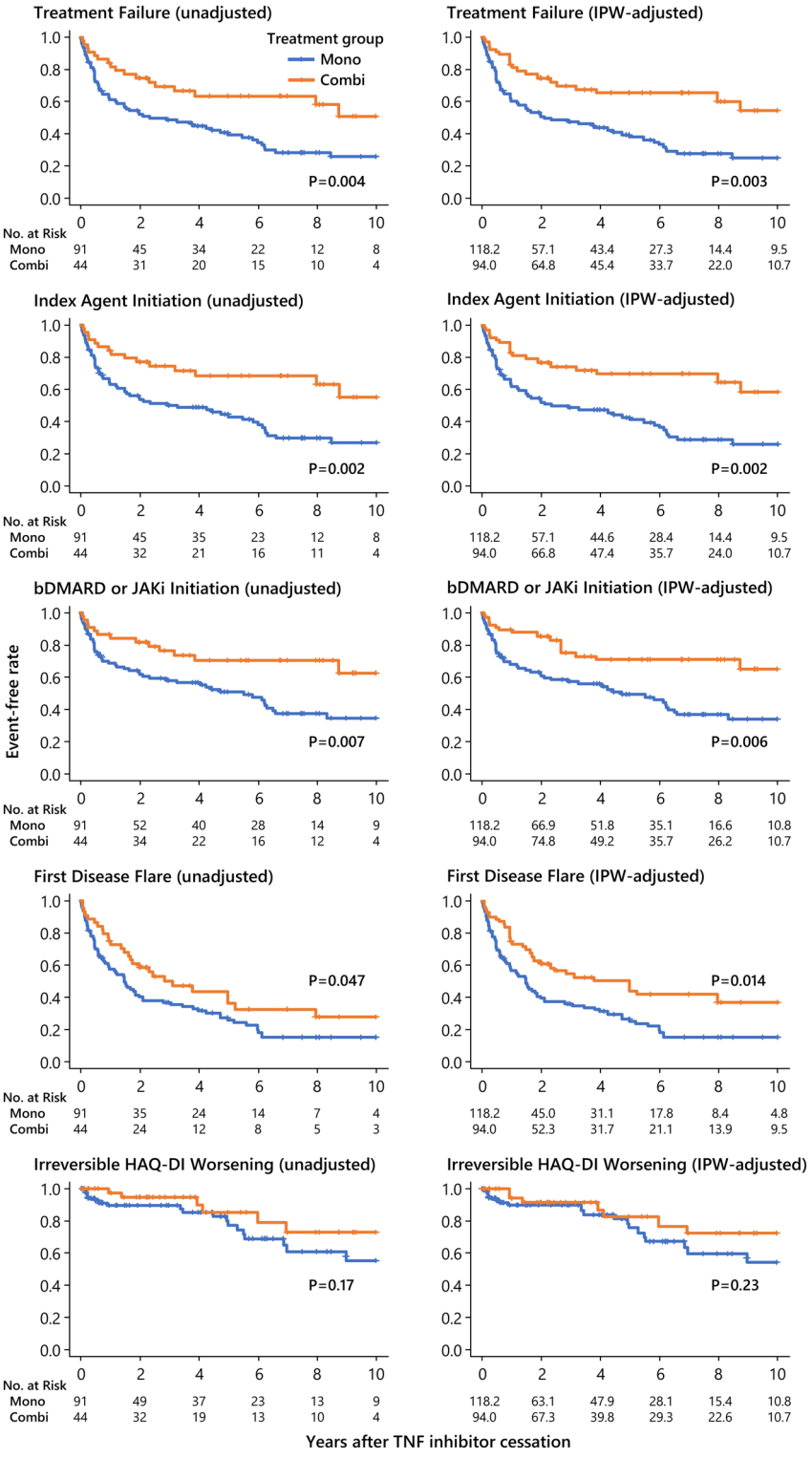

Fig. 3 (See legend on next page.)

(See figure on previous page.)

Fig. 3 Kaplan-Meier Curves Comparing Clinical Outcomes After TNF Inhibitor Discontinuation: Mono vs. Combi Groups. Unadjusted and IPW-adjusted Kaplan-Meier curves comparing the probability of remaining free from clinical events after TNF inhibitor discontinuation, using each patient's earliest observation in the Mono (n = 91) and Combi (n = 44) groups. The estimated 2-year event-free probabilities in the Combi versus Mono groups were as follows: Treatment failure: 0.75 (95% CI, 0.59–0.85) vs. 0.52 (0.41–0.62) (unadjusted), 0.75 (0.56–0.86) vs. 0.51 (0.40–0.61) (IPW-adjusted). Treatment intensification with index drugs: 0.77 (0.62–0.87) vs. 0.54 (0.43–0.63) (unadjusted), 0.77 (0.58–0.88) vs. 0.52 (0.41–0.62) (IPW-adjusted). Treatment intensification with bDMARDs or JAK inhibitors: 0.82 (0.67–0.90) vs. 0.63 (0.52–0.72) (unadjusted), 0.85 (0.72–0.93) vs. 0.62 (0.50–0.71) (IPW-adjusted). First disease flare: 0.59 (0.43–0.72) vs. 0.40 (0.30–0.50) (unadjusted), 0.61 (0.43–0.75) vs. 0.40 (0.29–0.50) (IPW-adjusted). Irreversible HAQ-DI worsening: 0.95 (0.80–0.99) vs. 0.90 (0.80–0.95) (unadjusted), 0.91 (0.67–0.98) vs. 0.90 (0.80–0.95) (IPW-adjusted). Tick marks indicate censored observations. P-values were calculated using the log-rank test or IPW-adjusted log-rank test. See Supplementary Data for details on statistical methods

non-significant interaction effect of concomitant tacrolimus on longitudinal creatinine changes (P = 0.06, Fig. 7).

Discussion

This study indicates that methotrexate-tacrolimus combination therapy significantly reduced treatment failure and relapse events compared to methotrexate monotherapy following TNF inhibitor discontinuation. These benefits were observed across multiple clinical outcomes and were robust across mixed-effects Cox regression models, various covariate adjustments, and sensitivity analyses. Notably, the combination therapy effectively controlled disease flares and prevented treatment intensification in patients who experienced flare-ups during methotrexate monotherapy after their previous TNF inhibitor discontinuations. These findings highlight the

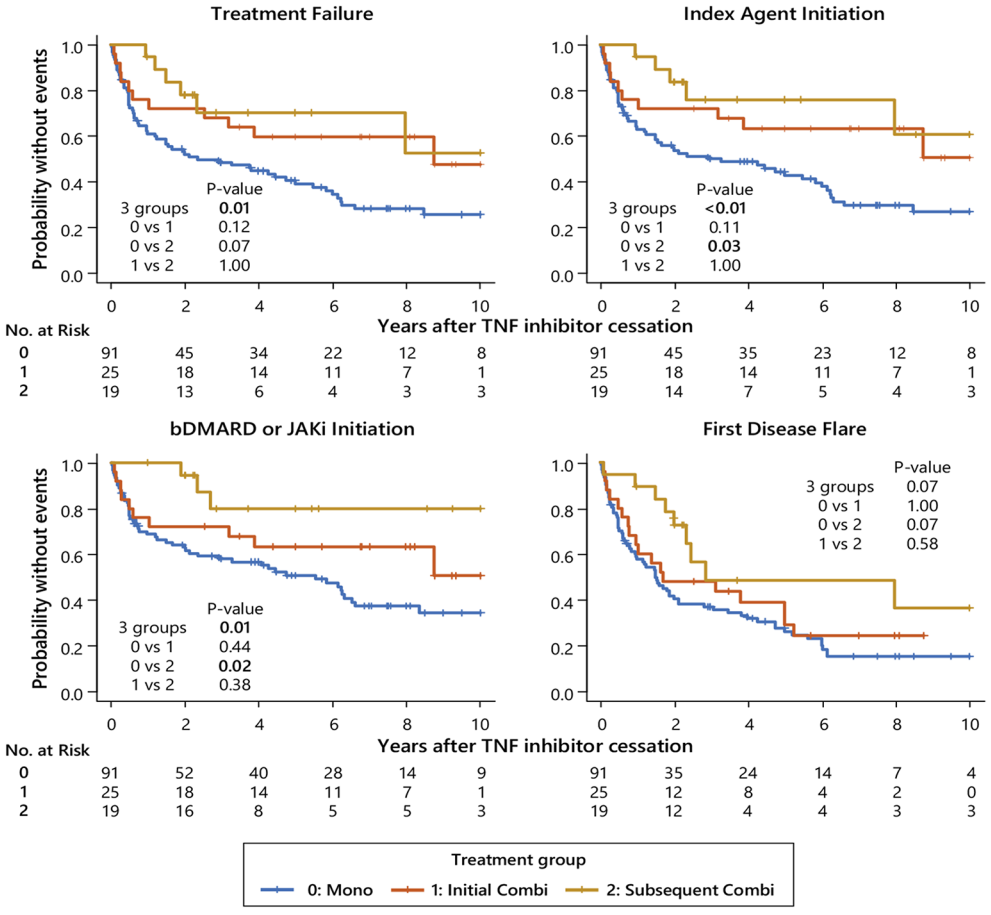

Fig. 4 Kaplan-Meier Curves for Treatment Outcomes Stratified by Timing of Tacrolimus Introduction After TNF Inhibitor Discontinuation. Kaplan-Meier curves comparing the time to clinical outcomes between the initial Combi group (n = 25), the subsequent Combi group (n = 19), and the Mono group (n = 91). The initial Combi group consisted of maintenance treatment episodes with methotrexate-tacrolimus combination therapy initiated after the first TNF inhibitor discontinuation, while the subsequent Combi group received combination therapy after the second or subsequent TNF inhibitor discontinuations. Tick marks indicate censored data. P-values were calculated using the log-rank test, and pairwise comparisons between the groups were performed using the Bonferroni method to adjust for multiple comparisons. Refer to the legend of Fig. 2 for abbreviations

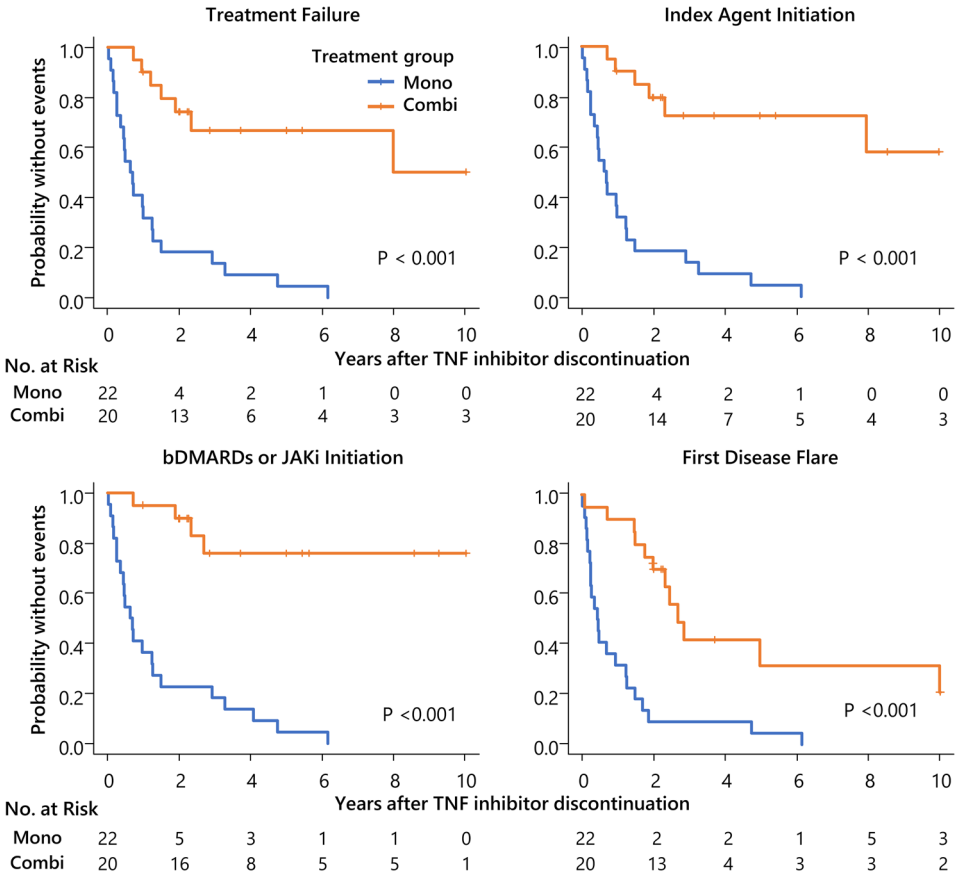

Fig. 5 Comparison of Mono and Combi Maintenance Therapy Outcomes: Within-Patient Paired Analysis. Kaplan-Meier curves comparing the probability of not experiencing clinical outcomes during methotrexate monotherapy and methotrexate-tacrolimus combination therapy. Data from 19 patients with multiple TNF inhibitor discontinuations at different times are included, with each patient receiving either methotrexate monotherapy or methotrexate-tacrolimus combination therapy following each discontinuation. The analysis is based on within-patient comparisons across different treatment periods. Tick marks indicate censored data. The p-values were obtained using the log-rank test. Refer to the legend of Fig. 2 for abbreviations

tacrolimus combination as a valuable option for maintaining remission after TNF inhibitor discontinuation. Additionally, the tacrolimus combination provided a methotrexate-sparing effect over time, potentially mitigating long-term methotrexate-associated risks.

Among patients who received combination therapy after their first TNF inhibitor discontinuation, 64% (16/25) had moderate or high disease activity (DAS28 > 3.2) at tacrolimus initiation despite TNF inhibitor therapy. These patients achieved sustained remission using triple therapy (methotrexate, TNF inhibitor, and tacrolimus) before successfully discontinuing TNF inhibitors. This finding aligns with previous studies showing tacrolimus's efficacy in overcoming resistance to biological DMARDs [35–38], suggesting its potential role in inducing remission and facilitating TNF inhibitor-free maintenance.

The time-dependent multivariable Cox models without random effects showed a reduced difference in the event-suppressing effectiveness of Combi treatment compared to the mixed-effects Cox proportional hazards model. This attenuation likely reflects the influence of treatment sequencing and baseline disease severity. In patients who received both treatments, Mono was always used first, and Combi was introduced as salvage therapy, where it was particularly effective. The mixed-effects model accounts for within-patient correlations, better capturing the superior efficacy of Combi in these high-risk cases. In contrast, the time-dependent Cox model without random effects treats each treatment episode independently, leading to an underestimation of Combi's benefit. Additionally, among patients who received Combi treatment from the outset, 64% had failed to achieve remission with TNF inhibitors and MTX alone but responded after adding tacrolimus, indicating higher baseline disease activity and an inherently greater risk of relapse. The inability of the time-dependent Cox model to adjust for these factors likely contributed to the reduced observed difference.

Concerns about tacrolimus-induced nephrotoxicity remain. Over a median follow-up of 8.6 years, with targeting tacrolimus blood trough concentrations at 3–5 ng/mL, tacrolimus users showed a marginally significant

Table 3 Summary of treatment failure events per maintenance treatment line

	Mono (n = 96)		Combi (n = 51)	
Number of treatment failure events	65	(67.7%)	22	(43.1%)
Details of treatment failure				
Initiation of Index drugs for rheumatoid arthritis flares	61	(93.8%)	18	(81.8%)
Resuming the TNF inhibitor	49	(75.4%)	15	(68.2%)
Initiation of glucocorticoids	3	(4.6%) [1]	2	(9.1%)
Initiation of leflunomide	3	(4.6%)	0	(0.0%)
Initiation of glucocorticoids and leflunomide	0	(0.0%)	1	(4.5%)
Initiation of tacrolimus	6	(9.2%) [2]	-	
Adverse events with discontinuation of treatment	4	(6.2%)	4	(18.2%)
Lymphoproliferative disorders	3	(4.6%)	1	(4.5%)
Other neoplasm	0	(0.0%)	1	(4.5%) [3]
Deterioration of renal function	0	(0.0%)	1	(4.5%) [4]
Sudden death	0	(0.0%)	1	(4.5%)
Other	1	(1.5%) [5]	0	(0.0%)

The denominator of the percent frequency of each classified treatment failure event was the number of treatment failure events in each group

1. Two of them relapsed with extra-articular lesions (organizing pneumonia in 1, vasculitis in 1)

2. Three of them had received conventional synthetic disease-modifying antirheumatic drugs other than the index drug prior to tacrolimus initiation

3. Lung cancer

4. Developed after stenting of abdominal aortic aneurysm

5. Severe anorexia

trend toward increased creatinine levels compared to non-users. However, the annual increase was only 0.0032 mg/dL, suggesting minimal clinical impact over decades, consistent with prior post-marketing long-term safety data in lupus nephritis [39]. In addition, the combination therapy did not significantly increase treatment discontinuation due to adverse events, indicating an acceptable safety profile.

An intriguing finding was the association between the duration of methotrexate treatment before TNF inhibitor initiation and relapse risk after TNF inhibitor discontinuation. This finding suggests that the cumulative burden of inflammation, despite methotrexate therapy, may play a critical role in achieving TNF inhibitor-free remission, more so than disease duration alone. Early initiation of effective treatment and prompt remission induction may improve long-term outcomes [29, 31, 40, 41].

We also observed irreversible worsening of HAQ-DI in some patients during the maintenance treatment period. The median age at the time of irreversible HAQ-DI deterioration was 74 years (tertile range: 63–82 years), with cases frequently presenting coexisting musculoskeletal problems unrelated to RA, such as knee osteoarthritis, degenerative spondylosis, and post-stroke sequelae. HAQ-DI has been reported to increase exponentially with age after 65 [42], suggesting that these changes were partly attributable to aging and other musculoskeletal issues rather than RA alone. This finding underscores the importance of distinguishing RA-specific functional decline from broader age-related factors when evaluating long-term outcomes following TNF inhibitor discontinuation.

The strengths of this study include a high follow-up rate (97% during the first two years) and a long median observation period (5.7 years), enabling robust assessment of long-term outcomes. Clinically relevant outcomes, including treatment intensification and drug discontinuation, were well-defined and consistently supported by mixed-effects Cox modeling, time-dependent Cox modeling without random effects, IPW-adjusted Kaplan-Meier estimation, and stratified analyses. These robust findings reinforce the effectiveness and safety of tacrolimus combination therapy in reducing RA flare risk after TNF inhibitor discontinuation, even in patients with prior inadequate responses to TNF inhibitors.

However, several limitations must be considered. As an observational study, susceptibility to selection bias and residual confounding is inherent. Unequal distribution of prior TNF inhibitor discontinuations and temporal asymmetry in treatment order may have influenced outcomes. The small sample size, limited number of participating centers, and predominantly Japanese patient population restrict the generalizability of findings.

Safety assessments also have constraints. The small number of patients limits the power to detect differences in less frequent adverse events, such as lymphoproliferative disorders, and renal dysfunction related to tacrolimus may emerge over a longer timeframe. Although creatinine elevations were minimal, caution about the potential for underestimated long-term risks is warranted.

Conclusions

Methotrexate-tacrolimus combination therapy significantly reduces RA relapse after TNF inhibitor discontinuation without compromising safety, offering a sustainable treatment option for patients considering de-escalation after sustained remission. Further research should focus on biomarkers, radiographic assessments, and comprehensive cost-benefit and safety analyses to validate these findings and optimize treatment strategies for diverse RA populations.

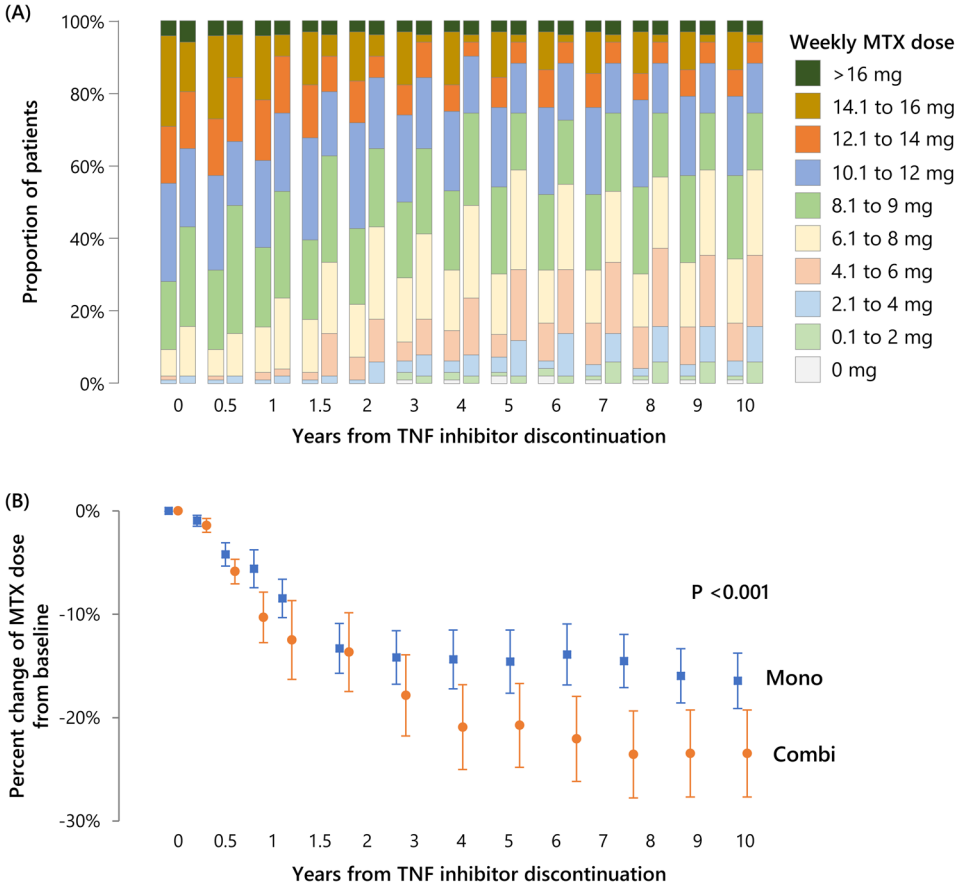

Fig. 6 The dose and percent change of methotrexate during the treatment failure-free period after TNF inhibitor discontinuation. Methotrexate dose and mean percent change during the treatment failure-free period post-TNF inhibitor discontinuation for the Mono (left bar and blue-filled square) and Combi (right bar and orange-filled circle) groups are shown. Error bars indicate standard error. Methotrexate doses decreased over time in both groups, with a significantly higher proportion of patients receiving 6 mg/week or less in the combi group (p = 0.01 by the Fisher exact test). Missing methotrexate doses due to censoring or treatment-failure events were imputed by the last observation carried forward method. P-values in Fig. 3B for the interaction effect of adding tacrolimus on the change in methotrexate dose over time were estimated by a mixed-effects model adjusted for gender, baseline age, and methotrexate dose

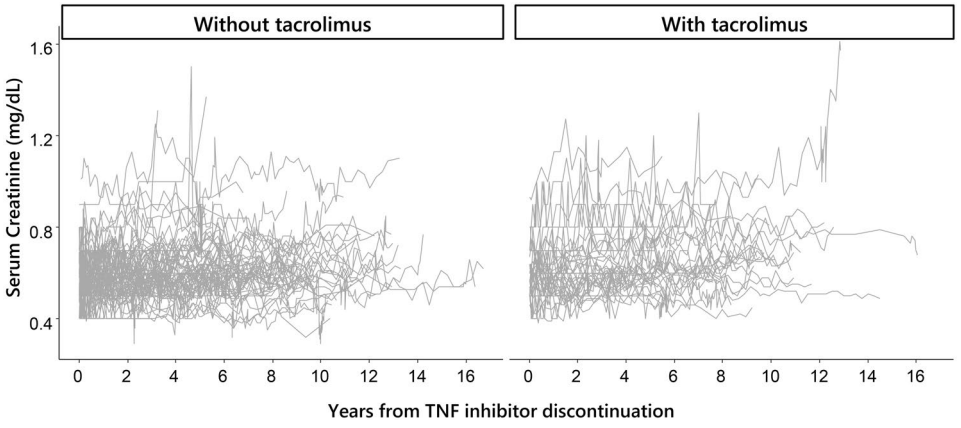

Fig. 7 Serum creatinine levels over time, stratified by tacrolimus use. These scatter plots depict serum creatinine values over time for all participants stratified by tacrolimus use. For this analysis, the observations where tacrolimus had been used consecutively were consolidated: 44 lines with tacrolimus treatment (median observation period: 8.6 years; interquartile range: 5.6–10.4; 1,847 data points) and 91 lines without prior and current tacrolimus treatment (7.5; 4.8–10.3; 3,985) were compared. The baseline for the tacrolimus-treated or non-tacrolimus-treated groups was determined using the earliest time points measured immediately around the start of tacrolimus or TNF inhibitor treatment, respectively

Abbreviations

bDMARDs	Biological DMARDs
CI	Confidence interval
Combi	Methotrexate plus tacrolimus combination therapy
csDMARD	Conventional synthetic DMARD
DAS28	Disease Activity Score in 28 Joints
DMARDs	Disease-modifying antirheumatic drugs
HAQ-DI	Health Assessment Questionnaire-Disability Index
HR	Hazard ratio
IPW	Inverse probability weighting
JAK	Janus kinase
Mono	Methotrexate monotherapy
RA	Rheumatoid arthritis
SDAI	Simplified Disease Activity Index
TNF	Tumor necrosis factor

Supplementary information

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Supplementary Material 1

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Author contributions

Conception and design of the work: TN, MK. Data management: TN. Statistical analysis and interpretation of data: TN. Manuscript draft: TN, MK. All authors reviewed and approved the final version of the manuscript prior to submission and agreed to be accountable for all aspects of the work.

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Data availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The Institutional Review Board and Ethics Committee of Nagoya City University Graduate School of Medical Sciences (IRB approval number: 60-21-0116), Japan, approved the study, following the principles of the Declaration of Helsinki and the local ethical guidelines. This study used an 'opt-out' approach. Patient data was included unless individuals opted out within the specified timeframe after notification.

Consent for publication

Not applicable

Disclaimer

No part of this manuscript, including text and figures, is copied or published elsewhere in whole or in part. While preparing this manuscript, the authors used generative AI tools like ChatGPT4, DeepL, and Grammarly to translate our original text into English, improve writing style, and check grammar and spelling. After using these tools, the authors reviewed and edited the content and take full responsibility for the publication's content.

Competing interests

The authors declare no competing interest.

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