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Clinical science

The impact of glucocorticoids on the efficacy of JAK inhibitors or non-TNF-targeted biologics in RA

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Abstract

Objectives: To evaluate the impact of oral low-dose glucocorticoids (GCs) on the effectiveness of Janus kinase inhibitors (JAKis) compared with non-TNF-targeted bDMARDs (other mechanisms of action [OMA] including tocilizumab, abatacept and rituximab) in RA patients with inadequate response to TNF inhibitors (TNFi-IRs).

Methods: Single-centre, retrospective cohort study. The primary outcome was the good EULAR response at 6, 12 and 24 months. Secondary outcomes included treatment discontinuation and remission rates. Statistical analyses included structural equation modeling (SEM), competing risks analysis and linear mixed-effects models.

Results: The study included 299 patients (JAKi = 161, OMA = 138). Baseline GC use was similar between the groups (JAKi = 66.5%, OMA = 76%; $P = 0.089$; mean (SD) daily dose 4.4 (5.5) vs 4.9 (4.5) mg/d; $P = 0.355$). The proportion of GC users treated with JAKi or OMA at 6, 12 and 24 months was 49.7% vs 63.8% ($P = 0.036$), 37.3% vs 40.6% ($P = 0.161$) and 27.3% vs 34.1% ($P = 0.430$). No statistically significant differences in GC dose reduction were observed between the two groups across any time interval. The EULAR response improved at 24 months, with JAKi outperforming OMA (SEM; $P = 0.040$). GC dosage at 6 months negatively affected the 24-month outcome ($\beta = -0.456$, $P = 0.020$). DAS28-CRP remission was more frequent in the JAKi group ($P < 0.05$), while discontinuation rates were similar (HR = 1.49, $P = 0.34$).

Conclusion: JAKi did not show superiority over OMA regarding steroid-sparing effects; however, JAKi yielded higher remission rates. Exposure to GC at 6 months predicted poorer 24-month outcomes.

Keywords: RA, glucocorticoids, tsDMARDs, JAKi, bDMARDs.

Rheumatology key messages

- Treatment with either JAK inhibitors or non-TNFi bDMARDs after TNFi failure allows GC tapering and discontinuation in a similar fashion.
- GC use at 6 months was associated with poorer clinical response at 24 months.
- Remission rates were higher in JAKi-treated patients.

Introduction

Nearly half of RA patients are treated with glucocorticoids (GCs) chronically (i.e. for >6 months) [1]. Despite known dose-dependent side effects, even low-dose GC therapy has been linked to increased cardiovascular and infectious risks [2, 3]. Real-world data show that 30–80% of RA patients initiating biologic DMARDs (bDMARDs) are on GCs [4]. This number rises to 70% in difficult-to-treat RA subset [5], a category defined in part by the inability to taper GC doses below 7.5 mg/day of prednisone equivalent [6]. Notably, GC discontinuation rates have remained relatively unchanged in the biologic era [1, 7], despite improved disease control with treat-to-target strategies [8]. While the combination of GCs and conventional synthetic DMARDs (csDMARDs) has long been a milestone of early RA management [9–11], chronic GC use is increasingly debated [12]. The latest EULAR recommendations discourage the routine use of combined GC and biologic or targeted synthetic DMARD (b/tsDMARD) therapy due to safety concerns [13].

Several phase III randomized controlled trials (RCTs) assessed Janus kinase inhibitors (JAKis) efficacy and safety in early-naive RA, and inadequate responders (IRs) to MTX or bDMARDs [14]. At baseline, up to 60% of patients in these trials were receiving concomitant GCs, in line with other RCTs and real-life data [15]. However, GC tapering or discontinuation was not permitted in RCTs, preventing the

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assessment of the GC-sparing potential of JAKi. A *post hoc* analysis of tofacitinib RCTs has suggested no significant clinical benefit from adding GCs to JAKi [16], though several studies showed that GC use may impact JAKi safety, notably by increasing herpes zoster risk [17, 18].

Other bDMARDs with non-TNF mechanisms of action (OMA), such as tocilizumab, abatacept and rituximab, are commonly used in TNFi-IR patients. However, comparative data on their efficacy and GC-sparing potential and long-term outcomes relative to JAKi are limited.

We hypothesize that JAKi could allow GC dose reduction or withdrawal in a greater proportion of patients compared with OMA. Thus, our study aimed to assess the impact of chronic oral low-dose GCs on the efficacy and retention rates of JAKi compared with OMA therapies in a cohort of RA patients with inadequate response to TNFi.

Methods

This monocentric retrospective cohort study assessed the effect of chronic GC use on clinical outcomes of RA patients treated with either JAKi (tofacitinib, baricitinib, upadacitinib or filgotinib), or OMA including abatacept, tocilizumab or rituximab. We examined whether GC use in the first 6 months impacted treatment outcomes at 6, 12 and 24 months, and if it influenced therapy discontinuation due to adverse events or inefficacy. The study was approved by the Ethics Committee of the Central—Eastern Veneto Area (CET—ACEV) with number 6007/AO/24 and conformed to the ethical guidelines of the Declaration of Helsinki as revised in 2000.

Study population

Patients aged ≥18 years with a confirmed RA diagnosis (2010 ACR/EULAR criteria), prior failure of at least one tumour necrosis factor inhibitor (TNFi) and therapy initiation with either JAKi or OMA between March 2018 and March 2024 were included. TNFi remains the most common first-line bDMARDs in RA patients, while JAKi or OMA is more commonly considered later in the treatment algorithm in several countries. Under national reimbursement policies, treatment with JAKi is approved only for patients with an inadequate response to csDMARDs and prior treatment with at least one TNFi. Consequently, we excluded patients who were bDMARD-naive from this analysis, as well as patients whose first biologic was a non-TNFi, as such choices may be influenced by comorbidities or extra-articular manifestations of RA. Further exclusion criteria included overlap syndromes and follow-up <6 months. For this analysis, only the first course of JAKi therapy was analysed. The study duration was 24 months. The study flow chart is illustrated in Supplementary Fig. S1.

Study endpoints

The primary outcome of the study was the good EULAR response at 6, 12 and 24 months. The secondary outcomes were treatment discontinuation at 24 months and disease activity score in 28 joints using CRP (DAS28CRP) and Boolean remission rates at 6, 12 and 24 months. EULAR Good Response was defined as a DAS28-CRP score ≤3.2 with a ≥1.2 reduction from baseline. DAS28-CRP remission was defined as <2.6, and Boolean remission required meeting all criteria: Tender Joint Count ≤1, Swollen Joint Count ≤1, CRP ≤10 mg/l and PGA ≤1. The proportion of patients achieving remission was evaluated using an intention-to-treat approach.

Data collection and preprocessing

Patients who started b/tsDMARD within the study period were identified from a local prospective electronic registry called the Piattaforma Servizi Farmaceutici (PSF). Demographic (sex, age at baseline, BMI), clinical characteristics (disease duration, presence of radiographic erosions, seropositivity for rheumatoid factor and/or anti-citrullinated peptide antibodies, extra-articular manifestations, comorbidities), disease assessment (DAS28CRP, CRP), treatment history (number of prior bDMARDs classes used, prior or concomitant use of csDMARDs, GC use and prednisone equivalent dosage) were mandatory variables in the registry. Data were verified through a review of patients' clinical records by three investigators (M.S., F.F., F.A.) The patients who experienced adverse events or treatment failure discontinued treatment according to clinical practice guidelines. Drug persistence and the main reason for drug discontinuation were recorded at each time point (primary or secondary failure, adverse events, intolerance, loss of follow-up, remission and other reasons).

Comorbidities were assessed at baseline and included cardiovascular disease (myocardial infarction, cerebrovascular disease, heart failure, peripheral artery disease), diabetes, osteoporosis, chronic pulmonary disease (asthma, chronic obstructive pulmonary disease), cancer, hypertension and dyslipidaemia.

During the data cleaning process, any duplicates and typographical errors were carefully identified and removed. Outliers were identified as values exceeding four standard deviations from the mean. Continuous variables were assessed for normality, and those showing non-normal distributions underwent logarithmic transformation (adding one to account for zero values).

Statistical analysis

A robust statistical approach was employed to investigate whether GC dosage impacts the clinical response in RA patients treated with JAK inhibitors or bDMARDs with OMA. The detailed statistical methodology, including the rationale for specific analytic choices, is provided in the Supplementary Data S1. All analyses were performed using R software (version 4.2.2). Statistical significance was determined at a P-value threshold of <0.05.

Briefly, given the complexity of the relationships being studied, structural equation modelling (SEM) was chosen as the primary analytic framework due to its capacity to estimate direct and indirect effects while incorporating multiple covariates and longitudinal outcomes (at 6, 12 and 24 months) [19]. Factorial Analysis of Mixed Data (FAMD) was applied to reduce the number of variables using the FactoMineR package in R. This approach generated composite factor scores from baseline covariates, balancing the mixed nature of the data (categorical and continuous) and ensuring the SEM remained statistically well-identified.

The SEM models were constructed to assess GC dosage and treatment group (JAKis or OMA) as predictors of clinical outcomes (EULAR good response) at each time point. The outcomes were modeled hierarchically, with earlier outcomes (e.g. 6 months) predicting subsequent ones (e.g. 12 and 24 months). Separate subgroup-specific models were also

developed to isolate the effects of GC dosage within each treatment group. Model parameters were estimated using the weighted least squares mean and variance (WLSMV) adjusted method, suitable for handling categorical outcomes. Model fit was evaluated using established indices, including the comparative fit index (CFI), Tucker–Lewis index (TLI), root mean square error of approximation (RMSEA) and standardized root mean square residual (SRMR), with benchmarks ensuring acceptable model performance. Path coefficients, *P*-values and *R*-squared values were reported for all paths, while SEM diagrams visually emphasized significant pathways.

To further address potential concerns regarding model specification and to validate the robustness of our findings, we conducted a supplementary time-to-event analysis using the Prentice–Williams–Peterson model with gap-time specification (PWP-GT).

For the DAS28-CRP remission outcome, simple logistic regression analyses were performed, adjusting for baseline DAS28-CRP values, to assess the association between the treatment group and remission rates at each time point.

Covariate selection

To address potential confounding factors and reduce bias, covariates were carefully selected based on their distribution across the treatment groups and their potential influence on outcomes (EULAR response). These included key demographic and clinical variables, such as sex, age, BMI, seropositivity, DAS28CRP at baseline, extra-articular manifestations, disease duration and prior treatment history (number of previous bDMARD classes, reason for treatment discontinuation) and comorbidities.

Linear mixed-effects models

To analyse differences in GC dosage between the treatment groups over time, linear mixed-effects models were utilized. Fixed effects accounted for time, treatment group and their interaction, while random effects addressed repeated measures within individuals.

Competing risks analysis

Competing risks analysis was performed to evaluate the time to treatment discontinuation due to adverse events, defined as the main event of interest while accounting for inefficacy as the competing event. The Fine and Gray subdistribution hazard model was employed to estimate the subdistribution hazard ratios (sHRs) for the cumulative incidence of the main event (adverse events). The covariates included in the competing risks analysis were selected based on their potential influence on the outcome and their distribution across the treatment groups. Covariates included factors derived from FAMD, baseline GC dosage, treatment group and the reason for stopping previous treatment. The cumulative incidence functions for adverse events and inefficacy were estimated and stratified by the treatment group to visualize the probability of each type of discontinuation. The statistical significance of the covariates was assessed using the Wald test.

Results

Patients' characteristics

A total of 299 patients (mean age 59 years, RA duration 16.6 years, 87% female) were included, comprising 161 in the JAK inhibitor group and 138 in the OMA group (Table 1). The OMA group included abatacept (46%), tocilizumab (49%) and rituximab (5%), while the JAKi group consisted of tofacitinib (24%), baricitinib (30%), upadacitinib (22%) and filgotinib (24%).

Notably, patients treated with JAK had lower baseline disease activity (mean DAS28CRP 3.81 (1.00) vs 4.45 (1.19)) and had failed a higher number of bDMARD classes.

Treatment response

After excluding incomplete cases, the 12- and 24-month models included 221 (118 JAK, 103 OMA) and 174 patients (87 in each group), respectively.

EULAR good response criteria were achieved by 36.8%, 35.5% and 28.1% at 6, 12 and 24 months, with no significant differences between the groups (Fig. 1 and Supplementary Table S1). Descriptive rates of DAS28CRP remission were 51.6% vs 24.6% at 6 months ($P < 0.001$), 46% vs 27.5% at 12 months ($P = 0.005$) and 36% vs 23.9% at 24 months ($P = 0.014$), as illustrated in Fig. 2. However, DAS28-CRP remission remained significantly more frequent in the JAKi group, even after adjusting for baseline disease activity. In logistic regression models including baseline DAS28-CRP as a covariate, treatment with JAKi was consistently associated with a higher likelihood of achieving remission compared with OMA: at 6 months (OR = 2.57, 95% CI: 1.91–3.45, $P < 0.001$), 12 months (OR = 1.86, 95% CI: 1.42–2.45, $P < 0.001$) and 24 months (OR = 1.76, 95% CI: 1.31–2.44, $P < 0.001$). Notably, baseline DAS28-CRP was negatively associated with remission at all time points (all $P < 0.001$), confirming that higher initial disease activity reduced the probability of achieving remission.

Factorial analysis of mixed data

Using the Kaiser criterion (eigenvalue > 1) (10.1037/met0000074), the first three dimensions of the FAMD were retained ($\lambda_1 = 1.31$, $\lambda_2 = 1.04$, $\lambda_3 = 1.01$; Supplementary Fig. S2). Factor 1 captured demographic and radiographic damage (highest loadings: age 0.42, erosions 0.47); Factor 2 reflected baseline disease severity (e.g. DAS28CRP 0.75) and Factor 3 was driven by demographic/serological aspects (e.g. sex 0.80). Importantly, the number of previous bDMARD classes contributed to the three factors retained in our final model. Factor 4, with an eigenvalue below 1, was excluded based on the Kaiser criterion.

Together, these factors explained 56.05% of the total variance. Detailed loadings are shown in Supplementary Table S3, and the factor structure is visualized in Supplementary Fig. S3.

GC use and trends

At baseline, chronic GC usage rates and prednisone-equivalent doses were similar between the two therapy groups (JAKi: 66.5% vs OMA: 76%; $P = 0.089$). The proportion of patients on GCs treated with JAKi or OMA at 6, 12 and 24 months was 49.7% vs 63.8% ($P = 0.036$); 37.3% vs 40.6% ($P = 0.161$); 27.3% vs 34.1% ($P = 0.430$). No statistically significant differences in mean GC dose and GC dose delta reduction were observed between the two groups across any time interval (Supplementary Tables S1 and S2).

Linear mixed-effects modelling revealed a significant reduction in GC dosage over time for both the groups (Fig. 3). Specifically, GC dosages were significantly lower at 6, 12 and 24 months compared with baseline ($P < 0.001$ for all comparisons). Although the OMA group had a marginally higher baseline GC dosage than the JAKi group (estimate = 0.207,

Table 1. Baseline characteristics of the study population stratified by the therapy group (JAK vs OMA)

Mean (SD), *n* (%)	Overall (*n* = 299)	JAK (*n* = 161)	OMA (*n* = 138)	*P*-value
Females	260 (87.0)	145 (90.1)	115 (83.3)	0.121
Age, years	58.96 (13.03)	57.85 (12.23)	60.25 (13.84)	0.113
BMI, kg/m^2	24.61 (4.18)	24.37 (4.16)	24.89 (4.21)	0.294
Disease duration, years	16.33 (9.87)	17.14 (10.13)	15.38 (9.51)	0.124
Erosions				
Yes	251 (83.9)	129 (80.1)	122 (88.4)	0.038 *
Missing	10 (3.3)	9 (5.6)	1 (0.7)	
Presence of extra-articular manifestations	55 (18.4)	35 (21.7)	20 (14.5)	0.144
RF or ACPA positive	233 (77.9)	118 (73.3)	115 (83.3)	0.023 *
Number of previous bDMARD classes				
1	208 (69.6)	77 (47.8)	131 (94.9)	<0.001 *
2	63 (21.1)	56 (34.8)	7 (5.1)	
≥3	28 (9.4)	28 (17.4)	0 (0.0)	
Reason for failure of previous bDMARD				
Inefficacy	231 (77.3)	119 (73.9)	112 (81.2)	0.176
Adverse events	68 (22.7)	42 (26.1)	26 (18.8)	
Diabetes mellitus	23 (7.7)	14 (8.7)	9 (6.5)	0.627
Osteoporosis	75 (25.1)	41 (25.5)	34 (24.6)	0.975
Cardiovascular disease	20 (6.7)	8 (5.0)	12 (8.7)	0.292
Chronic pulmonary disease	30 (10.0)	19 (11.8)	11 (8.0)	0.177
Hypertension	79 (26.4)	40 (24.8)	39 (28.3)	0.234
Dyslipidaemia	45 (15.1)	20 (12.4)	25 (18.1)	0.112
History of solid or hematological malignancy	16 (5.4)	11 (6.8)	5 (3.6)	0.150
DAS28CRP at baseline	4.10 (1.13)	3.81 (1.00)	4.45 (1.19)	<0.001 *
CRP at baseline mg/L	15.12 (22.68)	13.96 (21.93)	16.48 (23.53)	0.341
Concomitant csDMARD at baseline	95 (31.8)	46 (28.6)	49 (35.5)	0.246
Concomitant MTX at baseline	87 (91.6)	38 (82.6)	39 (79.6)	0.91
GC users at baseline	212 (70.9)	107 (66.5)	105 (76.1)	0.089
PDN equivalent dose at baseline, mg qd	4.64 (5.07)	4.39 (5.49)	4.93 (4.54)	0.355

bDMARDs, biologic DMARDs; csDMARDs, conventional synthetic DMARDs; GC, glucocorticoids; PDN, prednisone.

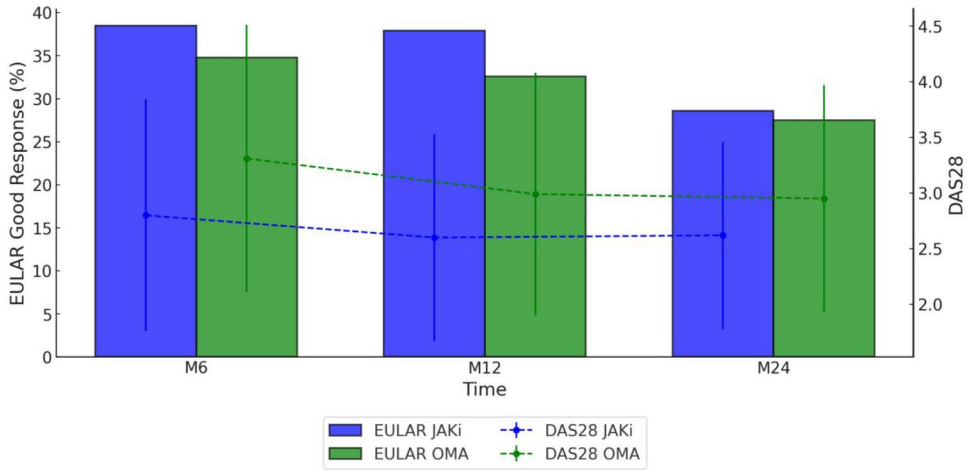

Figure 1. EULAR good response and DAS28 at 6, 12 and 24 months

95% CI: 0.001–0.412; $P = 0.05$), no significant differences in the temporal GC reduction dosage trend were observed. Interaction terms between time points and the therapy group were not significant ($P > 0.3$ for all interactions), indicating that the pattern of GC dosage reduction over time was consistent across the groups.

Longitudinal SEM of GC effect and treatment outcome

12-month model results

The 12-month SEM demonstrated an excellent fit (Fig. 4a). The model included 14 free parameters and showed no significant discrepancy ($P = 0.321$ for chi-squared test), with CFI and TLI values of 1.000 and RMSEA of 0.000. The model explained 18.9% of the variance in the 6-month outcome (EULAR response at 6 months) and 69.1% in the 12-month outcome (EULAR response at 12 months). Factor 2 (disease activity) had a significant positive effect on 6-month ($\beta = 0.497$, $P < 0.001$) and 12-month outcomes ($\beta = 0.197$, $P = 0.014$), indicating that higher diseases activity was associated with greater EULAR response. The baseline GC dose positively influenced the 12-month outcome ($\beta = 0.185$, $P = 0.035$), however, the strongest predictor of the 12-month outcome was the 6-month outcome ($\beta = 0.726$, $P < 0.001$).

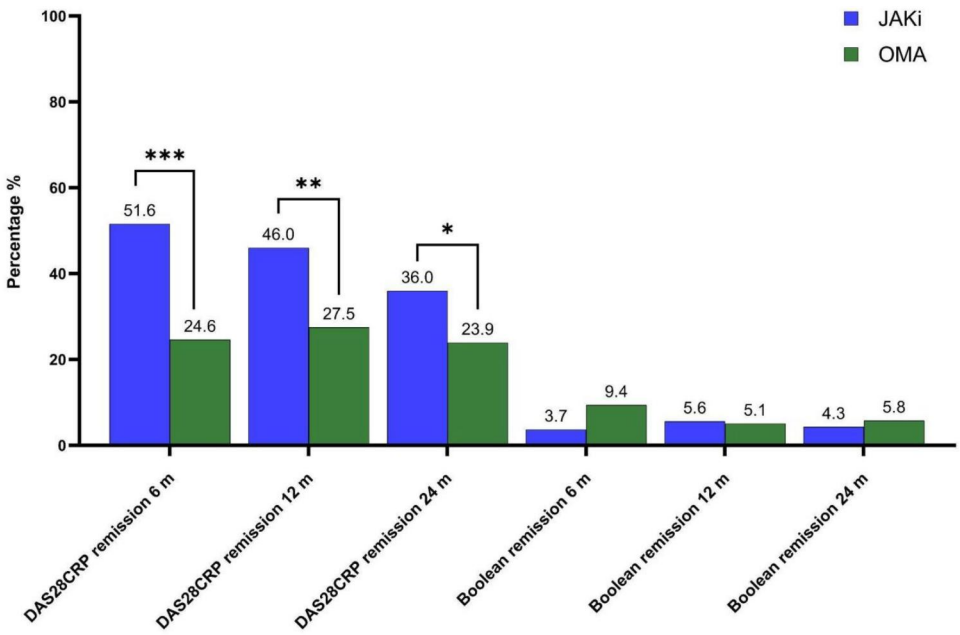

Figure 2. DAS28CRP and Boolean remission at 6, 12 and 24 months (intention-to-treat analysis). DAS: disease activity score. $^{*}P \leq 0.05$, $^{**}P \leq 0.01$, $^{***}P \leq 0.001$

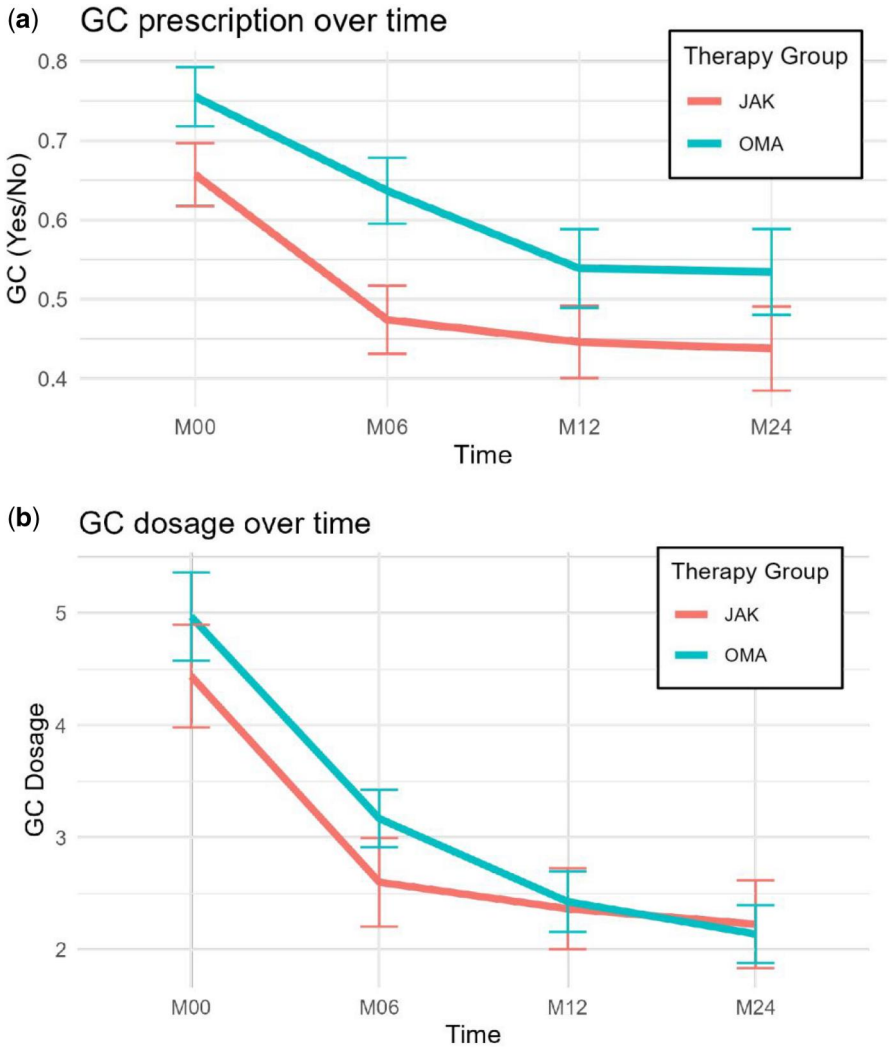

Figure 3. Glucocorticoid (GC) use over time for patients on JAK inhibitors (red) and OMA therapy (blue). (**a**) Average GC prescription rates (yes/no) at baseline (M00), 6 months (M06), 12 months (M12) and 24 months (M24), derived from the linear mixed-effects model. (**b**) GC dosage (mg of prednisone equivalent per day) over the same time points, based on the same model. Error bars represent standard errors

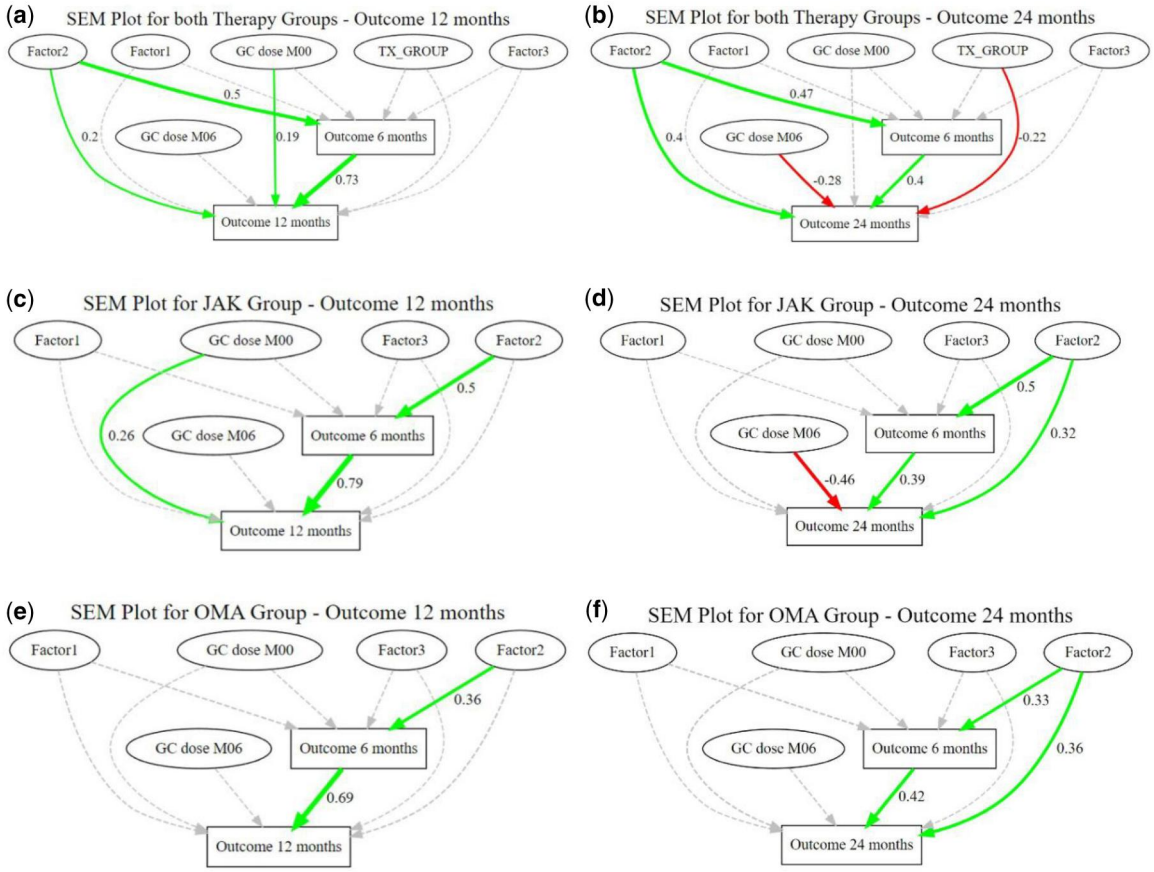

Figure 4. SEM plots for both generic and therapy-specific analyses at 12 and 24 months. The outcome at 6, 12 and 24 months is the EULAR response. Panels (**a**) and (**b**) depict the generic model outcomes, panels (**c**) and (**d**) focus on the JAK therapy-specific models and panels (**e**) and (**f**) present the OMA therapy-specific models. TX_GROUP refers to OMA vs JAKi as reference. Green arrows represent positive path coefficients, while red arrows indicate negative path coefficients. Solid lines denote statistically significant paths ($P < 0.05$), whereas dashed lines represent non-significant paths ($P \geq 0.05$). The thickness of the arrows corresponds to the magnitude of the standardized effect, with thicker arrows illustrating stronger effects. The latent variables were derived from FAMD. Factor 1 reflects demographics, radiographic damage and number of previous bDMARD classes. Factor 2 captures baseline disease activity and previous bDMARD classes. Factor 3 reflects mainly sex and serological status. Full details of the factor loadings are provided in Supplementary Table S2 and Supplementary Fig. S3

The JAK-specific model showed an acceptable fit (Fig. 4c), with 12 free parameters and explained 25.7% of the variance at 6 months and 78.8% at 12 months. Higher baseline GC doses significantly improved 12-month outcomes ($\beta = 0.261$, $P = 0.024$), with Factor 2 (disease activity) and the 6-month outcome also contributing positively.

The OMA-specific model (Fig. 4e) had an excellent fit. This model also included 12 free parameters and explained 16.5% of the variance at 6 months and 61.1% at 12 months. Factor 2 significantly predicted better outcomes at both 6 months ($\beta = 0.363$, $P = 0.019$) and 12 months ($\beta = 0.197$, $P = 0.014$).

24-month model results

The 24-month SEM demonstrated an excellent fit (Fig. 4b). The model had 14 free parameters and explained 17.9% of variance at 6 months and 42.6% at 24 months. Factor 2 (disease activity) positively influenced both 6-month ($\beta = 0.465$, $P < 0.001$) and 24-month outcomes ($\beta = 0.396$, $P = 0.001$) (EULAR response at 6 and 24 months, respectively), indicating that patients with higher baseline disease activity were more likely to achieve a good EULAR response. GC dosage at 6 months negatively affected 24-month outcomes ($\beta = -0.282$, $P = 0.018$). The 6-month outcome remained a strong predictor of 24-month outcomes ($\beta = 0.398$, $P < 0.001$). The treatment group (coded as OMA vs JAKi as reference) had a significant negative effect on the 24-month outcome (estimate = −0.523, SE = 0.255, $P = 0.040$, standardized coefficient = −0.220), indicating that patients treated with JAKi achieved better responses compared with those receiving OMA. For JAK patients, the model, with 12 parameters, explained 25.3% of the variance at 6 months and 48.5% at 24 months (Fig. 4d). GC dose at 6 months had a significant negative effect on 24-month outcomes ($\beta = -0.456$, $P = 0.020$). Factor 2 (disease activity) showed a significant positive effect on both the 6-month outcome (estimate = 0.646, SE = 0.169, $P = 0$, standardized coefficient = 0.496) and the 24-month outcome (estimate = 0.453, SE = 0.191, $P = 0.018$, standardized coefficient = 0.319).

For OMA patients (Fig. 4f), the model, with 12 free parameters, explained 17.9% of variance at 6 months and 43.4% at 24 months. Factor 2 continued to significantly influence both 6-month ($\beta = 0.331$, $P = 0.040$) and 24-month outcomes ($\beta = 0.363$, $P = 0.026$). GC dose was not significant for either the 6- or 12-month outcome.

Comparison between the groups

Z-tests comparing GC dosage effects across groups showed no significant differences in short-term or long-term outcomes. For example, baseline GC dose effects on 12-month outcomes ($Z = 1.199$, $P = 0.230$) and GC dose at 6 months on 24-month outcomes ($Z = -1.360$, $P = 0.174$) were not significantly different.

PWP-GT model

The analysis included 616 observations and 266 events. Patients treated with OMA exhibited a significantly lower hazard of achieving a EULAR good response compared with those treated with JAK inhibitors (HR = 0.52, 95% CI: 0.37–0.75, $P = 0.0005$). A higher GC dose at 6 months was associated with a decreased probability of good response (HR = 0.93, 95% CI: 0.88–0.99, $P = 0.021$), suggesting that continued GC exposure is a marker of persistent disease activity or suboptimal therapeutic effect. Baseline GC dose showed no significant association with the outcome (HR = 1.01, 95% CI: 0.97–1.06, $P = 0.55$), while Factor2 (reflecting baseline disease activity) was strongly associated with increased response (HR = 1.96, 95% CI: 1.64–2.35, $P < 2.8 \times 10^{-13}$). Neither Factor 1 nor Factor 3 reached statistical significance. The model's overall fit was good (Likelihood ratio test: $\chi^2 = 92.95$ on 6 df, $P < 2e{-}16$; concordance = 0.734, SE = 0.028). Despite their different statistical assumptions, both the SEM and PWP-GT models converged on the same key findings, suggesting that the observed associations, treatment effects, GC exposure and baseline severity reflect real and robust patterns in the clinical data.

Competing risks analysis

The Fine and Gray competing risks analysis did not identify any covariates significantly associated with the risk of treatment discontinuation due to adverse events or inefficacy. Factor-derived covariates, including Factor 1 (demographic and radiographic damage) (sHR = 1.33, 95% CI: 0.87–2.04), Factor 2 (sHR = 1.11, 95% CI: 0.81–1.53) and Factor 3 (demographic and serological aspects) (sHR = 0.91, 95% CI: 0.64–1.29), were not significantly predictive of treatment discontinuation. Similarly, baseline GC dose (log-transformed sHR = 0.77, 95% CI: 0.52–1.13) and the reason for discontinuing previous treatments (sHR = 1.65, 95% CI: 0.78–3.48) showed no statistically significant association. Additionally, the therapeutic group, assessed via a dummy variable as the JAK group (sHR = 1.49, 95% CI: 0.66–3.35), did not show a significant impact on treatment discontinuation outcomes (Fig. 5).

Discussion

In our cohort of RA patients with inadequate response to TNFi, subsequent treatment with either a JAKi or a bDMARD demonstrated comparable EULAR good response rates at 6, 12 and 24 months (Fig. 1). Notably, Factor 2, reflecting baseline disease activity, positively influenced the achievement of a good EULAR response both in the 12- and 24-months SEM model, indicating that higher disease activity was associated with increased response. This finding is consistent with the definition of EULAR response, which is based on both relative change from baseline and absolute DAS28 value, such that patients starting with higher disease activity have a greater likelihood of reaching the ΔDAS28 threshold required for a good response. The SEM model (Fig. 4b) revealed that treatment with OMA, compared with JAKi, had a negative effect on the EULAR response at 24 months. Patients treated with JAKi achieved significantly higher rates of DAS28-CRP remission at all assessed time points compared with those treated with OMA, after adjusting for baseline DAS28-CRP (Fig. 2). This result is in line with previous observations from the SELECT-CHOICE trial and its long-term extension study [20, 21]. Similarly, the Jakpot study, a large real-world investigation of international registers, reported comparable CDAI response rates across TNF inhibitors, JAKis, IL-6 inhibitors and abatacept at 1 year, with slightly lower rates of LDA and remission for abatacept compared with other therapeutic groups [22].

On the other hand, the proportion of patients who met Boolean remission criteria was low overall and consistent between the two groups. This data underscores the complexity of achieving stringent remission criteria in real-world settings, particularly in long-standing RA. One key factor limiting Boolean remission rates is the PGA, which often reflects pain more than inflammation in patients with established disease [23]. In our model, treatment response at 6 months was the strongest predictor of outcomes at 12 and 24 months, with JAKi showing a potential long-term advantage.

At baseline, 70% of patients used GC. Encouragingly, both the treatment groups demonstrated a steroid-sparing effect throughout the study, with 40% of patients discontinuing GC therapy. Despite this, ∼30% of patients remained on GC at 24 months, highlighting challenges in complete discontinuation in a subset of patients. Higher GC dosage at baseline was positively associated with the EULAR response at 12 months. This advantage, however, did not persist at 24 months and was absent in the OMA group, suggesting that any eventual benefit was not sustained over time and not uniform across therapies. The lack of sustained benefit of baseline GC dosage may indicate an effect in symptom control rather than true disease modification. Notably, higher GC doses at 6 months correlated with poorer outcomes at 24 months (Fig. 4). Patients requiring higher GC doses at 6 months likely represented a more severe or 'refractory' subgroup, in whom disease control remains suboptimal despite treatment with b/tsDMARDs. Persistent GC use at this time point may mask an insufficient treatment response and potentially delay therapeutic escalation when treatment targets are not achieved. Chronic GC use, even at very-low doses, is associated with persistent moderate disease activity [24] and b/tsDMARD failure [25]. Chronic GC use may act as a surrogate marker for ongoing subclinical inflammation or refractory disease, which ultimately leads to poorer long-term outcomes as previously shown by ours [5] and other groups [26]. Finally, these findings support the notion that GC dependence reflects underlying treatment failure rather than a sustainable disease management strategy [13].

Evidence supporting a sustained benefit of GCs when used concomitantly with advanced therapies is limited. The GLORIA trial has demonstrated the benefit of long-term low-dose GC therapy in elderly patients with RA [27], however, the proportion of participants receiving biologics at baseline was limited to 16% in the prednisolone group and 13% in the placebo group. In patients with long-standing disease treated with advanced therapies, chronic use of GC may be explained by their analgesic rather than disease-modifying

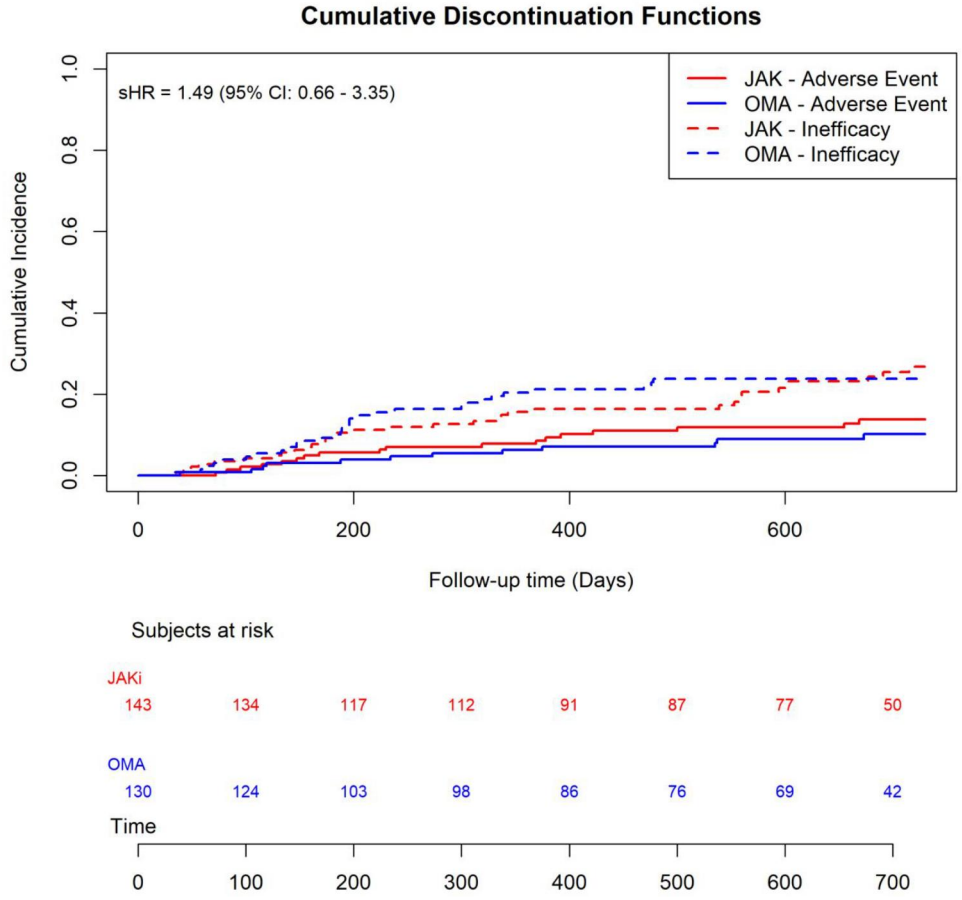

Figure 5. Cumulative incidence functions for the two therapy groups. JAK (red lines) and OMA (blue lines) are stratified by the reasons for treatment discontinuation (solid lines for adverse events and dashed lines for inefficacy). The *x*-axis represents the time (in days) since treatment initiation, while the *y*-axis indicates the cumulative probability of discontinuation

effect. The 2022 EULAR recommendations for the management of RA regard dependence on GCs for more than 4 months as a treatment failure, but also highlight the need to distinguish between chronic GC use for pain rather than persistent inflammation [13]. Evidence suggests that GCs effectively reduce pain in active RA, yet the magnitude of their effect on pain declines beyond 6 months of use [28]. The gap between GC discontinuation rates observed in real-world practice and those achieved in clinical trials [29] may also reflect suboptimal adherence of rheumatologists to the current recommendation of GC use. However, we observed a 40% discontinuation rate of GC, which is consistent with previous research that followed a predefined tapering and discontinuation protocol [30].

The GC-sparing potential of b/tsDMARD has been investigated with TNFi [31] and subsequently with other drug classes. Many of these earlier studies [32, 33] were conducted during a period when baseline GC doses were higher and chronic steroid use was more permissive, reflecting evolving treatment paradigms and expectations. One limitation of prior research is the frequent absence of a control group when evaluating GC-sparing effects, which limits the ability to draw definitive conclusions about comparative efficacy in GC reduction [30, 32–34]. Data from a large international registry support similar outcomes in GC reduction across different treatments (IL-6 inhibitors and abatacept compared with TNFi) [4, 35]. In this analysis, GC use varied widely across national registries (30–85%), with 70% of IL6i-treated patients and 63% of abatacept-treated patients receiving GC at baseline (median daily dose of 5 mg/day of prednisolone equivalent). Importantly, all treatments demonstrated comparable steroid-sparing effects at 1 year, with a median GC discontinuation time of 2 years [4]. In a large Australian cohort, treatment with JAKi or bDMARDs (TNFi, abatacept, tocilizumab) allowed for significant GC dose reduction and GC discontinuation at 1–2 years in 20% of patients treated with JAKi and 22% of those treated with bDMARDs [36], which is lower compared with that observed in our study. Another study showed that JAKi treatment led to faster GC dose reduction than bDMARDs within the first 6 months of treatment [37]. Importantly, 38–82% of patients were naive to b/tsDMARDs, and comparators included mostly TNFi (76%), suggesting a higher baseline likelihood to reduce GC therapy compared with our study.

Though some studies suggest a higher risk of discontinuation due to adverse events in OMA-treated patients (mainly driven by anti-IL6 drugs) compared with JAKi [38], we did not observe significant differences in retention or reasons for discontinuation between the two groups. Furthermore, while we explored potential predictors of treatment discontinuation, we did not identify any clear factors influencing this outcome. This apparent discrepancy with previous literature may be partly explained by sample size, differences in study populations, definitions of prior treatment failure and the

specific drugs included within the OMA and JAKi categories. Our cohort consisted of patients with inadequate response to TNFi as a class, potentially reflecting a more homogeneous and treatment-refractory population. Additionally, the composition of the OMA group (abatacept, tocilizumab, rituximab) and JAKi group (tofacitinib, baricitinib, upadacitinib, filgotinib) differs from other studies, which may affect generalizability and observed discontinuation patterns. While we explored potential predictors of discontinuation, no significant associations emerged. However, this may reflect limited statistical power—given the relatively small number of discontinuation events (31 for AE, 69 for inefficacy)—rather than a true absence of effect. Moreover, despite careful covariate selection, residual confounding by unmeasured variables cannot be ruled out.

Study limitations

Our study's limitations include its retrospective design, which introduces the possibility of selection bias, sample size and lack of a protocol-defined GC tapering schedule. Due to the small sample size, the SEM analyses were not adequately powered to draw robust causal inferences, as shown by *post hoc* power analysis reported in the Supplementary Data. Thus, the results should be interpreted as descriptive trends within this specific cohort. For the same reason, we were unable to perform subgroup analyses on patients who had failed only one class of biologic DMARD or to distinguish treatment-specific effects between JAKi and OMA. Nevertheless, the sample size remains considerable for a monocentric study involving patients with inadequate response to first-line biologic therapy. Importantly, external validation in larger, independent cohorts will be necessary to confirm the observed associations and generalize our findings. Finally, our findings are might not be generalizable to other GC regimens, such as intramuscular and intra-articular administration.

Conclusions

JAKi did not allow GC dose reduction in a significantly greater proportion of patients compared with OMA. Both treatments demonstrated GC-sparing effects; however, a higher proportion of patients receiving JAKi achieved DAS28 remission at any time point. The combination of GC and b/tsDMARDs did not provide additional clinical benefits, suggesting that chronic GC use alongside advanced therapies should be avoided.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data supporting this study cannot be shared as they were collected with consent for use only in the current study or for predefined research purposes.

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