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ABSTRACT

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THE EFFECTIVENESS OF RHEUMATOID ARTHRITIS TREATMENT IS NEGATIVELY ASSOCIATED WITH SIGNS OF CENTRAL SENSITIZATION

Introduction. Modern treatment of rheumatoid arthritis faces such major problems as the lack of etiotropic therapy and the high cost of biological drugs. This necessitates a detailed analysis of the effectiveness of existing treatment methods and the study of factors that influence its results. The main goal of treating rheumatoid arthritis is to achieve remission or, if this is not possible, to reduce disease activity to a minimal level. One of the key factors influencing the course of the disease is a pronounced pain syndrome, which is due not only to inflammation of the joints, but also to the phenomenon of central sensitization, which makes the pain chronic even with adequate control of the inflammatory process. In this regard, this study aimed to assess the impact of symptoms associated with central sensitization on the effectiveness of standard treatments for rheumatoid arthritis.

Materials and Methods. 122 patients with rheumatoid arthritis were examined. To assess disease activity, the DAS-28, SDAI, and CDAI were used. To assess the general health of patients, a visual analog scale (VAS) was used (patient-rated VAS-p and doctor-rated VAS-d). The functional status of patients was assessed using the Health Assessment Questionnaire – Disability Index. Symptoms associated with central sensitization (CS) were assessed using the Ukrainian version of the CSI questionnaire. Treatment efficacy was assessed using ACR20/50/70 criteria.

Results. A recommended cutoff score was used to divide the sample into high and low CSI subgroups.

Rheumatoid arthritis patients with high CSI score had worse post-treatment indicators ($p<0.01$) than patients with low CSI score: ESR – 20.1±5.54 vs. 14.53±7.51, DAS-28 – 5.1±0.49 vs. 4.47±0.91, SDAI – 28.8±6.74 vs. 20.1±7.26, CDAI – 26.54±6.49 vs. 20.6±6.54, VAS-p – 6.44±1.09 vs. 4.55±1.41, VAS-d – 5.5±0.99 vs. 4.08±1.02, HAQ –

1.3±0.44 vs. 0.76±0.52. These results suggest lower therapy efficacy in patients with more pronounced CS-associated symptoms.

Analysis of rheumatoid arthritis treatment effectiveness according to ACR20 criteria found that after 12 weeks of therapy, 63.1% of patients were responders and 36.9% were non-responders. According to the ACR50 criteria, 29.5% of patients were responders after 12 weeks of therapy. Only patients with low CSI scores (5.4%) achieved ACR70, while there were no responders among patients with high CSI scores.

It was found that patients with subclinical, mild, and moderate manifestations of CS demonstrated a significantly better response to treatment than those with severe and extreme manifestations of CS. Thus, 72.7% of patients with subclinical, mild, and moderate CS achieved the ACR20 criteria, while only 21.7% of patients with severe and extreme CS demonstrated a response to standard RA therapy according to this criteria ($p<0.01$). 35.4% of patients with subclinical, mild, and moderate forms of CS achieved the ACR50 criteria, while only 4.3% of patients with severe and extreme CS demonstrated improvement according to the specified criteria ($p<0.01$).

Conclusions. Standard treatment of rheumatoid arthritis does not always provide remission, but helps reduce disease activity and improve the condition of patients, while severe CS makes it difficult to achieve a therapeutic effect. It has been found that severe CS-related symptoms are associated with more severe initial disease activity, reduced treatment efficacy, and worse functional status after 12 weeks of therapy as compared to mild CS-related symptoms, suggesting the need to consider additional treatment components to address these symptoms.

Keywords: rheumatoid arthritis, central sensitization, central sensitization inventory, treatment.

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ЕФЕКТИВНІСТЬ ЛІКУВАННЯ РЕВМАТОЇДНОГО АРТРИТУ НЕГАТИВНО АСОЦІЮЄТЬСЯ З ОЗНАКАМИ ЦЕНТРАЛЬНОЇ СЕНСИТИЗАЦІЇ

Вступ. Сучасне лікування ревматоїдного артриту стикається з такими основними проблемами, як відсутність етіотропної терапії та висока вартість біологічних препаратів. Це обумовлює необхідність детального аналізу ефективності наявних методів лікування та вивчення факторів, що впливають на його результати. Основна мета лікування ревматоїдного артриту - досягнення ремісії або, якщо це неможливо, зниження активності захворювання до мінімального рівня. Одним із ключових чинників, що впливають на перебіг захворювання, є виражений больовий синдром, який формується не лише через запалення суглобів, а й унаслідок формування феномену центральної сенситизації, що робить біль хронічним навіть за адекватного контролю запального процесу. У зв'язку з цим метою даного дослідження було оцінити вплив симптомів пов'язаних з центральною сенситизацією на ефективність стандартних методів лікування ревматоїдного артриту.

Матеріали і методи дослідження. Обстежено 122 хворих на ревматоїдний артрит. Для оцінки активності захворювання

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використовували індекси DAS-28, SDAI, CDAI. Загальний стан здоров'я пацієнтів оцінювали за візуально-аналоговою шкалою (ВАШ) (за оцінкою пацієнта – ВАШ-п та за оцінкою лікаря – ВАШ-л). Функціональні можливості хворих оцінювали за опитувальником HAQ. Симптоми пов'язані з центральною сенситизацією (ЦС) оцінювали за допомогою україномовної версії анкети CSI. Ефективність лікування оцінювали за критеріями ACR20/50/70.

Результати дослідження. Для розподілу вибірки на підгрупи з високим і низьким CSI використовувався рекомендований граничний бал.

У хворих на ревматоїдний артрит з високим CSI після лікування показники залишалися значно гіршими ($p<0,01$), ніж у пацієнтів з низьким CSI: ШОЕ - 20,1±5,54 проти 14,53±7,51, DAS-28 – 5,1±0,49 проти 4,47±0,91, SDAI – 28,8±6,74 проти 20,1±7,26, CDAI – 26,54±6,49 проти 20,6±6,54, ВАШ-п – 6,44±1,09 проти 4,55±1,41, ВАШ-л – 5,5±0,99 проти 4,08±1,02, HAQ – 1,3±0,44 проти 0,76±0,52. Ці результати свідчать про нижчу ефективність терапії у пацієнтів з підвищеною симптоматикою, пов'язаною з ЦС.

Аналіз ефективності лікування ревматоїдного артриту за критеріями ACR20 встановив, що загалом після 12-тижневої терапії респондерами були 63,1% пацієнтів, відповідно нереспондерами – 36,9%. За критеріями ACR50 було встановлено, що після 12-тижневої терапії респондерами були 29,5% пацієнтів. ACR70 досягли лише пацієнти з низьким CSI (5,4%), тоді як серед хворих з високим CSI не було жодного респондера за цим критерієм.

Встановлено, що пацієнти з субклінічними, легкими та середніми проявами ЦС демонструють значно кращу відповідь на лікування, ніж ті, у кого ЦС виражена у важкому та екстремальному ступені. Таким чином, 72,7% хворих із субклінічною, легкою та середньою ЦС досягли критерію ACR20. В той час, як лише 21,7% хворих із важкою та екстремальною ЦС продемонстрували відповідь на стандартну терапію РА за даним критерієм ($p<0,01$). 35,4% пацієнтів із субклінічною, легкою та середньою формою ЦС досягли критерію ACR50. І лише 4,3% хворих із важкою та екстремальною ЦС продемонстрували покращення за вказаним критерієм ($p<0,01$).

Висновки. Стандартне лікування ревматоїдного артриту не завжди забезпечує ремісію, але сприяє зниженню активності захворювання та покращенню стану пацієнтів, тоді як виражена ЦС ускладнює досягнення терапевтичного ефекту. Встановлено, що виражена симптоматика, пов'язана з ЦС, асоціюється з більш серйозною початковою активністю захворювання, зниженням ефективності лікування та погіршенням функціонального стану після 12 тижнів терапії, ніж у пацієнтів зі слабкою симптоматикою, пов'язаною з ЦС, що свідчить про необхідність розглядати додаткові компоненти лікування, для усунення цих симптомів.

Ключові слова: ревматоїдний артрит, центральна сенситизація, central sensitization inventory, лікування.

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ABBREVIATIONS

CDAI – Clinical Disease Activity Index;

CSI – Central Sensitization Inventory;

DAS-28 – The Disease Activity Score-28;

HAQ – Health Assessment Questionnaire-Disability Index;

SDAI – Simple Disease Activity Index;

VAS-d – general assessment of health status in doctor's opinion;

VAS-p – general assessment of health status in patient's opinion;

OR – odds ratio;

TJC– tender joint count;

SJC– swollen joint count;

RA – rheumatoid arthritis;

CS – central sensitization;

ESR – erythrocyte sedimentation rate

INTRODUCTION / ВСТУП

Today the main problem in the treatment of rheumatoid arthritis (RA) is the lack of etiotropic therapy and the high cost of modern biological drugs. This, in turn, necessitates not only a thorough study and assessment of the effectiveness of existing treatment methods, but also an analysis of the maximum number of significant factors that influence the treatment outcome [9, 16].

The main goal of antirheumatic therapy is to achieve clinical remission according to ACR and EULAR criteria or low disease activity if remission cannot be achieved [14]. At the same time, the key to remission is reducing disease activity, eliminating pain syndrome, restoring functional ability, and improving patients' quality of life [11].

Severe pain syndrome is an important factor in modifying the clinical course of RA [15]. It is known that in patients with RA, in addition to nociceptive and neuropathic mechanisms, the phenomenon of central sensitization (CS) plays a major role in the development and persistence of pain syndrome [4]. Unlike pain caused solely by joint inflammation, pain in CS is chronic and may persist even despite adequate control of inflammatory processes [8]. The results of individual studies highlight the relationship between CS and the long-term course of RA, disease activity, and the severity of pain syndrome [3, 7].

Thus, the objective of this study was to evaluate the effectiveness of treatment in RA patients with and without CS.

MATERIALS AND METHODS

In order to assess the impact of CS on the clinical course of RA, we examined 122 patients who were treated at the Highly Specialized Clinical Center for Rheumatology, Osteoporosis, and Biological Therapy of the Municipal Non-Profit Enterprise “Vinnytsia Regional Clinical Hospital named after M.I. Pirogov” of the Vinnytsia Regional Council. The diagnosis of RA was made according to the criteria of the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) 2010. The DAS-28 (The Disease Activity Score-28) [17], SDAI (Simple Disease Activity Index) [12], and CDAI (Rheumatoid Arthritis Clinical Disease Activity Index) [1] were used to assess RA activity. To assess the general health of patients, a visual analog scale (VAS) was used (patient-rated VAS-p and doctor-rated VAS-d). The functional status of patients was assessed using the Health Assessment Questionnaire (HAQ) – Disability Index [2].

CS-related symptoms were assessed using the validated and cross-culturally adapted Ukrainian version of the Central Sensitization Inventory (CSI) [5, 13].

The effectiveness of standard 12-week RA therapy was assessed using the American College of Rheumatology criteria – ACR20/50/70 [10].

The licensed Microsoft Excel office package and variational statistics methods in the SPSS22 application package (©SPSS Inc.) were used to statistically process the obtained results. The odds ratio (OR) with a 95% confidence interval was used to estimate the relative risk. The results are presented as the mean and standard deviation (M±SD). Differences were considered significant at $p<0.05$.

RESULTS

According to the results of the CSI, the examined patients were divided into two groups: 48 patients with pronounced symptoms associated with CS (CSI score of 40 points and above) and 74 patients with mild symptoms associated with CS (CSI score up to 40 points).

The clinical and demographic characteristics of the examined patients are presented in Table 1.

Thus, RA patients with high CSI scores did not differ in age and were characterized by a longer disease duration: 13.1±8.93 vs. 7.04±6.3 ($p<0.01$). The group of patients with high CSI scores had a higher number of individuals with seropositive RA – 77.1% versus 52.7% ($p<0.01$). Among patients with high CSI scores, there were significantly more patients with radiological stages III and IV, while in the group of patients with low CSI scores, patients with stages I and II predominated. Also, patients with high CSI scores had greater TJC (15.38±4.44 vs. 10.57±4.44) and SJC (8.67±3.0 vs. 5.99±3.16) compared to patients with low CSI scores, $p<0.01$.

Table 1 – **Clinical and demographic characteristics of RA patients depending on the presence of CS-associated symptoms**

Indicator	Patients with low CSI score, n=74	Patients with high CSI score, n=48	p
Age, years	51.2±12.81	57.42±9.27	0.120
Gender, male/female, n (%)	17/57 (14/86%)	4/44 (8/92%)	0.315
Duration of the disease, years	7.04±6.3	13.1±8.93	<0.01
Seropositivity, n (%)	39 (52.7%)	37 (77.1%)	<0.01
Radiological stage I, n (%)	24 (28.9%)	4 (8.3%)	<0.01
Radiological stage II, n (%)	38 (53.9%)	22 (45.8%)	0.348
Radiological stage III, n (%)	9 (9.6%)	17 (35.4%)	<0.01
Radiological stage IV, n (%)	4 (3.9%)	5 (10.4%)	0.155
Tender joint count	10.57±4.44	15.38±4.44	<0.01
Swollen joint count	5.99±3.16	8.67±3.0	<0.01

Note: p = statistical significance of differences relative to the group without CS

Analysis of the effectiveness of 12-week RA therapy showed positive changes in the treatment process in both groups (Table 2, Fig. 1–2).

It was found that all parameters, including ESR, DAS-28, SDAI, CDAI, VAS-p, VAS-l, and HAQ, significantly improved after 12 weeks of standard RA therapy in both groups of patients (p<0.01). However, RA patients with high CSI score had worse indicators after treatment than patients with low CSI score: ESR – 20.1±5.54 vs. 14.53±7.51, DAS-28 – 5.1±0.49 vs. 4.47±0.91, SDAI – 28.8±6.74 vs. 20.1±7.26, CDAI – 26.54±6.49 vs. 20.6±6.54, VAS-p – 6.44±1.09 vs. 4.55±1.41, VAS-d – 5.5±0.99 vs. 4.08±1.02, HAQ – 1.3±0.44 vs. 0.76±0.52. The significance of the differences for post-treatment indicators was p<0.01 between the groups of patients with high and low CSI scores. This suggests less effective therapy in patients with low CSI scores, which may be related to mechanisms of chronic pain and neuroplasticity.

Table 2 – **Changes in disease-specific indicators in RA patients with high and low CSI scores under the influence of treatment**

Indicator		Indicator value, M ± SD	
		Patients with low CSI score, n=74	Patients with high CSI score, n=48
ESR, mm/h	before treatment	22.28±15.41	30.77±14.62*
	after 12 weeks	14.53±7.51#	20.1±5.54*#
DAS-28, points	before treatment	5.06±0.94	6.34±0.77*
	after 12 weeks	4.47±0.91#	5.1±0.49*#
SDAI, points	before treatment	30.13±9.14	38.2±8.99*
	after 12 weeks	20.1±7.26#	28.8±6.74*#
CDAI, points	before treatment	27.2±8.41	38.35±8.5*
	after 12 weeks	20.6±6.54#	26.54±6.49*#
Visual Analog Scale (patient), points	before treatment	6.08±1.33	7.65±1.04*
	after 12 weeks	4.55±1.41#	6.44±1.09*#
Visual Analog Scale (doctor), points	before treatment	5.28±1.1	6.46±1.13*
	after 12 weeks	4.08±1.02#	5.5±0.99*#
HAQ, points	before treatment	0.94±0.61	1.8±0.53*
	after 12 weeks	0.76±0.52#	1.3±0.44*#

Notes. *1. * – p<0.01 as compared to the group of patients with low CSI score, n=74;*
2. # – p<0.01 as compared to the pre-treatment state

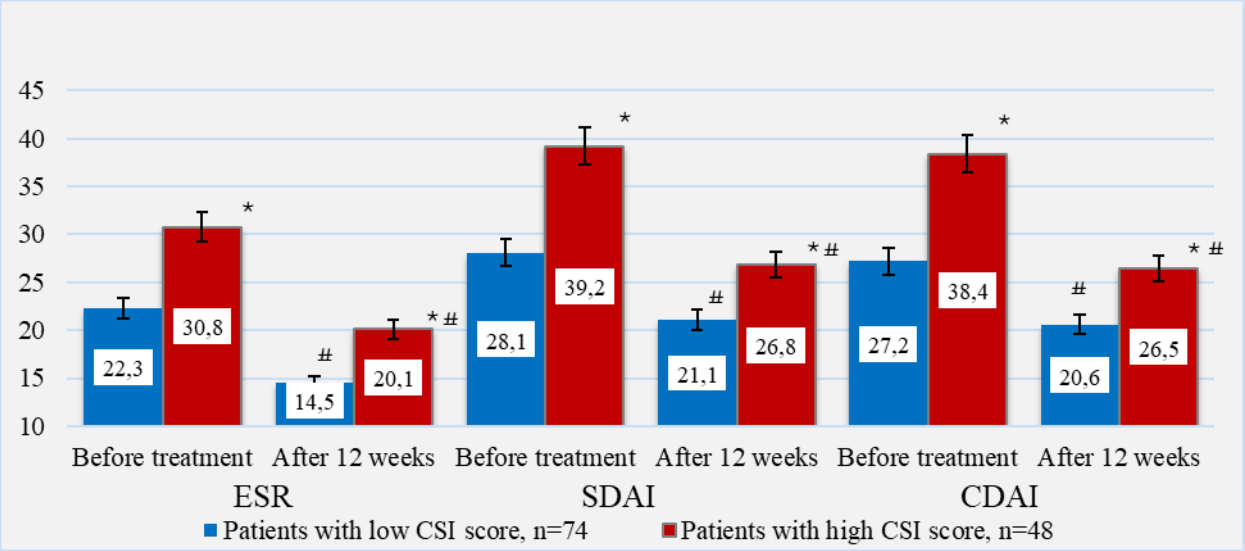

Figure 1 – Disease-specific indicators as a treatment outcome in RA patients with high and low CSI scores.
** – p<0.01 as compared to the group of patients with low CSI scores;*
 # – p<0.01 as compared to the pre-treatment state

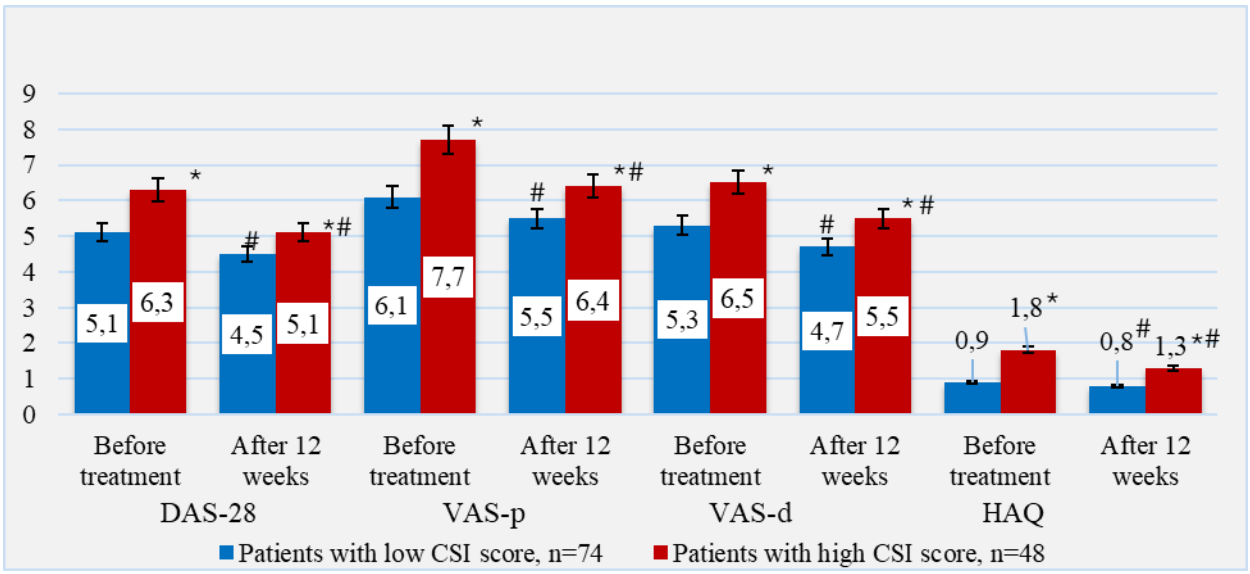

Figure 2 – Disease-specific indicators as a treatment outcome in RA patients with high and low CSI scores.
** – p<0.01 as compared to the group of patients with low CSI score;*
 # – p<0.01 as compared to the pre-treatment state

The changes in RA activity according to DAS-28 during 12 weeks of treatment in RA patients with high and low CSI scores are presented in Table 3 and Fig. 3.

We can see that no patient in the high CSI group achieved remission or low activity after 12 weeks of treatment, while in the low CSI group, there were 10.9% of such patients. In patients with low CSI scores, the proportion of individuals with moderate activity, according to the DAS-28, increased from 51.4% to 63.5%. In the group of patients with high CSI scores, this indicator increased from 6.3% to 52.1%, mainly due to decreased transition of patients to the group with low activity and no remission. Although the proportion of patients with high activity decreased in the high CSI group from 93.7% to 47.9%, it still remained significantly higher than in patients with low CSI scores (25.6%).

The odds ratio showed that CS was a predictor of high RA activity according to DAS-28 after 12 weeks of RA therapy with a standard treatment regimen: OR – 2.7; 95% CI 1.23 – 5.75, p <0.05.

The effectiveness of standard 12-week RA therapy was assessed using the American College of Rheumatology criteria – ACR20/50/70.

Table 3 – **Treatment outcomes in RA patients with high and low CSI scores**

Treatment effectiveness		Patients with low CSI score, n=74	Patients with high CSI score, n=48
Remission (DAS-28 score less than 2.6 points), n (%)	before treatment	0 (0)	0 (0)
	after 12 weeks	1 (1.4)	0 (0)
Low activity (DAS-28 score from 2.6 points to 3.2 points), n (%)	before treatment	2 (2.7)	0 (0)
	after 12 weeks	7 (9.5)	0 (0)*
Moderate activity (DAS-28 score from 3.2 points to 5.1 points), n (%)	before treatment	38 (51.4)	3 (6.3)**
	after 12 weeks	47 (63.5)	25 (52.1)#
High activity (DAS-28 score above 5.1 points), n (%)	before treatment	34 (45.9)	45 (93.7)**
	after 12 weeks	19 (25.6)#	23 (47.9)*#

Notes. *1. * – p<0.05 as compared to the group of patients with low CSI scores;*
*2. ** – p<0.01 as compared to the group of patients with low CSI scores;*
3. # – p<0.01 as compared to the pre-treatment state

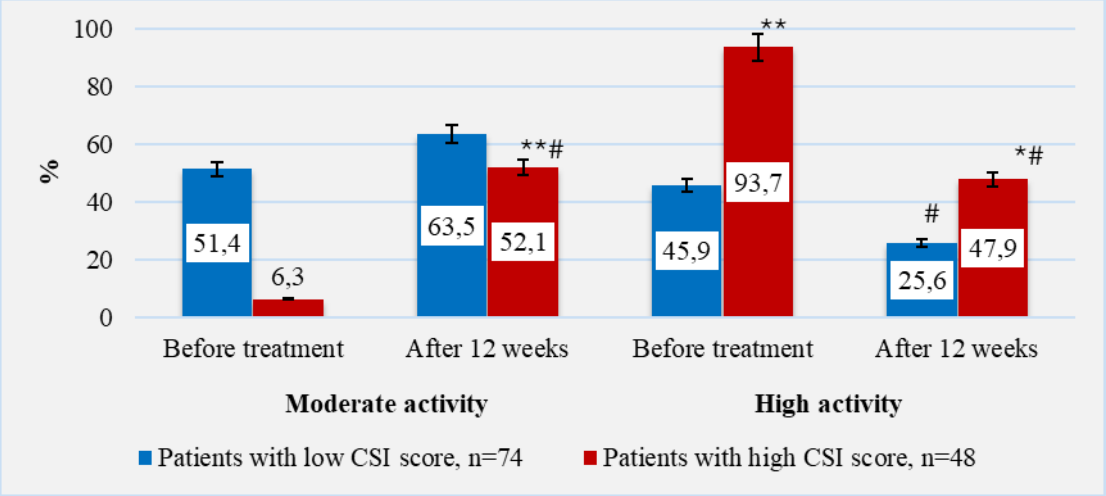

Figure 3 – Treatment outcomes in RA patients with high and low CSI scores.
** – p<0.05 as compared to the group of patients with low CSI score;*
*** – p<0.01 as compared to the group of patients with low CSI score;*
 # – p<0.01 as compared to the pre-treatment state

Analysis of RA treatment effectiveness according to ACR20 criteria found that after 12 weeks of therapy, 63.1% of patients were responders and 36.9% were non-responders. At the same time, the number of responders according to these criteria was higher in RA patients with low CSI scores.

Using the ACR50 criteria, it was found that 29.5% of patients were responders after 12 weeks of therapy. A higher number of responders was observed in the group with a low CSI score: 33.8%, while in patients with a high CSI score, this value was 22.9%.

Only patients with low CSI scores (5.4%) achieved ACR70, while there were no responders among patients with high CSI scores.

OR calculation showed that RA patients with mild CS-associated symptoms, unlike patients with severe symptoms of CS, had a higher chance of being a responder according to the ACR20 criterion after 12 weeks of standard therapy.

In the next step, we analyzed the response according to the ACR20/50/70 criteria depending on the level of severity of CS (Table 4). To do this, we divided patients according to the value of the CS index, where the subclinical level was defined as CSI score from 0 to 29 (47 patients), mild level – from 30 to 39 (27 patients), moderate level – from 40 to 49 (25 patients), severe level – from 50 to 59 (16 patients), and extreme level – 60 and more (7 patients) [6]. To understand whether there is a relationship between the level of CS severity and response to treatment, two

groups of patients were formed: the first group (99 patients) included RA patients with subclinical, mild, and moderate levels of CS, and the second group (23 patients) included patients with severe and extreme levels of CS.

Thus, 72.7% of patients with subclinical, mild, and moderate CS achieved the ACR20 criteria, while only 21.7% of patients with severe and extreme CS demonstrated a response to standard RA therapy according to this criteria (p<0.01).

Table 4 – **Compliance with ACR20/50/70 criteria as a treatment outcome in RA patients depending on the severity of CS**

Category	Subclinical + Mild + Moderate, n=99		Severe + Extreme, n=23		p
	Abs.	%	Abs.	%	
ACR20 responders	72	72.7%	5	21.7%	<0.01
ACR50 responders	35	35.4%	1	4.3%	<0.01

Note: p = statistical significance of differences between groupsIt was found that patients with subclinical, mild, and moderate manifestations of CS demonstrated a significantly better response to treatment than those with severe and extreme manifestations of CS

Similar patterns were observed in the response to treatment according to the ACR50 criteria. 35.4% of patients with subclinical, mild, and moderate forms of CS achieved the ACR50 criteria, while only 4.3% of patients with severe and extreme CS demonstrated improvement according to the specified criteria (p<0.01).

As noted above, the group of RA patients with high CSI scores did not include responders according to ACR70 criteria.

Analysis of the CSI results (Table 5) over the course of 12 weeks of RA therapy showed that the manifestations of CS decreased more significantly in the group of patients with mild CS-related symptoms – by 20.5%, while in patients with severe CS symptoms, a decrease of 10.8% was observed.

Table 5 – **Changes in CSI score as a treatment outcome in RA patients with and without CS-associated symptoms**

Indicator		Indicator value, M ± SD		
		All patients, n=122	Patients with low CSI score, n=74	Patients with high CSI score, n=48
CSI	before treatment	34.08±16.88	19.92±9.02	51.5±7.91*
	after 12 weeks	27.67±16.09#	15.84±6.87#	45.92±5.7*##

Notes. *1. * – p<0.01 as compared to the group of patients with low CSI score;*
2. # – p<0.05 as compared to the pre-treatment state;
3. ## – p<0.01 as compared to the pre-treatment state

DISCUSSION

The results of our study indicate that CS modifies the course of RA and is associated with higher disease activity, worse patient health, and worse functional capacity. The complexity of the pathogenetic mechanisms of RA, especially in combination with the phenomenon of CS, necessitates a comprehensive assessment and therapeutic impact on the manifestations of the disease. When choosing the optimal therapy for RA patients, the presence of CS should be taken into account, especially the degree of its severity, since patients with severe and extreme CS demonstrate a significantly worse response to treatment: almost 80% of patients do not have a positive response to treatment according to the ACR20 criteria and 95.7% of patients do not obtain clinically significant relief according to the ACR50 criteria after therapy. RA patients with high CSI scores are 3.3 times less likely to achieve ACR20 criteria (21.7% vs. 72.7%) and 8 times less likely to achieve ACR50 criteria (4.3% vs. 35.4%). Although the CSI scores decreased in both groups after 12 weeks of RA therapy, however, in patients with high CSI scores, the decrease in CS severity was twice as bad as in patients with low CSI scores, which should also be taken into account when managing such patients.

CONCLUSIONS

1. Current standard treatment for RA does not lead to remission in a significant number of cases, but it does reduce RA activity and improve the health and functional capabilities of patients. The proportion of responders according to ACR20 criteria was 63.1%, according to ACR50 – 29.5%, according to ACR70 – 3.3%.
2. We established an association of CS with treatment response: the higher the CS severity, the more difficult it is to achieve a response to standard RA treatment.
3. CS is a predictor of both high RA activity and worse clinical outcomes of therapy. Patients with severe symptoms of RA retain significantly worse RA activity indicators, health status, and functional capacity after 12 weeks of therapy than patients with mild symptoms of RA, which necessitates considering more aggressive anti-inflammatory therapy in such patients.
4. After 12 weeks of RA therapy, patients with severe CS-associated symptoms had twice as bad a decrease in CS severity compared to those with mild CS-associated symptoms.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

In our opinion, further study of the impact of central sensitization on the modification of disease-specific indicators in patients with RA, the severity of pain syndrome, and the functional capabilities of patients is a promising direction. It is advisable to conduct future studies on the impact of central sensitization on the health status of patients with RA in order to select the optimal therapy for ensuring control of the inflammatory process, disease activity, and pain intensity.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors made substantial contributions to the development of the initial and revised versions of this article. They are fully responsible for all aspects of the work and resolving issues related to the accuracy or integrity of the information provided.

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