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DO BIOLOGICAL THERAPIES HAVE ANY EFFECT ON NEUROPATHIC PAIN IN RHEUMATOID ARTHRITIS? WHAT ARE THE RELATED FACTORS?

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Abstract

Aim: The objective of this study was to investigate the frequency of neuropathic pain (NeP) in patients with rheumatoid arthritis (RA) who are receivers and non-receivers of biological treatment. The secondary objective of our study was to identify NeP-related factors in RA.

Material and Methods: This was a sectional case–control study that measured the frequency of NeP using painDETECT (pDETECT) in patients with RA being monitored in our rheumatology outpatient clinic and in the control group. In addition, along with the demographic data of the patients, the disease activity score in 28 joints calculated with C-reactive protein (DAS28-CRP), visual analog scale (VAS) pain, VAS fatigue, Beck depression index, Beck anxiety index, health assessment questionnaire, and RA quality of life index were used.

Results: A total of 105 patients with RA (60 biological, 45 conventional treatment) and 106 healthy controls were enrolled in the study. According to pDETECT, NeP was n=15 (7.1%), n=9 (4.3%), and n=13 (6.2%) in the Biological disease-modifying antirheumatic drugs (bDMARD), non-receivers, and control groups, respectively. There was no statistical difference between groups who were bDMARD receivers and non-receivers ($p>0.05$). There was a moderate positive correlation between pDETECT and RA duration ($r=0.363$), VAS pain score ($r=0.594$), VAS fatigue score ($r=0.589$), DAS28-CRP score ($r=0.489$), Beck depression index ($r=0.402$), Beck anxiety index ($r=0.606$), erythrocyte sedimentation rate (ESR) value ($r=0.226$), and tender joint count (TJC) ($r=0.367$) ($p<0.05$).

Conclusion: NeP is commonly observed in patients with RA, and treatment with bDMARDs did not change the frequency of NeP. A positive correlation was observed between NeP and RA disease duration, DAS28-CRP, VAS pain, VAS fatigue, Beck depression index, Beck anxiety index, ESR, and TJC. When measuring disease activity in patients with RA, NeP should not be ignored.

Keywords: Biological treatment, neuropathic pain, painDETECT, rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common chronic inflammatories arthritides and leads to deformity and disability due to widespread joint involvement and damage. RA causes extra-articular involvement and systemic comorbidities and may shorten life span. In recent years, the use of biological medicines for RA has ensured a more efficient treatment of the disease (1). Approximately 90% of patients present to the physician with severe pain. Pain in RA manifests through different mechanisms, such as inflammatory, degenerative, central, and peripheral sensitization. Although conventional or biological or targeted disease-modifying agents [conventional disease-modifying antirheumatic drugs (cDMARDs)/biologic disease-modifying antirheumatic drugs (bDMARD)/ targeted synthetic disease modifying antirheumatic drugs (tsDMARD)] suppress the inflammatory activity, decreasing the progression of RA, they are often inadequate in relieving the pain entirely, which causes a decrease in the quality of life of patients (2,3).

Pain in RA is generally accepted as peripheral nociceptive pain originating from structures like synovium. The response of peripheral and central neurons increases in response to the inflammatory event and may continue after the inflammation resolves. This hypersensitivity may cause chronic pain originating from the central nervous system. This condition may manifest itself as increased neuropathic pain (NeP) in RA patients (4). Apart from central nervous system sensitization (nociplastic pain), NeP may manifest itself due to different causes like entrapment neuropathy, peripheral neuropathy, and small fiber neuropathy. The prevalence of NeP in rheumatoid diseases varies between 3% and 50% in different studies, and this proportion is higher than the NeP proportion in patients with chronic pain. The prevalence of NeP has been reported to be approximately 20% in RA (5). Pain due to NeP in patients with RA does not respond well to anti-inflammatory medicines and medicines like opioids. In addition, the presence of NeP may cause a higher manifestation of disease activity in RA (5,6).

Biological therapies like anti-tumor necrosis factor alpha (tumor necrosis factor) used in the treatment of RA are effective in controlling disease activity and reducing pain. However, over the course of years, even though the inflammatory activity does not increase, the severity of the pain can intensify, and bDMARDs are inadequate in patients with RA who have high sensitivity to pain (6,7). However, in some studies, it has been demonstrated that medicines like anti-tumor necrosis factor (anti-TNF) can decrease peripheral NeP and hyperalgesia (8-10). Again, bDMARDs and tsDMARDs have been shown to decrease chronic pain in RA, however, with which mechanisms this happens and via which nociceptive, neuropathic, or oncoplastic pathways they demonstrate efficacy could not have been explained (11). Our objective in this study was to investigate whether there is a difference in NeP frequency between RA patients who receive bDMARDs and those who do not. Our secondary objective was to identify NeP-related factors in patients with RA in the investigated population.

MATERIALS AND METHODS

Our study was conducted between June 2021 and December 2021 and enrolled 105 patients who were monitored in the rheumatology outpatient clinic and had a diagnosis of RA according to the American College of Rheumatology (ACR)/ European League Against Rheumatism 2010 or ACR 1987 classification criteria and 106 healthy control group participants whose age and gender corresponded to the RA patients. This is a sectional case–control study in which patients aged >18 years who fulfilled the criteria and accepted to participate in the trial were recruited. Patients with neurological diseases, history of spinal surgery, and endocrinological diseases, such as diabetes mellitus (DM), that may cause NeP, who use drugs for NeP, pregnant women, patients with cancer, and patients with active infection were excluded from the study. Demographic data, clinical and laboratory data regarding the disease, tobacco use, additional diseases, medications used, and body mass index (BMI) were identified, and planned measurements with regard to the study were performed.

RA disease activity was calculated using disease activity score 28 (DAS28-CRP). Additionally, visual analog scale (VAS) pain score, VAS fatigue score, health assessment questionnaire (HAQ), RA quality of life index, Beck depression index, and Beck anxiety index were measured. The painDETECT (pDETECT) scoring system was used to assess NeP. As per pDETECT, 0-12, 13-18, and >18 were accepted as no NeP; the result was unidentified, but the NeP component was found and the NeP presence was observed.

Statistical Analysis

Compliance of data with normal distribution in the statistical method was evaluated with Kolmogorov-Smirnov test, and a normal distribution of data was detected. The independent t-test was used to compare two independent groups with normal distribution. Comparisons of more than two groups were made using the One-Way Analysis of Variance test. Correlations between variables were examined using Spearman's rho coefficient. Median ± standard deviation, minimum and maximum values were given for numeric variables as descriptive statistics, and number and percentage were given for categorical variables.

SPSS for Windows version 23.0 software package was used for statistical analyses, and $p<0.05$ was accepted as statistically significant.

The study was approved by the Hatay Mustafa Kemal University Non-Interventional Clinical Research Ethics Committee. Signed informed consent forms were obtained from the patients participating in the study. (approval number: 05, date: 01.07.2021).

RESULTS

One hundred-five patients diagnosed with RA who fulfilled the study criteria were enrolled in the study. Of these patients, 60 were bDMARD receivers and 45 were non-receivers. The average ages of the patients who were in the groups of receivers and non-receivers of bDMARD and the control group were 51.2 (min. 21–max. 77), 53.6 (min. 20–max. 77), and 46.8 (min. 24–max. 83), respectively, and there was no difference between the groups ($p>0.005$). 78% of the study participants were female and 22% were male; 22.3% were smokers; BMI values were 27.9, 27.6, and 27.1 in RA patients who received and did not receive biological medicine and in the control group, respectively. No significant difference was observed between the BMI averages in the groups. The demographic data of the patient and control groups are presented in Table 1. According to pDETECT, NeP was n=15 (7.1%) in the bDMARD group, n=9 (4.3%) in the group not receiving bDMARD, n=13 (6.2%) in the control group. There was no statistical difference between bDMARD and non-receivers ($p>0.05$) (Table 1).

Average values in patients who were receivers and non-receivers of bDMARD were observed as follows, respectively; disease duration 13.6 and 8.7, VAS pain 5.6 and 4.6, VAS fatigue 5.3 and 4.2, DAS28-CRP 3.4 and 3.3, CRP 13.5 and 11.6, swollen joint count 2.4 and 2.8, tender joint count (TJC) 3.5 and 3.2, erythrocyte sedimentation rate (ESR) in both groups 22.6, Beck anxiety index 15.9 and 15.3, Beck depression index 11.7 and 11.9, HAQ score 11.1 and 10.0, RA quality of life index 13.4 and 11.8. Compared with the control group, there was a significant difference in the average scores of the RA quality of life index ($p=0.000$), HAQ score ($p=0.003$), pDETECT ($p=0.000$), CRP ($p=0.008$), ESR ($p=0.007$), DAS28-CRP ($p=0.00$), VAS fatigue ($p=0.02$), and VAS pain ($p=0.00$). There were no significant differences between Beck's depression index ($p=0.094$) and BMI ($p=0.570$) (Table 2).

A moderate positive correlation was observed between pDETECT and RA duration ($r=0.363$), VAS pain score ($r=0.594$), VAS fatigue score ($r=0.589$), DAS28-CRP score ($r=0.489$), Beck depression index ($r=0.402$), Beck anxiety index ($r=0.606$), and ESR value ($r=0.226$). In addition, there was a moderate positive correlation between pDETECT and TJC, and TJC increased as the pDETECT score increased ($p<0.05$). A moderately negative correlation was observed between pDETECT and RA in terms of the number of medicines used ($r=-0.344$ and $p<0.05$). On the other hand, no significant difference was observed between BMI and pDETECT (Table 3).

DISCUSSION

In our study, we observed that whether or not taking bDMARD does not have any effect on RA patients. The frequency of NeP was 11.4% in patients with RA, and there was no difference between patients receiving bDMARDs and cDMARDs with regard to NeP ($p>0.05$). A positive correlation was observed between pDETECT scoring, which evaluates NeP, and RA disease duration, DAS28-CRP, VAS pain, VAS fatigue, Beck depression index, Beck anxiety index, ESR, and TJC. Interestingly, we observed a negative correlation between the total number of medicines used and pDETECT and did not observe any relationship between BMI and pDETECT.

Chronic pain is the leading cause of RA, and it can occur via different mechanisms. Pain in RA may arise from nociceptive pain originating from the synovium and periarticular tissues, pains such as NeP occurring via central or peripheral sensitization, or comorbid conditions like osteoarthritis or fibromyalgia or psychological causes (12). Although the pathogenesis of NeP is not entirely understood, it is a pain where the peripheral and central nervous systems are affected and is non-nociceptive and unrelated to peripheral articular damage. Medicines, comorbid conditions like DM and vasculitis, can also cause NeP (13). On the other hand, it has been established that cytokines such as tumour necrosis factor alpha (TNFα), interleukin 1, and interleukin 6, which play a role in the pathogenesis of RA, partake in the formation of NeP by being involved in peripheral and central sensitization mechanisms apart from inflammation and articular damage (14).

However, there are controversial studies regarding whether or not bDMARD treatments like anti-TNFα are effective against NeP. It has been demonstrated that TNFα blockade affects the pain sensitivity of the central nervous system, thereby reducing pain before the onset of the peripheral anti-inflammatory effect starts (15). In addition, it has been shown that TNFα blockade reduces pain with antinociceptive effects by impacting peripheral efferent C nerve fibers. This may explain why anti-TNFα medicines decrease pain rapidly before the anti-inflammatory effect starts in the joints (16). However, many studies have demonstrated that non-steroidal anti-inflammatory drugs do not have an effect on the treatment of NeP (17). A study conducted in 112 patients

Table 1. Demographic data of patients and control group

	bDMARD	non-bDMARD	Control	Total	p
Number of patients					
n	60	45	106	211	-
Age					
Average	51.2	53.6	46.9	49.5	0.47
Gender					
Female n (%)	53 (25.1)	39 (18.5)	73 (34.6)	165 (78.2)	0.004
Male n (%)	7 (3.3)	6 (2.8)	33 (15.6)	46 (21.8)	
Marital status					
Married n (%)	48 (22.7)	41 (19.4)	78 (37)	167 (79.1)	0.52
Single n (%)	12 (5.7)	4 (1.9)	28 (13.3)	44 (20.9)	
Educational status					
Below primary education n (%)	13 (6.2)	17 (8.1)	19 (9)	49 (23.2)	0.003
Primary education n (%)	44 (20.9)	23 (10.9)	61 (28.9)	128 (60.7)	
Undergraduate n (%)	2 (0.9)	5 (2.4)	25 (11.8)	32 (15.2)	
Postgraduate n (%)	1 (0.9)	0 (0)	1 (0.5)	2 (0.9)	
Smoking					
Yes n (%)	9 (4.3)	9 (4.3)	29 (13.7)	47 (22.3)	0.16
No n (%)	51 (24.2)	36 (17.1)	77 (36.5)	164 (77.7)	
BMI					
Average	27.9	27.6	27.1	27.4	0.85
Other medication					
Yes n (%)	22 (10.4)	23 (10.9)	28 (13.3)	73 (34.6)	0.013
No n (%)	38 (18)	22 (10.4)	78 (37)	138 (65.4)	
RF					
Positive n (%)	33 (15.5)	24 (11.4)	0 (0)	57 (27)	0.00
Negative n (%)	27 (12.8)	21 (10)	106 (50.2)	154 (73)	
Anti-CCP					
Positive n (%)	28 (13.3)	11 (5.2)	0 (0)	39 (18.5)	0.00
Negative n (%)	32 (15.2)	34 (16.1)	106 (50.2)	172 (81.5)	
Deformity					
Yes n (%)	17 (8.1)	7 (3.3)	0 (0)	24 (11.4)	0.00
No n (%)	43 (20.4)	38 (18)	106 (50.2)	187 (88.6)	
painDETECT					
No NeP	28 (13.3)	29 (13.7)	72 (34.1)	129 (61.1)	0.06
NeP unspecified	17 (8.1)	7 (3.3)	21 (10.0)	45 (21.3)	
NeP possible	15 (7.1)	9 (4.3)	13 (6.2)	37 (17.5)	

BMI: Body mass index, RF: Rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated peptide, NeP: Neuropathic pain, bDMARD: Biological disease-modifying antirheumatic drugs

with RA showed that methotrexate, hydroxychloroquine, and leflunomide, which are cDMARDs, may be associated with NeP (18). In our study, we found that bDMARD or cDMARD use does not have any effect on NeP. In another study, the NeP frequency was observed as 38% and, similar to our study, it has been reported that cDMARD and bDMARD use does not have any effect on NeP (19). However, in this study, a lower number of patients used bDMARD, and the control group did not receive NeP. In another study that we conducted, we did not observe any relationship between NeP and anti-TNFα agents in patients with ankylosing spondylitis, again as in RA, but it was correlated with the NeP disease activity indicators (20).

It was previously reported that RA patients in whom a change of treatment is performed or treatment is intensified commonly exhibit NeP. NeP frequency is higher in patients with a poor quality of life index, disability, pain, fatigue, and anxiety (21). Similarly, in our study, NeP was also higher in patients with high HAQ scores, VAS pain, VAS fatigue, and the Beck anxiety index and Beck depression index. In addition, there was a positive correlation between the DAS28-CRP score and pDETECT.

Table 2. Clinical properties of the patients and control group

		n	Mean	SD	p
PainDETECT	Control group	106	8.03	7.61	0.00
	Receiver of biological medicine	60	13.90	5.81	
	Non-receiver of biological medicine	45	11.68	7.06	
	Total	211	10.48	7.45	
VAS pain	Control group	106	3.44	3.27	0.00
	Receiver of biological medicine	60	5.65	2.50	
	Non-receiver of biological medicine	45	4.62	2.77	
	Total	211	4.32	3.10	
VAS fatigue	Control group	106	3.70	3.14	0.02
	Receiver of biological medicine	60	5.38	2.57	
	Non-receiver of biological medicine	45	4.26	2.56	
	Total	211	4.30	2.95	
DAS28-CRP	Control group	106	2.65	1.14	0.00
	Receiver of biological medicine	60	3.46	1.26	
	Non-receiver of biological medicine	45	3.36	1.29	
	Total	211	3.03	1.26	
ESR	Control group	106	16.50	10.52	0.007
	Receiver of biological medicine	60	22.66	16.92	
	Non-receiver of biological medicine	45	22.64	16.94	
	Total	211	19.56	14.33	
CRP	Control group	106	6.82	8.22	0.008
	Receiver of biological medicine	60	13.59	19.37	
	Non-receiver of biological medicine	45	11.60	16.64	
	Total	211	9.76	14.37	
Beck anxiety index	Control group	106	11.37	10.70	0.01
	Receiver of biological medicine	60	15.93	10.52	
	Non-receiver of biological medicine	45	15.35	10.64	
	Total	211	13.52	10.81	
Beck depression index	Control group	106	9.25	8.77	0.09
	Receiver of biological medicine	60	11.75	8.38	
	Non-receiver of biological medicine	45	11.91	8.12	
	Total	211	10.53	8.58	
RA quality of life index	Control group	106	8.32	7.56	0.00
	Receiver of biological medicine	60	13.46	7.26	
	Non-receiver of biological medicine	45	11.80	8.06	
	Total	211	10.52	7.89	
HAQ score	Control group	106	6.39	8.55	0.003
	Receiver of biological medicine	60	11.18	10.44	
	Non-receiver of biological medicine	45	10.08	9.48	
	Total	211	8.54	9.53	

VAS: Visual analog scale, DAS28-CRP: Disease activity score in 28 joints calculated with C-reactive protein, ESR: Erythrocyte sedimentation rate, RA: Rheumatoid arthritis, HAQ: Health assessment questionnaire, SD: Standard deviation

Table 3. Correlation analysis of clinical and demographic properties of the patients and control group

		BMI	PainDETECT	HAQ	Beck depression index	VAS pain	RA disease duration	VAS fatigue	DAS28 CRP	Beck anxiety index	ESR	TJC	Number of drugs used for RA
BMI	**r**	1.00	0.02	0.02	-0.04	0.04	0.10	0.05	0.14	-0.03	0.99	0.59	0.90
	p		0.76	0.67	0.47	0.53	0.14	0.41	0.03	0.60	0.15	0.39	0.19
PainDETECT	**r**		1.00	0.60	0.40	0.59	0.56	0.59	0.48	0.60	0.22	0.36	0.34
	p			0.00	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000
HAQ	**r**			1.00	0.56	0.52	0.30	0.46	0.51	0.52	0.23	0.34	-0.27
	p				0.00	0.00	0.00	0.00	0.00	0.00	0.001	0.00	0.00
Beck depression index	**r**				1.00	0.25	0.17	0.30	0.28	0.56	0.97	0.24	-0.21
	p					0.00	0.01	0.00	0.00	0.00	0.16	0.00	0.00
VAS pain	**r**					1.00	0.32	0.68	0.59	0.34	0.25	0.30	-0.25
	p						0.00	0.00	0.00	0.00	0.00	0.00	0.00
RA disease duration	r						1.00	0.27	0.33	0.26	0.17	0,69	-0.91
	p							0.00	0.00	0.00	0.01	0.00	0.00
VAS fatigue	**r**							1.00	0.42	0.44	0.21	0.20	-0.20
	p								0.00	0.00	0.00	0.003	0.003
DAS28 CRP	**r**								1.00	0.30	0.60	0.50	0.32
	p									0.00	0.00	0.00	0.00
Beck anxiety index	**r**									1.00	0.05	0.24	0.25
	p										0.45	0.00	0.00
ESR	r										1.00	0.18	-0.34
	p											0.008	0.01
TJC	**r**											1.00	-0.73
	p												0.00

BMI: Body mass index, HAQ: Health assessment questionnaire, VAS: Visual analog scale, RA: Rheumatoid arthritis, DAS28-CRP: Disease activity score in 28 joints calculated with C-reactive protein, ESR: Erythrocyte sedimentation rate, TJC: Tender joint count

This may cause a higher detection of DAS28-CRP, which is considered to demonstrate disease activity and hence inflammatory activity in RA patients with NeP. In our study, we observed that deformity had no effect on NeP. However, the number of patients with deformities was 24 (11.4%), which should be noted as low. A study conducted by Martins Rocha et al. (18) demonstrated, similar to our study, that structural damage has not been effective on NeP. In this study, it was also stated that the duration of the disease and anti-CCP therapy were not effective against NeP. In our study, although no relationship with anti-CCP was detected, NeP was found to be related to disease duration. In the studies carried out, NeP was more common in those in their 40s and 50s (22). Patient's age might be affecting this condition when the duration of the disease is being evaluated.

Although NeP has a similar frequency to that of RA in patients with connective tissue diseases such as systemic sclerosis, the patient load due to NeP is higher in patients with RA (23). Furthermore, NeP seems to affect remission success even in early RA patients (24). It should be noted that NeP may be affected by not only the primary disease but also the medicines used and conditions such as vitamin deficiency as well (25). In our study, we observed a negative correlation between increased medication use and NeP, but we did not investigate the relationship between vitamin deficiency and NeP.

Although the relationship between NeP and obesity is not clearly identified, NeP is unfavorably affected by weight gain unfavorably (26). In a study conducted by Ito et al. (27) in 300 patients with RA, a significant relationship was reported between

NeP and BMI, and because the study was conducted in the Japanese population, BMI was calculated as >22. In another study carried out by Ahmed et al. (7), again on RA patients, a significant association was observed between NeP and BMI, and here BMI was taken as >30. Interestingly, in our study, we did not observe any relationship between BMI and NeP. The BMI of the patients and control group were similar, and there was no difference. This result may be attributed to the fact that the BMI was approximately 27 kg/m^2 in our study. This should be re-studied in patients with higher BMI.

Study Limitations

The strengths of the study are that it compared the patients who received bDMARDs and cDMARD sand performed detailed measurements of disease activity, used anxiety and depression scales, and HAQ, as well as the RA quality of life index. Fibromyalgia and vitamin examinations were not performed. However, we used a control group with similar age and gender. Another limitation of this study was that we measured the efficacy of each medicine individually. It should also be noted that the sample size was relatively small. To this end, prospective monitoring of a high number of patients may lead to more detailed data on the medicines.

CONCLUSION

As a result, NeP is common in patients with RA, and treatment with bDMARDs does not change the frequency of NeP. The possibility of NeP is higher in RA patients with long disease duration, high disease activity scales, high pain and fatigue scores, high TJC, and anxiety and depression. When measuring disease activity, the presence of NeP should be investigated to increase the quality of life of patients with RA.

Ethics

Ethics Committee Approval: The study was approved by the Hatay Mustafa Kemal University Non-Interventional Clinical Research Ethics Committee (approval number: 05, date: 01.07.2021).

Informed Consent: Signed informed consent forms were obtained from the patients participating in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.K., B.K., M.A., M.E.E., Concept: G.K., B.K., M.A., M.E.E., Design: G.K., B.K., M.A., M.E.E., Data Collection or Processing: G.K., B.K., Analysis or Interpretation: G.K., B.K., Literature Search: G.K., B.K., M.A., M.E.E., Writing: G.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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