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Original Article

Implications of Persistent Pain in Patients With Rheumatoid Arthritis Despite Remission Status: Data From the KOBIO Registry

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Objective: This study aimed to assess the prevalence of pain in patients with RA in clinical remission and analyze the demographic and clinical characteristics of those who experienced persistent pain despite remission status.

Methods: Data from 1,891 patients with RA registered on the Korean College of Rheumatology Biologics and Targeted Therapy registry were obtained. Remission was defined as a Disease Activity Score of 28 joints-erythrocyte sedimentation rate (ESR) <2.6. Pain intensity was classified as severe (pain visual analog scale [VAS] ≥7), moderate (4≤VAS<7), or mild (VAS <4).

Results: Our analysis showed that 52.6% of patients complained of severe pain at the start of or during switching biological disease-modifying anti-rheumatic drugs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs). Despite having a 36.0% (n=680) remission rate after the use of bDMARDs or tsDMARDs at their 1-year follow-up, 21.5% (n=146) of these patients had moderate-to-severe pain, higher frequency of foot erosions, and comorbidities, such as mental illness, endocrine, renal, and neurological disorders, than patients with a milder degree of pain. The multivariable regression analysis showed that presence of foot erosions, neurological disorders, and use of corticosteroids were independently associated with moderate-to-severe pain in patients with RA despite being in remission. The level of ESR and use of Janus kinase inhibitors were inversely associated with moderate-to-severe pain.

Conclusion: Persistent pain and discomfort continue to be a problem for patients with RA in clinical remission. Continued research on insistent pain in patients with RA is warranted to better alleviate distress and improve the quality of life in patients.

Keywords: Biologics, Disease modifying antirheumatic drugs, JAK inhibitors, Pain, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the destruction of synovial joints and systemic inflammation. Initial symptoms include joint pain, fatigue, and stiffness; and if inappropriately managed, can lead to joint damage, reduced function, and impaired quality of life [1]. The emergence of biological or targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs or tsDMARDs) have contributed to the recent improvements in the treatment of RA, and recommended treatments have evolved to focus on a targeted approach to achieve either remission or low disease activity. There has been a dramatic improvement in outcomes of RA treatment with the introduction of bDMARDs or tsD-

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MARDs and a targeted approach [2,3]. However, patient-reported symptoms, such as pain and fatigue, may persist despite RA remission, with the experience of pain among the top three complaints, alongside functional disability and fatigue [4]. Approximately 40% and 51.6% of patients treated with bDMARDs and tsDMARDs, respectively, complain of significant pain [5]. After 6 months of the targeted approach in patients with early RA, 40.2% of patients reported unsatisfactory pain relief, which was defined as a subjective improvement <3 points on the visual analog score (VAS) for pain [6]. The prognostic factors for achieving a satisfactory improvement in pain were symmetrical joint involvement, positivity for anti-citrullinated protein antibody (anti-CCP Ab), and fewer tender joints at baseline [6].

This study assessed the pain prevalence in patients with RA in clinical remission (according to the Disease Activity Score of 28 joints-erythrocyte sedimentation rate [DAS28-ESR]) and analyzed the demographic and clinical characteristics of those who experienced persistent pain.

MATERIALS AND METHODS

Study population

The Korean College of Rheumatology Biologics and Targeted Therapy (KOBIO) registry is a nationwide, multicenter, prospective, web-based observational cohort that was launched in 2012 [2,7]. For our study, we selected adults (>18 years) from the KOBIO registry's RA group who met the 1987 American College of Rheumatology (ACR) or 2010 ACR/European League Against Rheumatism (EULAR) RA classification criteria that either had bDMARD or tsDMARD or switched to another drug [8,9]. These patients underwent follow-up assessments by individual investigators at 12-month intervals. DAS28-remission was defined as a DAS28-ESR <2.6. To determine remission rates, patients who were followed up for 1 year were included. Ethics approval for this study and the use of the KOBIO Registry was provided by the Institutional Review Boards (IRB) of the researchers' affiliated hospitals and all 58 participating institutions (AJIRB-MED-MDB-21-684), respectively. The study was conducted in compliance with the principles of the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

Data collection

Medical information was obtained from data uploaded to the KOBIO web server (http://www.rheum.or.kr/kobio/) [2]. Clinical characteristics, such as age, sex, body weight, height, body mass index, smoking habits, comorbidities, previous or current medications, and laboratory tests, such as rheumatoid factor, anti-CCP Ab, ESR, and C-reactive protein (CRP), were collected. The number of tender and swollen joints, pain (VAS) score, and patient's and physician's global assessment (GA) were evaluated at the start of bDMARD or tsDMARD treatment or when the regimen was switched and at each annual follow-up. Quantitative measurements of RA disease activity, such as the DAS28 based on ESR and CRP levels and clinical disease activity index (CDAI), were calculated using the obtained data. Pain intensity was classified as severe (VAS≥7), moderate (4≤VAS<7), or mild (VAS<4). The Routine Assessment of Patient Index Data 3 (RAPID3) and EuroQol (EQ)-VAS score were used to measure the patient's functional capacity and quality of life relative to their pain, respectively. Comorbidities were defined as other chronic episodic disorders, classified as cardiovascular, neurological, pulmonary, endocrine, renal, gastrointestinal, and viral/infectious disorders, drug abuse/dependence, mental illness, and hematology and oncology in KOBIO [2]. Cardiovascular disorders include hypertension, ischemic heart disease, hyperlipidemia, congestive heart failure, cardiac arrhythmias, peripheral vascular disorder, and stroke. Neurological disorders include headache, migraine, and other neurologic disorders. Pulmonary disorders include restrictive or interstitial lung disease, chronic obstructive pulmonary disease, and asthma. Endocrine disorders include osteoporosis, diabetes, hyperthyroidism, hypothyroidism, obesity, and weight loss. Renal disorders include renal failure and fluid or electrolyte disorders. Gastrointestinal disorders include peptic ulcer and liver diseases. Viral/infectious disorders include tuberculosis, hepatitis B or C, and human immunodeficiency virus infection. Mental illnesses include depression and psychosis. Hematology and oncology include anemia, hematologic malignancy, solid tumors without metastasis, and metastatic cancer.

Statistical analysis

Patient baseline characteristics were analyzed using descriptive statistics, and data are presented as the mean±standard deviation or the median with interquartile range. Categorical variables were compared using the chi-squared test or Fisher's exact test, and continuous variables were analyzed using the independent t-test or Mann–Whitney U-test. The association between

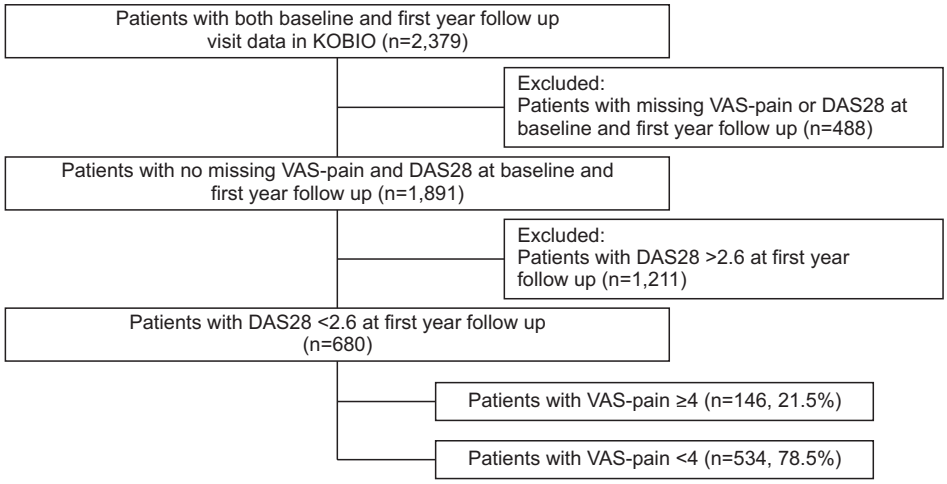

Figure 1. Inclusion of patients in the study. KOBIO: Korean College of Rheumatology Biologics and Targeted Therapy, VAS: visual analog scale, DAS28: disease activity score of 28 joints.

Table 1. Clinical characteristics of enrolled patients at 1 year follow-up

Characteristics	All patients with DAS28 <2.6 at first year follow up (n=680)	Patients with DAS28 <2.6 and VAS-pain ≥4 (n=146)	Patients with DAS28 <2.6 and VAS-pain <4 (n=534)	p-value
Age (yr)	53.6±12.9	55.4±13.5	53.7±12.8	0.059
Female	553 (81.3)	121 (82.9)	432 (80.9)	0.587
Marital status, married	602 (88.5)	126 (86.3)	476 (89.1)	0.340
Smoking history				0.986
Ex-smoker	63 (9.3)	13 (8.9)	50 (9.3)	
Current smoker	42 (6.2)	9 (6.2)	33 (6.2)	
Never	575 (84.5)	124 (84.9)	451 (84.5)	
BMI (kg/m^2)*	22.7 (20.5~24.9)	22.7 (20.3~25.0)	22.7 (20.7~24.9)	0.407
Disease duration (yr)	9.4±7.4	11.1±9.0	8.9±6.8	0.012
Tender joint count*	0.5±1.1	0.7±1.3	0.4±1.0	<0.001
Swollen joint count*	0.3±0.8	0.3±0.8	0.3±0.8	0.008
ESR (mm/h)*	6.0 (2.0~13.0)	4.0 (2.0~9.8)	7.0 (2.0~14.0)	<0.001
CRP (mg/dL)*	0.1 (0.0~0.2)	0.1 (0.0~0.1)	0.1 (0.0~0.2)	0.372
Rheumatoid factor (positivity) (n=589)	467/589 (79.3)	93/120 (77.5)	374/469 (79.7)	0.588
Anti-CCP antibody (positivity) (n=443)	363/443 (81.9)	72/89 (80.9)	291/354 (82.2)	0.775
Physician's GA*	2.0 (1.0~3.0)	3.0 (2.0~4.0)	2.0 (1.0~3.0)	<0.001
Patient's GA*	2.0 (1.0~3.0)	4.0 (3.0~5.0)	2.0 (1.0~3.0)	<0.001
CDAI*	4.0 (3.0~7.0)	8.0 (6.0~10.0)	4.0 (2.0~6.0)	<0.001
EQ-VAS (n=63)*	3.0 (2.0~4.0)	6.0 (5.8~7.0)	3.0 (2.0~3.0)	<0.001
RAPID3*	5.3 (3.0~8.7)	12.0 (9.4~14.7)	4.3 (2.4~6.3)	<0.001
Presence of hand erosions (n=352)	117/352 (33.2)	24/73 (32.9)	93/279 (33.3)	0.941
Presence of foot erosions (n=246)	88/246 (35.8)	28/53 (52.8)	60/193 (31.1)	0.003

Data are presented as number (%), mean±standard deviation, or median (interquartile range), unless otherwise indicated. DAS28: disease activity score of 28 joints, VAS: visual analog scale, BMI: body mass index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, CCP: cyclic citrullinated peptide, GA: global assessment, CDAI: clinical disease activity index, EQ-VAS: EuroQol visual analog scale, RAPID3: routine assessment of patient index data 3. Continuous data were assessed by independent t-test and categorical data were analyzed by chi-square test. *These data were assessed by Mann–Whitney U-test.

clinical characteristics and pain VAS after one year of treatment with bDMARDs or tsDMARDs was assessed using a univariable and multivariable logistic regression model. Variables, such as Physician's GA, patient's GA, CDAI, EQ-VAS, and RAPID3, were excluded in the analysis of univariate and multivariate logistic regression model, because these were variables that might interact with the pain VAS. All statistical analyses were performed using SPSS version 25.0 (IBM Co., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The data from 2,379 patients with RA who were registered in the KOBIO registry from December 2012 to September 2020 were obtained. Among them, 1,891 patients completed the 1-year assessment. Our analysis showed that 995 (52.6%) patients complained of severe pain (VAS≥7) at the start of or during switching bDMARDs or tsDMARDs. After treatment with bDMARDs or tsDMARDs, the proportion of patients who achieved DAS28-remission in the first year was 36.0% (n=680). Patients with DAS28 ≥2.6 (n=1,211) at the 1-year follow-up were excluded from this study (Figure 1). Among the patients who achieved DAS28-remission, 21.5% (n=146; mean age, 55.4±13.5 years; 82.9% were female; Table 1) complained of moderate-to-severe pain (VAS pain≥4). Their disease duration (11.1±9.0 years) was longer than that of patients with a lower degree of pain (8.9±6.8 years, p=0.012). The marital status of the

Table 2. Current medication, extraarticular manifestations, and comorbidities of enrolled patients

Characteristics	All patients with DAS28 <2.6 at first year follow up (n=680)	Patients with DAS28 <2.6 and VAS-pain ≥4 (n=146)	Patients with DAS28 <2.6 and VAS-pain <4 (n=534)	p-value
Previous treatment				
Prior use of methotrexate	579 (85.1)	117 (80.1)	462 (86.5)	0.055
Prior use of bDMARDs or tsDMARDs	159 (23.4)	45 (30.8)	114 (21.3)	0.017
Current treatment				
bDMARDs or tsDMARDs				0.001
Anti-TNF	270 (39.7)	53 (36.3)	217 (40.6)	
Rituximab	3 (0.4)	0 (0.0)	3 (0.6)	
Tocilizumab	294 (43.2)	82 (56.2)	212 (39.7)	
Abatacept	63 (22.5)	7 (4.8)	56 (10.5)	
JAKis	50 (7.4)	4 (2.7)	46 (8.6)	
Corticosteroid use	444 (65.3)	116 (79.5)	328 (61.4)	<0.001
Concomitant cDMARDs use	598 (87.9)	126 (86.3)	472 (88.4)	0.492
Comorbidities*				
Cardiovascular disorders	296 (43.5)	72 (49.3)	224 (41.9)	0.112
Neurological disorders	16 (2.4)	8 (5.5)	8 (1.5)	0.005
Pulmonary disorders	31 (4.6)	5 (3.4)	26 (4.9)	0.458
Endocrine disorders	263 (38.7)	67 (45.9)	196 (36.7)	0.043
Renal disorders	6 (0.9)	4 (2.7)	2 (0.4)	0.021
Gastrointestinal disorders	23 (3.4)	5 (3.4)	18 (3.4)	0.975
Viral/infectious disorders	28 (4.1)	7 (4.8)	21 (3.9)	0.642
Drug abuse/dependence	1 (0.1)	0 (0.0)	1 (0.2)	0.999
Mental illness	14 (2.1)	6 (4.1)	8 (1.5)	0.049
Hematology & Oncology	152 (22.4)	33 (22.6)	119 (22.3)	0.935

Data are presented as number (%). DAS28: disease activity score of 28 joints, VAS: visual analog scale, bDMARDs: biologic disease modifying anti-rheumatic drugs, tsDMARDs: targeted synthetic DMARDs, TNF: tumor necrosis factor, JAKis: janus kinase inhibitors, cDMARDs: conventional DMARDs. *These data were assessed by chi-square test or Fisher exact test due to low frequency.

population with moderate-to-severe pain was similar (86.3% vs. 89.1%, p=0.340). The patients with moderate-to-severe pain had a higher frequency of foot erosions than that of patients with a lower degree of pain (52.8% vs. 31.1%, p=0.003). The median physician's and patient's GA, CDAI, EQ-VAS, and RAPID3 scores of patients with moderate-to-severe pain were higher than those of patients with a lower degree of pain. However, the ESR of the patients with moderate-to-severe pain was lower than that of patients with a lower degree of pain (p<0.001).

Table 2 shows the previous and current medications and comorbidities of patients that achieved DAS28-remission, and the difference in the proportions of bDMARD or tsDMARDs prescribed between the two groups. The proportion of patients who had prior use of bDMARDs or tsDMARDs was higher in the moderate-to-severe pain (30.8%) group than those with mild pain (21.3%, p=0.017). In patients with moderate-to-severe pain, the most frequently prescribed DMARDs were tocilizumab (56.2%), anti-tumor necrosis factor (TNF) agents (36.3%), and abatacept (4.8%), whereas for patients with mild pain, the most frequently prescribed DMARDs were anti-TNF agents (40.6%), tocilizumab (39.7%), and abatacept (10.5%). The frequency of corticosteroid use was higher in the moderate-to-severe pain (79.5%) group than those with mild pain (61.4%, p<0.001). Despite clinical remission, the moderate-to-severe pain population had a higher frequency of comorbidities such as neurological, endocrine, and renal disorders, and mental illness than those with a milder degree of pain.

Baseline clinical characteristics of the enrolled patients at the start of or during switching bDMARD or tsDMARDs are shown in Supplementary Tables 1 and 2.

Factors associated with moderate-to-severe pain

The results of the logistic regression analysis for the risk factors of moderate-to-severe pain are presented in Table 3. Univariable logistic regression analysis indicated that the presence of foot erosion (odds ratio [OR] 1.87, 95% confidence interval [CI] 1.146~3.065, p=0.012) and comorbidities, such as neurological (OR 3.81, 95% CI 1.405~10.338, p=0.009), endocrine (OR 1.46, 95% CI 1.010~2.117, p=0.044), and renal disorders (OR 7.49, 95% CI 1.359~41.323, p=0.021), were significantly associated with moderate-to-severe pain. Corticosteroid use was significantly associated with moderate-to-severe pain, with an OR of

Table 3. Predictors of moderate-to severe pain despite achieving DAS28 remission

Variable	Univariable regression analysis				Multivariable regression analysis			
	OR	95% CI		p-value	OR	95% CI		p-value
		Lower	Upper			Lower	Upper	
Presence of foot erosions	1.87	1.146	3.065	0.012	2.14	1.240	3.696	0.006
Neurological disorders	3.81	1.405	10.338	0.009	3.93	1.342	11.482	0.013
Endocrine disorders	1.46	1.010	2.117	0.044	1.48	0.988	2.229	0.057
Renal disorders	7.49	1.359	41.323	0.021	4.08	0.690	24.102	0.121
Mental illness	1.48	0.456	4.776	0.516				
Corticosteroid use	2.43	1.568	3.762	<0.001	2.37	1.489	3.775	<0.001
Prior use of bDMARDs or tsDMARDs	1.64	1.092	2.468	0.015	1.55	0.983	2.438	0.060
Current biologic agents or JAKis (reference: anti-TNF agents)								
Rituximab	1.72×10^{-06}	0	Inf	0.979				
Tocilizumab	1.95	1.344	2.817	<0.001	0.95	0.605	1.497	0.832
Abatacept	0.43	0.192	0.964	0.041	0.42	0.171	1.005	0.051
JAKis	0.30	0.106	0.844	0.023	0.26	0.086	0.809	0.020
Disease duration	1.04	1.014	1.062	0.002	1.02	0.996	1.048	0.105
Tender joint count	1.24	1.070	1.441	0.004	1.17	0.988	1.373	0.069
Swollen joint count	1.14	0.930	1.404	0.204				
ESR	0.94	0.916	0.972	<0.001	0.95	0.918	0.983	0.003

DAS28: disease activity score of 28 joints, OR: odds ratio, CI: confidence interval, bDMARDs: biologic disease modifying anti-rheumatic drugs, tsDMARDs: targeted synthetic DMARDs, JAKis: Janus kinase inhibitors, TNF: tumor necrosis factor, ESR: erythrocyte sedimentation rate.

2.43 (95% CI 1.568~3.762, p<0.001). Prior use of bDMARDs or tsDMARDs was associated with moderate-to-severe pain, with an OR of 1.64 (95% CI 1.092~2.468, p=0.015). In comparison with anti-TNF agents, abatacept (OR 0.43, 95% CI 0.192~0.964, p=0.041) and Janus kinase inhibitors (JAKis) (OR 0.30, 95% CI 0.106~0.844, p=0.023) had a lesser likelihood of eliciting moderate-to-severe pain, but tocilizumab (OR 1.95, 95% CI 1.344~2.817, p<0.001) was associated with moderate-to-severe pain. Furthermore, tender joint count was significantly associated with moderate-to-severe pain (OR 1.24, 95% CI 1.070~1.441, p=0.004), but ESR had a lesser likelihood of eliciting moderate-to-severe pain (OR 0.94, 95% CI 0.916~0.972, p<0.001).

In the multivarible regression analysis, presence of foot erosions (OR 2.14, 95% CI 1.240~3.696, p=0.006), and neurological disorders (OR 3.93, 95% CI 1.342~11.482, p=0.013) were independently associated with moderate-to-severe pain despite remission status. Corticosteroid use (OR 2.37, 95% CI 1.489~3.775, p<0.001) was associated with moderate-to-severe pain. Patient using of JAKis (OR 0.26, 95% CI 0.086~0.809, p=0.020) and had higher ESR levels (OR 0.95, 95% CI 0.918~0.983, p=0.003) had a lesser likelihood of having moderate-to-severe pain.

DISCUSSION

In this study, the proportion of patients who achieved DAS28-remission in the first year after using either bDMARDs or tsDMARDs was 36.0% (n=680). Among them, 21.5% (n=146) had moderate-to-severe pain, longer disease duration, and higher frequency of foot erosion, mental illness, and endocrine, renal, and neurological comorbidities than patients with a milder degree of pain. Further evaluation with multivariable regression analysis showed that the presence of foot erosions and neurological disorders were independently associated with moderate-to-severe pain in patients with RA despite clinical remission. Corticosteroid use was associated with moderate-to severe pain, in contrast, patients using JAKis and had higher ESR levels had a lesser likelihood of having moderate-to-severe pain.

Pain is generally considered a surrogate marker of inflammatory disease activity in RA [10]; and is not only the single dominant determinant of patient's GA, but also a prominent component of the ACR/EULAR criteria for remission [11,12]. In our study, multiple regression data showed that the presence of foot erosions was a predictor of moderate-to-severe pain, although ESR levels had a lesser likelihood of eliciting moderate-to-severe pain. This result may be related to the fact that DAS28 does not include the feet, and indicates that disease control beyond the 28 joints is also important for proper pain control in patients with RA. In terms of the inverse association between ESR and moderate-to-severe pain, we can consider the following. First, it seems questionable whether the clinical implication of ESR in predicting pain is meaningful when the mean levels of ESR in both groups were below 10 mm/hr. Second, corticosteroid use, which was an independent factor for predicting moderate-to-severe pain, could have affected the ESR value leading to the inverse association. And third, tocilizumab was prescribed more frequently in patients with moderate-to-severe pain (56.2% vs. 39.7%), which could have resulted in a lower mean level of ESR at remission than patients with a milder degree of pain.

Persistent pain is not always relative to inflammatory conditions, whereby persistent pain in RA is a complex and multifactorial phenomenon linked to central pain mechanisms such as central and peripheral sensitization as well as peripheral (neurogenic) inflammation [5,13]. A previous study identified clusters of patients with RA with different causes of pain, treatment options, and prognoses, and found three subgroups of patients based on pain, inflammation, fatigue, and psychological distress [14]. One subgroup showed minimal inflammation but high levels of pain, psychosocial distress, and fatigue. Indeed, the prevalence of comorbid fibromyalgia in populations with RA is significantly higher than that in the general population, with pooled prevalence estimates of 18%~24% [15]. Central sensitization and fibromyalgia may explain the disconnect between persistent pain and improved inflammation in pain in RA [15,16]. However, since the KOBIO study did not accurately collect data regarding fibromyalgia, anxiety, and depression, this study could not evaluate the association between pain and these components.

This study showed that the moderate-to-severe pain population had a higher frequency of comorbidities, such as neurological, endocrine, and renal disorders, than those with a milder degree of pain despite clinical remission. In the univariable regression analysis, comorbidities, such as neurological, endocrine, and renal disorders, were associated with moderate-to-severe pain in patients with RA. Further evaluation with multivariable regression analysis showed that neurological disorders with an OR of 3.93 were independently associated with moderate-to-severe pain in patients with RA despite clini-

cal remission. These results are consistent with a previous study that showed that patients with chronic pain had a higher prevalence of comorbidities [17]. A significantly higher prevalence of comorbidities and up to four times the OR of multimorbidity in the chronic pain group compared to those in the non-chronic pain group was demonstrated [17]. Furthermore, a recent study evaluated contributing factors in difficult-to-treat patients with RA and showed that several contributing factors, such as limited drug options related to adverse events, comorbidities, and concomitant fibromyalgia, were independently associated with difficult-to-treat RA [18]. Therefore, our results, as with previous studies, suggest that it may be important to manage comorbidities as well as treat disease activity for pain control in patients with RA. However, further research to support that pain in patients with RA improves when comorbidities are well-managed is needed.

Immune cells and their mediators, including pro-inflammatory cytokines, have been identified as important contributors to various types of pain [19]. RA treatment, including both bDMARDs and tsDMARDs with cytokine-blocking effects, may have pain-reducing effects independent of their anti-inflammatory effects [20,21]. Recent reports have shown that patients with RA treated with JAKis significantly achieved improvements in pain over those treated with anti-TNF, although standard clinical measures and markers of inflammation were similarly improved in both treatment groups [21]. In this study, there was a difference in the proportions of bDMARD or tsDMARDs prescribed to patients with moderate-to-severe pain and those with mild or no pain. Considering the proportion of prescribed DMARDs for mild and moderate-to-severe pain and that JAKis were observed on multivariate analysis to have a lesser likelihood to eliciting moderate-to-severe pain despite remission status, it is suggestive of different mechanisms for each anti-cytokine drug resulting in different pain control, and that even if DAS28-remission is reached, pain control may differ depending on the drug used. However, in-depth etiopathological mechanisms or comparative clinical studies that identify the effect of both bDMARDs and tsDMARDs on pain in RA have not been conducted, and further research is needed to support this suggestion.

This study has some limitations. First, as fatigue, anxiety, and depression were not quantitatively assessed in the KOBIO registry, we could not analyze the relationship between pain and these conditions. Second, we could not assess how fibromyalgia affected pain in these populations. Third, this study was cross-sectional and did not assess pain fluctuations over time. However, this study presents real-world data in patients with RA treated with both bDMARDs and tsDMARDs, and data on factors influencing pain were evaluated in patients with RA in remission. Furthermore, this study recommends the evaluation of the cause of pain from various angles in patients with RA and formulation of a new therapeutic plan for these patients. Further prospective studies from multiple centers will provide a better understanding of pain in patients with RA and development of therapeutics targeting pain.

CONCLUSION

Persistent pain and discomfort continue to be a problem for many patients with RA in clinical remission. Irrespective of the increase in remission rate after the use of bDMARDs and tsDMARDs, pain that affects the quality of life cannot be easily eliminated. Therefore, continued research on insistent pain in patients with RA is warranted to better alleviate distress and improve the quality of life in patients.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.22.0005.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

H.-A.K. and K.S. contributed to the study design and data

collection, analysis, and interpretation. S.-Y.P. contributed to the data collection and/or data interpretation. All authors revised the manuscript and gave final approval for submission.

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