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Sex Differences in Treatment Response to Targeted Therapy in Rheumatoid Arthritis: A Post Hoc Analysis of a Prospective Observational Study

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ABSTRACT

Background: Sex differences in treatment outcomes for rheumatoid arthritis (RA) have been inconsistently reported. This study aimed to investigate whether male and female patients with RA have different treatment responses to their first-line targeted therapies.

Methods: This post hoc analysis used data from a prospective multicenter observational study of patients with RA initiating biologic disease-modifying anti-rheumatic drugs or Janus kinase inhibitors for the first time. The primary outcome was remission measured by the 28-joint Disease Activity Score with erythrocyte sedimentation rate (DAS28-ESR) at week 24. Remission rates were compared between male and female patients. Conditional logistic regression models, matched on RA disease duration and baseline disease activity, were used to analyze the independent effect of sex on remission.

Results: Overall, 78 male and 428 female patients were included. In the per-protocol analysis, the DAS28-ESR remission rates at week 24 were higher in male patients (44.3%) than in female patients (28.9%) ($P = 0.025$). Conditional logistic regression showed that male sex was independently associated with achieving remission (adjusted odds ratio [aOR], 2.76; 95% confidence interval [CI], 1.25–6.08). In the subgroup of patients with early RA (disease duration ≤ 2 years), male patients had significantly higher odds of achieving remission than female patients (aOR, 11.59; 95% CI, 2.56–52.54). A similar trend was observed in the subgroup of patients who initiated Janus kinase inhibitors (aOR, 2.37; 95% CI, 1.02–5.52).

Conclusion: Male patients with RA achieve higher remission rates than female patients when initiating first-line targeted therapies, particularly in early disease. These findings suggest the need for sex-specific strategies in RA management.

Keywords: Rheumatoid Arthritis; Sex Factors; Treatment Outcome

INTRODUCTION

Sex differences in rheumatoid arthritis (RA) have long been a focal point of interest in rheumatology.¹ Prevalence and clinical features of RA differ between male and female patients. Women are two to four times more frequently affected by RA than men.² Biological

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Disclosure

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Author Contributions

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factors such as X-linked genetics³ and sex hormones,⁴ as well as social and environmental factors including smoking,⁵ may contribute to differential susceptibility between sexes. The phenotype of RA also varies between sexes. Male patients experience a later onset of RA⁶ and are more susceptible to extraarticular manifestations such as interstitial lung disease and vasculitis.^{7,8} Conversely, female patients tend to exhibit more aggressive arthritis in the early stages of the disease and suffer from more significant disability.⁹⁻¹²

Despite these recognized differences, the relationship between sex and treatment response in patients with RA remains incompletely understood. A meta-analysis of early clinical trials suggested that female patients were less likely to respond to conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) compared to male patients.¹³ However, more recent observational studies have shown no significant differences in treatment response between sexes when treated with methotrexate, the cornerstone conventional synthetic DMARD.^{14,15} The response to tumor necrosis factor (TNF) inhibitors also remains contentious, with some studies indicating that female patients are less likely to respond to TNF inhibitors^{16,17} while others report no significant sex differences.¹⁸

These conflicting findings highlight the complexity of sex differences in RA treatment outcomes. Moreover, few studies have examined the effect of sex on treatment response to biologic DMARDs other than TNF inhibitors¹⁹ or to targeted synthetic DMARDs.²⁰ Therefore, this study aimed to investigate sex differences in treatment responses to first-line targeted therapies—including biologics and targeted synthetic DMARDs—among patients with RA who had experienced inadequate response to conventional synthetic DMARDs.

METHODS

Study design

We conducted a post hoc analysis using data from a prospective, multicenter, observational study involving patients with RA initiating targeted therapy for the first time. The original study aimed to compare the efficacy and safety of biologic DMARDs and Janus kinase (JAK) inhibitors in patients with RA who had inadequate response to conventional synthetic DMARDs. A detailed study protocol has been previously reported.²¹ Patients receiving first-line targeted therapy were enrolled from 17 centers throughout the Republic of Korea between April 2020 and August 2022. Disease activity was assessed at baseline and at 12, 24, and 48 weeks after initiating targeted therapies. This post hoc analysis included all 506 patients from the original study, incorporating data collected over a 48-week follow-up period.

Study population

A total of 506 patients (78 male, 428 female) were included in this post hoc analysis. All participants were adults aged ≥ 19 years and met the revised 1987 American College of Rheumatology (ACR) criteria²² or the 2010 ACR/European Alliance of Associations for Rheumatology classification criteria²³ for RA. All participants had active RA despite treatment with conventional synthetic DMARDs and were initiated on biologic DMARDs or JAK inhibitors. Biologic DMARDs included TNF inhibitors (etanercept, adalimumab, and golimumab) and non-TNF inhibitors (abatacept and tocilizumab). JAK inhibitors included baricitinib, tofacitinib, and upadacitinib.

Outcome

The primary outcome was remission defined by the 28-joint Disease Activity Score with erythrocyte sedimentation rate (DAS28-ESR) at week 24. Secondary outcomes included sustained remission at week 48, defined as remission at both week 24 and week 48, along with remission based on the 28-joint Disease Activity Score with C-reactive protein (DAS28-CRP), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) at week 24. Remission states were determined following established thresholds for each composite score.²⁴

Covariates

Demographic data, comorbidities, clinical characteristics of RA, the type of targeted therapy initiated, concomitant use of conventional synthetic DMARDs, and baseline disease activity were collected at enrollment. Depressive symptoms were defined as a patient-reported score of $\geq$ moderate anxiety/depression on the EuroQol-5D-5L questionnaire. Treatment compliance at the week 24 follow-up visit was evaluated and was considered good if patients missed < 15 doses over a 90-day period.

Statistical analysis

Demographic and clinical characteristics of male and female patients were compared using the χ^2 or Fisher's exact test for categorical variables, and the independent t -test or Wilcoxon rank-sum test for continuous variables, as appropriate. The primary outcome, remission based on DAS28-ESR at week 24, was assessed through per-protocol analysis. Proportions of patients achieving remission were compared between male and female patients using the χ^2 test. An intention-to-treat (ITT) analysis was also conducted using non-responder imputation. Additionally, DAS28-ESR and its individual components were compared between sexes at each time point using the t -test under a per-protocol analysis. To further evaluate the effect of sex, the conditional logistic regression was performed after matching male and female patients based on two factors: RA duration (≤ 2 years [early RA] vs. > 2 years [established RA]) and baseline disease activity (DAS28-ESR ≤ 5.1 [low/moderate activity] vs. > 5.1 [high activity]). Similar analyses were conducted for secondary outcomes, including remission defined based on DAS28-CRP, CDAI, and SDAI, using a per-protocol analysis. Multivariable conditional logistic regression models were constructed to adjust for potential confounders, incorporating sex, age, concomitant methotrexate use, and additional covariates—such as seropositivity, comorbidities including fibromyalgia and depressive symptoms, and treatment compliance—selected using stepwise variable selection based on the Akaike information criterion. Subgroup analyses were performed based on RA duration (early vs. established RA) and the type of initial targeted therapy (JAK inhibitors vs. biologic DMARDs).

All analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC, USA) and R software version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Two-tailed P values < 0.05 were considered statistically significant.

Ethics statement

The study was conducted in compliance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Hanyang University Hospital (approval No. HYUN 2019-11-031). Written informed consent was obtained from all patients.

RESULTS

Baseline characteristics

When initiating targeted therapy among 78 male and 428 female patients, male patients were older (mean age: 56.7 vs. 53.2 years), more likely to have a smoking history (78.2% vs. 8.2%), and had a shorter RA duration (mean duration: 6.5 vs. 8.7 years) than female patients (Table 1). Female patients had a higher prevalence of fibromyalgia (4.9% vs. 1.3%) and reported depressive symptoms (25% vs. 11.5%) more often than male patients. The number of conventional synthetic DMARDs used before initiating targeted therapy was similar

Table 1. Baseline characteristics of the study population

Characteristics	Male patients (n = 78)	Female patients (n = 428)	P value
Demographics			
Age at enrollment, yr	56.7 ± 11.7	53.2 ± 13.5	0.034
BMI, kg/m ²	24.0 ± 3.5	23.0 ± 3.8	0.024
Ever smoked	61 (78.2)	35 (8.2)	< 0.001
Alcohol use	57 (73.1)	159 (37.1)	< 0.001
Clinical features of RA			
RA duration, yr	6.5 ± 9.0	8.7 ± 8.3	0.036
RF or anti-CCP seropositivity	68 (87.2)	396 (92.5)	0.177
No. of csDMARDs ever used	3 (2.2–4)	3 (2–4)	0.257
Comorbidities			
Diabetes mellitus	13 (16.7)	30 (7.0)	0.010
Hypertension	28 (35.9)	120 (28.0)	0.205
Chronic pulmonary disease	9 (11.5)	10 (2.3)	0.001
Peptic ulcer disease	2 (2.6)	10 (2.3)	0.999
Mild liver disease	5 (6.4)	31 (7.2)	0.981
Renal disease	4 (5.1)	5 (1.2)	0.036
Fibromyalgia	1 (1.3)	21 (4.9)	0.254
Depressive symptoms	9 (11.5)	107 (25.0)	0.014
Charlson comorbidity index	1.6 ± 1.1	1.3 ± 0.7	0.046
Disease activity at baseline			
ESR, mm/hr	45.4 ± 28.2	46.5 ± 25.7	0.730
CRP, mg/dL	2.3 ± 2.3	1.7 ± 2.0	0.035
Tender 28-joint count	8 (6–11)	10 (6–14)	0.020
Swollen 28-joint count	6 (3–8)	6 (4–9)	0.254
Physician global VAS, mm	75.5 ± 12.9	72.7 ± 14.3	0.110
Patient global VAS, mm	76.5 ± 14.7	76.3 ± 15.2	0.912
DAS28-ESR	5.8 ± 0.8	6.1 ± 0.8	0.037
DAS28-CRP	5.2 ± 0.8	5.3 ± 0.9	0.506
CDAI	30.1 ± 8.3	32.3 ± 9.4	0.057
SDAI	32.4 ± 8.9	34.0 ± 9.8	0.184
Initiating agent of targeted therapy			
TNF inhibitors	24 (30.8)	128 (29.9)	0.985
Non-TNF inhibitors	19 (24.4)	82 (19.2)	0.367
Abatacept	12 (15.4)	52 (12.1)	0.545
Tocilizumab	7 (9.0)	30 (7.0)	0.706
JAK inhibitors	35 (44.9)	218 (50.9)	0.389
Concomitant medications at baseline			
Methotrexate	70 (89.7)	382 (89.3)	> 0.999
NSAID	55 (70.5)	341 (79.7)	0.098
Oral glucocorticoids	66 (84.6)	330 (77.1)	0.183
Glucocorticoid dose, ^a mg/day	6.2 ± 4.2	4.9 ± 2.4	0.017

Values are presented as number (%), mean ± standard deviation, or median (first and third quartiles).

Categorical variables are compared using the χ^2 or Fisher's exact test, and continuous variables using the independent t-test or the Wilcoxon rank-sum test.

BMI = body mass index, RA = rheumatoid arthritis, RF = rheumatoid factor, CCP = cyclic citrullinated peptide, csDMARD = conventional synthetic disease-modifying anti-rheumatic drug, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, VAS = visual analogue scale, DAS28 = Disease Activity Score 28-joint count, CDAI = Clinical Disease Activity Index, SDAI = Simplified Disease Activity Index, TNF = tumor necrosis factor, JAK = Janus kinase, NSAID = nonsteroidal anti-inflammatory drug.

^aRegularly prescribed oral glucocorticoids are included in the calculation, with average dose presented as equivalent doses of prednisolone.

between male and female patients. DAS28-ESR scores were higher in female patients than in male patients. However, disease activity measured by DAS28-CRP, SDAI, and CDAI did not differ significantly between the two groups. The choice of the initial targeted therapy agent was comparable between groups, as was the concomitant use of methotrexate and glucocorticoids.

Treatment response based on DAS28-ESR

Of the 506 patients who initiated targeted therapy, 68 of 78 male patients (87.2%) and 375 of 428 female patients (87.6%) completed the 24-week follow-up visit (**Supplementary Fig. 1**). Overall, 96.4% of patients demonstrated good treatment compliance at week 24. In the per-protocol analysis using complete cases, the DAS28-ESR remission rate was significantly higher in male than in female patients at weeks 12 and 24 (**Fig. 1A**). At week 24, remission rates were 44.3% in male patients and 28.9% in female patients ($P = 0.025$). Additionally, sustained remission at week 48 was higher in male patients (39.3%) than in female patients (23.2%) ($P = 0.012$). The ITT analysis using the non-responder imputation approach to adjust for drug discontinuation demonstrated the same pattern (**Fig. 1B**).

To evaluate the contribution of ESR to the observed sex differences in DAS28-ESR remission rates, the individual components of DAS28-ESR were examined (**Supplementary Fig. 2**). ESR levels at each time point, including week 24, were comparable between the two groups (week 24: 23.38 vs. 23.46, $P = 0.980$), while tender joint count and patient global assessment showed numerically more favorable values in male patients.

Sex as a predictor of DAS28-ESR remission

In the conditional logistic regression analyses, following matching for RA disease duration and baseline disease activity, male sex was associated with higher odds of achieving DAS28-ESR remission at week 24 (unadjusted odds ratio [OR], 1.72; 95% confidence interval [CI], 1.00–2.94) (**Table 2**). Depressive symptoms (unadjusted OR, 0.49; 95% CI, 0.29–0.82), fibromyalgia (unadjusted OR, 0.50; 95% CI, 0.14–1.75), and seropositivity (unadjusted OR, 0.61; 95% CI, 0.30–1.26) were associated with trends toward poorer response. Conversely, good treatment compliance (unadjusted OR, 1.42; 95% CI, 0.44–4.55) and concomitant methotrexate use (unadjusted OR, 4.12; 95% CI, 0.91–18.70) were associated with trends toward better response.

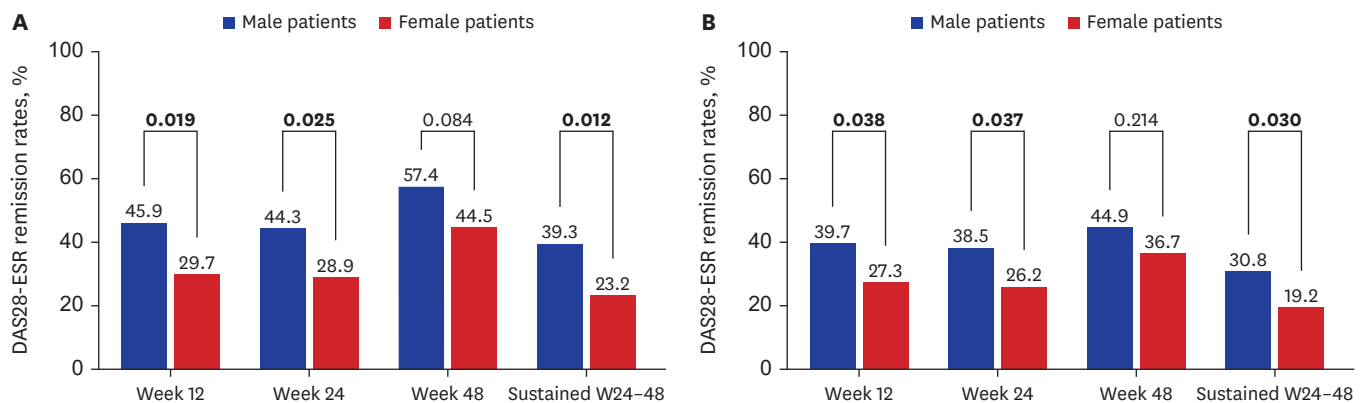


Fig. 1. Comparison of the 28-joint Disease Activity Score with erythrocyte sedimentation rate remission rates between male and female patients with rheumatoid arthritis. **(A)** Per-protocol analysis based on complete cases ($n = 414$). **(B)** Intention-to-treat analysis with non-responder imputation ($n = 506$). Remission rates are presented as percentages (%) and compared between groups using the χ^2 test. Bold text indicates statistically significant P values (< 0.05).

Table 2. Predictors of DAS28-ESR remission at week 24 following matching for disease duration and baseline disease activity (n = 443)

Variables of interest	Univariable analyses		Multivariable analysis	
	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Sex, male	1.72 (1.00–2.94)	0.048	2.76 (1.25–6.08)	0.012
Age, yr	1.00 (0.98–1.01)	0.827	1.00 (0.98–1.02)	0.978
BMI, kg/m ²	1.01 (0.95–1.06)	0.800		
Ever smoked	1.01 (0.61–1.68)	0.956	0.52 (0.25–1.08)	0.079
Alcohol use	0.94 (0.62–1.42)	0.767		
Diabetes mellitus	1.56 (0.78–3.12)	0.204	2.16 (0.82–5.71)	0.119
Hypertension	1.06 (0.68–1.66)	0.784		
Depressive symptoms	0.49 (0.29–0.82)	0.007	0.52 (0.30–0.91)	0.022
Fibromyalgia	0.50 (0.14–1.75)	0.274		
Charlson comorbidity index	0.91 (0.68–1.22)	0.541	0.72 (0.47–1.11)	0.136
RF or anti-CCP seropositivity	0.61 (0.30–1.26)	0.182	0.50 (0.24–1.08)	0.079
No. of csDMARDs, ever used	0.87 (0.72–1.06)	0.173	0.81 (0.66–1.00)	0.053
Initiating JAK inhibitors (ref. bDMARD)	0.99 (0.66–1.48)	0.954		
Good treatment compliance ^a	1.42 (0.44–4.55)	0.555		
Methotrexate	4.12 (0.91–18.70)	0.066	5.13 (1.07–24.60)	0.041
NSAID	0.78 (0.45–1.38)	0.396	0.63 (0.35–1.15)	0.135
Oral glucocorticoid	1.01 (0.54–1.89)	0.987		

Stratification variables used in the conditional logistic regression were rheumatoid arthritis duration (≤ 2 vs. > 2 years) and baseline disease activity (DAS28-ESR ≤ 5.1 vs. > 5.1). The multivariable conditional logistic regression model was constructed, incorporating sex, age, concomitant methotrexate use, and additional covariates selected through stepwise variable selection based on the Akaike information criterion.

DAS28 = Disease Activity Score 28-joint count, ESR = erythrocyte sedimentation rate, OR = odds ratio, CI = confidence interval, BMI = body mass index, RF = rheumatoid factor, CCP = cyclic citrullinated peptide, csDMARD = conventional synthetic disease-modifying anti-rheumatic drug, JAK = Janus kinase, bDMARD = biologic disease-modifying anti-rheumatic drug, NSAID = nonsteroidal anti-inflammatory drug.

^aTreatment compliance was considered good if patients missed < 15 doses over a 90-day period (96.4%; 427 of 443 patients).

After adjusting for covariates using stepwise variable selection in the multivariable model, male sex remained significantly associated with achieving DAS28-ESR remission (adjusted OR, 2.76; 95% CI, 1.25–6.08; $P = 0.012$). Depressive symptoms (adjusted OR, 0.52; 95% CI, 0.30–0.91; $P = 0.022$) and concomitant methotrexate use (adjusted OR, 5.13; 95% CI, 1.07–24.60; $P = 0.041$) were associated with poorer and better responses, respectively.

Treatment response based on DAS28-CRP, CDAI, and SDAI

Additionally, treatment response was evaluated using DAS28-CRP, CDAI, and SDAI. In the per-protocol analysis, male patients exhibited numerically higher remission rates than female patients across all disease activity indices (**Supplementary Fig. 3**); however, these differences were not statistically significant. At week 24, the DAS28-CRP remission rates were 60.7% and 51.0% for males and females, respectively; the CDAI remission rates were 14.8% and 12.2%, and the SDAI remission rates were 21.3% and 17.3%, respectively. Conditional logistic regression analyses revealed consistent trends indicating that male sex was associated with higher odds of achieving remission at week 24, as measured using DAS28-CRP (adjusted OR, 2.13; 95% CI, 0.97–4.69), CDAI (adjusted OR, 1.51; 95% CI, 0.65–3.47), or SDAI (adjusted OR, 1.71; 95% CI, 0.81–3.62); however, these associations did not reach statistical significance (**Table 3, Supplementary Table 1**).

Subgroup analysis

Subgroup analyses were conducted based on RA disease duration and the type of initial targeted therapy. At week 24, 60.9% and 36.9% of male and female patients with early RA achieved DAS28-ESR remission, respectively ($P = 0.061$) (**Supplementary Fig. 4**).

In contrast, the difference in remission rates between the sexes was smaller among patients with established RA (35.9% and 26.4% for males and females, respectively; $P = 0.294$).

Conditional logistic regression analysis revealed that male sex was associated with higher odds

Table 3. ORs for RA remission at week 24 in male versus female patients, after matching for disease duration and baseline disease activity (n = 443)

Variables	Univariable analyses		Multivariable analysis	
	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
DAS28-ESR	1.72 (1.00–2.94)	0.048	2.76 (1.25–6.08)	0.012
Early RA	2.66 (1.09–6.49)	0.032	11.59 (2.56–52.54)	0.001
Established RA	1.30 (0.65–2.61)	0.464	1.26 (0.62–2.59)	0.524
JAK inhibitors	2.48 (1.12–5.50)	0.025	2.37 (1.02–5.52)	0.045
bDMARD	1.30 (0.62–2.74)	0.483	1.37 (0.63–3.01)	0.427
DAS28-CRP	1.36 (0.80–2.30)	0.258	2.13 (0.97–4.69)	0.059
CDAI	1.23 (0.58–2.58)	0.589	1.51 (0.65–3.47)	0.337
SDAI	1.32 (0.70–2.50)	0.390	1.71 (0.81–3.62)	0.159

Stratification variables used in conditional logistic regression included RA duration (≤ 2 vs. > 2 years) and baseline disease activity (DAS28-ESR/CRP ≤ 5.1 vs. > 5.1 , CDAI ≤ 22 vs. > 22 , or SDAI ≤ 26 vs. > 26).

OR = odds ratio, RA = rheumatoid arthritis, CI = confidence interval, DAS28 = Disease Activity Score 28-joint count, ESR = erythrocyte sedimentation rate, JAK = Janus kinase, bDMARD = biologic disease-modifying anti-rheumatic drug, CRP = C-reactive protein, CDAI = Clinical Disease Activity Index, SDAI = Simplified Disease Activity Index.

of achieving DAS28-ESR remission at week 24 in patients with early RA (adjusted OR, 11.59; 95% CI, 2.56–52.54) (Table 3, Supplementary Table 2). This association was not statistically significant in patients with established RA (adjusted OR, 1.26; 95% CI, 0.62–2.59).

In similar subgroup analyses based on the type of initial targeted therapy, male sex was associated with higher odds of achieving DAS28-ESR remission at week 24 among patients who initiated JAK inhibitors (adjusted OR, 2.37; 95% CI, 1.02–5.52) (Table 3, Supplementary Table 2). In contrast, the predictive effect of male sex was not statistically significant among patients who started biologic DMARDs (adjusted OR, 1.37; 95% CI, 0.63–3.01).

DISCUSSION

In this study, male patients with RA achieved DAS28-ESR remission at week 24 and sustained remission through week 48 more frequently than female patients when initiating first-line targeted therapy. The odds of achieving remission were significantly higher in male patients than in female patients, even after adjusting for disease duration, baseline disease activity, and other baseline characteristics. Treatment response assessed using DAS28-CRP, CDAI, and SDAI also showed similar trends, although without statistical significance. The sex difference was particularly prominent among patients with early disease (≤ 2 years) and those initiating JAK inhibitors.

The characteristics of male and female patients who initiated their first targeted therapy in real-world settings differed in our cohort. Male patients were older and more frequently had a history of smoking, whereas female patients had a longer disease duration, higher disease activity at baseline, and more frequently had fibromyalgia than male patients. Such baseline characteristic differences might contribute to variations in treatment response.^{13-16,18} Moreover, female patients who experience delays in referral to rheumatologists^{25,26} or whose subjective symptoms are undervalued due to comorbidities such as fibromyalgia may also have poorer clinical responses.²⁷ To address potential confounding, we adjusted for these clinical factors to assess the independent effect of sex on treatment response and found that male sex was associated with higher odds of achieving remission, even after accounting for these baseline differences. These findings indicate that sex-related disparities in treatment response are influenced by multifactorial determinants, with sex itself being an important predictive factor to consider.

Previous studies have reported that female patients with RA achieve lower remission rates than male patients throughout the disease course.^{9,10,28,29} However, these studies included patients at varying disease stages and severity levels. In our study, we focused on patients initiating targeted therapy for the first time to better understand the predictive value of sex in this specific population with active disease. We observed that DAS28-ESR remission rates were significantly higher in male patients than in female patients at 6 months following the initiation of targeted therapy, and that sustained remission at 1 year showed similar pattern. Given that inherent ESR differences exist between sexes,³⁰ we also evaluated the individual components of DAS28-ESR, including ESR levels, between male and female patients and confirmed that ESR levels did not differ significantly. These findings suggest that the observed sex differences in DAS28-ESR remission rates reflect clinically meaningful differences in disease activity rather than confounding effects of physiological ESR variation between sexes.

Considering the recognized differences in the performance of composite disease activity measures between sexes,^{31,32} we also evaluated treatment responses based on DAS28-CRP, CDAI, and SDAI. Remission rates assessed by these indices were consistently higher in male patients than in female patients. The odds of achieving remission based on these indices were also higher in male patients, although they did not reach statistical significance owing to wide CIs. The small sample size of our study population, particularly the limited number of male patients, likely reduced the statistical power to detect significant differences. Future studies with larger cohorts are warranted to further investigate the association between sex and remission outcomes across various composite disease activity measures and to determine which measures best capture clinically meaningful sex differences in treatment response.

When patients were stratified by disease duration, the effect of male sex differed between those with early and established RA. Male patients within 2 years of RA diagnosis had higher odds of achieving remission than female patients with similar disease duration. However, this association was not observed in patients with longer disease duration. Our findings are consistent with previous large cohort studies reporting that men responded better to TNF inhibitors than women, particularly in the early stage of RA.^{17,33} In our subgroup analysis based on initial therapy, the effect of sex was more pronounced with JAK inhibitors than with biologic DMARDs; however, this difference was smaller than that observed between the disease-duration subgroups. Furthermore, the wide CIs associated with the ORs warrant cautious interpretation.

This study has several strengths. First, our real-world dataset included comprehensive clinical information, such as comorbidities and patient-reported factors (e.g., fibromyalgia and depressive symptoms), which allowed appropriate adjustment for potential confounding factors. Although the number of male patients was relatively small—reflecting the known female predominance in RA—the availability of detailed clinical data enabled meaningful statistical adjustments and the identification of sex as an independent predictor of remission. Second, we conducted a comprehensive evaluation of treatment responses using multiple established disease activity measures (DAS28-ESR, DAS28-CRP, CDAI, and SDAI), providing a more thorough understanding of treatment outcomes in patients with RA. In addition, subgroup analyses stratified by disease duration and class of treatment offered important insights into how sex differences may vary across different disease stages and treatment modalities in RA.

Some limitations should also be considered when interpreting our findings. First, as a post hoc analysis, inherent biases related to patient selection and treatment decisions may exist. The original study was designed to compare biologic DMARDs and JAK inhibitors, rather than to examine sex-related differences. Therefore, the possibility of selection bias and unmeasured confounding factors should be acknowledged. Second, the relatively small number of male patients reduces statistical power, and the wide CIs observed in the subgroup analyses warrant cautious interpretation. Third, our study population consisted of patients initiating targeted therapy for the first time, which may not fully represent all patients with RA.

In conclusion, this study demonstrates sex-related differences in treatment response to targeted therapy in RA. While male patients achieved higher remission rates overall, the magnitude of this difference was greatest in early disease. These findings underscore the importance of personalized treatment strategies that account for both sex and disease stage.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

DAS28-CRP, CDAI, and SDAI remission at week 24 after matching by disease duration and activity (n = 443)

Supplementary Table 2

DAS28-ESR remission at week 24 after matching by disease duration and activity in various subgroups (n = 443)

Supplementary Fig. 1

Flowchart of patient follow-up.

Supplementary Fig. 2

Longitudinal changes in DAS28-ESR and its individual components.

Supplementary Fig. 3

Comparison of remission rates based on DAS28-CRP, CDAI, and SDAI.

Supplementary Fig. 4

Comparison of DAS28-ESR remission rates in various subgroups.

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