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LIFE QUALITY OF PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH BIOTHERAPY

KVALITET ŽIVOTA PACIJENATA SA REUMATOIDNIM ARTRITISOM LEČENIH BIOLOŠKOM TERAPIJOM

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Summary

Introduction. Rheumatoid arthritis is a chronic disease that causes joint damage and loss of function, thus impairing quality of life. Administration of biological drugs can change the course of the disease and improve life quality and functional capacity of patients. The objective of the study is to examine the quality of life in patients with rheumatoid arthritis treated with biological therapy. **Material and Methods.** The prospective cross-sectional study followed 56 patients of both sexes treated with biological drugs at the Special Hospital for Rheumatic Diseases, Novi Sad. The data were collected using a standardized questionnaire for monitoring the quality of life (Health Assessment Questionnaire-disability index) and a general questionnaire, containing socio-demographic data, disease and therapy data. Computer program Statistical Package for the Social Sciences version 24 was used for data processing. **Results.** The results of the assessment of the life quality of patients with rheumatoid arthritis undergoing biological therapy showed that the values of the Health Assessment Questionnaire-disability index range from Min=0.00 to Max=2.25, with the mean M=0.76. Observed by category, 39.3% of participants are in remission, while the rest (60.7%) have low disease activity. The Health Assessment Questionnaire-disability index has a statistically significant correlation with the place of residence ($p<0.05$), as well as with the duration of morning stiffness ($p<0.01$). The Health Assessment Questionnaire-disability index has no statistically significant correlation with other general data, disease and therapy data. **Conclusion.** Application of biotherapy on patients with rheumatoid arthritis leads to low disease activity and remission, which results in good quality of life.

Key words: Quality of Life; Arthritis, Rheumatoid; Biological Therapy; Surveys and Questionnaires; Disability Evaluation

Sažetak

Uvod. Reumatoidni artritis je hronična bolest koja uzrokuje oštećenje zglobova i gubitak njihove funkcije, čime se narušava kvalitet života. Primena bioloških lekova može menjati tok bolesti i popraviti kako kvalitet života, tako i funkcionalnu sposobnost obolelih. Cilj ovog istraživanja je ispitivanje kvaliteta života pacijenata sa reumatoidnim artritisom lečenih biološkom terapijom. **Materijal i metode.** Prospektivnom studijom preseka obuvaćeno je 56 pacijenata oba pola, koji se leče biološkim lekovima u Specijalnoj bolnici za reumatske bolesti u Novom Sadu. Podaci su prikupljeni korišćenjem standardizovanog upitnika za praćenje kvaliteta života (*Health Assessment Quiestionnaire-disability index*) i opšteg upitnika koji sadrži sociodemografske podatke, podatke o bolesti i terapiji. Za obradu podataka korišćen je kompjuterski program *Statistical Package for the Social Sciences* verzija 24. **Rezultati.** Rezultati merenja kvaliteta života pacijenata sa reumatoidnim artritisom lečenih biološkom terapijom pokazali su da se vrednosti *Health Assessment Quiestionnaire-disability index*-a kreću se od min = 0,00 do max = 2,25, dok prosečna vrednost iznosi m = 0,76. Posmatrano po kategorijama, u remisiji je 39,3% ispitanika, dok ostali (60,7%) imaju nisku aktivnost bolesti. *Health Assessment Quiestionnaire-disability index* je u statistički značajnoj vezi sa mestom stanovanja ($p < 0,05$), kao i sa dužinom trajanja jutarnje ukočenosti ($p < 0,01$). Sa ostalim opštim podacima, podacima o bolesti i terapiji *Health Assessment Quiestionnaire-disability index* nije u statistički značajnoj vezi. **Zaključak.** Primena biološke terapije kod pacijenata sa reumatoidnim artritisom dovodi do niske aktivnosti bolesti i remisije, što daje dobar kvalitet života.

Ključne reči: kvalitet života; reumatoidni artritis; biološka terapija; ankete i upitnici; procena onesposobljenosti

Introduction

Rheumatoid arthritis (RA) is a symmetrical polyarticular arthritis primarily affecting the small joints of hands and feet [1]. Inadequately treated, it leads to irreversible joint deformities and consequent disability as well as premature mortality [2].

Treatment is carried out by non-pharmacological and pharmacological methods. Non-pharmacological and pharmacological treatment methods have a syn-

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Abbreviations

RA – rheumatoid arthritis
DMARD – disease modifying anti-rheumatic drugs
bDMARD – biological disease modifying anti-rheumatic drugs
cDMARD – conventional disease modifying anti-rheumatic drugs
HAQ-DI – Health Assessment Questionnaire-disability index
RF – rheumatoid factor

ergistic effect in RA treatment, as well as in maintaining joint mobility and delaying the progression of the disease [3]. Pharmacological therapy involves the use of different drug groups, which include disease modifying anti-rheumatic drugs (DMARDs), as well as symptomatic therapy using non-steroidal anti-inflammatory drugs and glucocorticoids [4]. DMARDs represent the most important measure in successful RA treatment. DMARDs can be divided into conventional (cDMARDs) and biological (bDMARDs). Methotrexate stands out among cDMARDs as the gold standard in RA therapy. Biological DMARDs is a group of drugs that target specific molecules or molecular pathways involved in the inflammatory processes in RA [5]. These drugs have played a significant role in improving clinical symptoms and life quality of patients [6]. They have been in use in Serbia since 2006 and have significantly improved the treatment of patients with RA [7]. The Special Hospital for Rheumatic Diseases in Novi Sad has used biological drugs since 2007. According to the 2019 recommendations of the European Alliance of Associations for Rheumatology (EULAR), treatment of RA patients should begin immediately upon the diagnosis. Treatment should be goal-oriented, i.e., aiming at remission or low disease activity in each patient [8].

According to the World Health Organization (WHO), the quality of life is defined as "an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns" [9]. Self-assessment of the quality of life can be obtained in a systematic way through interviews, as well as qualitative assessments and questionnaires [10]. Fries et al. developed the Health Assessment Questionnaire-disability index - HAQ-DI [11, 12]. This is a self-assessment questionnaire and is the most frequently used questionnaire for assessing quality of life and physical function of patients with rheumatic diseases [10]. Quality of life in patients with RA is affected by the degree of disease activity and functional ability, which depends on the effectiveness of the applied therapy [13].

The aim of our study is to examine the quality of life in patients with rheumatoid arthritis treated with biological therapy.

Material and Methods

The study was conducted as a prospective cross-sectional study at the day hospital of the Special Hospital for Rheumatic Diseases in Novi Sad. The sample included 56 patients of both sexes who were diagnosed with RA and treated with biological therapy. The participants were chosen by a random selection method. All participants included in the study were assessed according to the biotherapy inclusion criteria by the Drug Use in the Treatment of Insured Persons Approval Committee of the Health Insurance Fund of the Republic of Serbia. The study was approved by the Ethics Committee of the Special Hospital for Rheumatic Diseases in Novi Sad (14/32-6/1-22).

Data were collected using a standardized questionnaire for monitoring the quality of life (HAQ-DI) of the RA patients included in the study. The questionnaire includes questions about independence in dressing, maintaining personal hygiene, rising, eating, ability to reach or lift objects, and other daily activities. The value of the questionnaire ranges from 0 to 3, where 0 indicates that the patient has no limitations in daily functioning, while 3 indicates complete disability. The participants also filled out a general questionnaire made by the researcher, which contains socio-demographic data (age, sex, place of residence, work status) and seven questions that include information on the diagnosis and therapy.

The study examined whether the HAQ-DI has a statistically significant correlation with the participants' general data, disease data, as well as therapy data.

The results obtained from the research were statistically processed with an adequate selection of statistical methods, depending on the type and distribution of data, in order to ensure an optimal model for observing dependencies and differences between the analysed data obtained in the study. Some of the measures of the used descriptive statistics were the arithmetic mean, with the corresponding standard deviation, the minimum and maximum. Both frequencies and percentages were used. Differences between groups were determined with use of the χ^2-test. Statistical significance is defined at the null hypothesis probability level of $p \leq 0.05$. Statistical processing and analysis were done in the computer program Statistical Package for the Social Sciences ver. 24.

Results

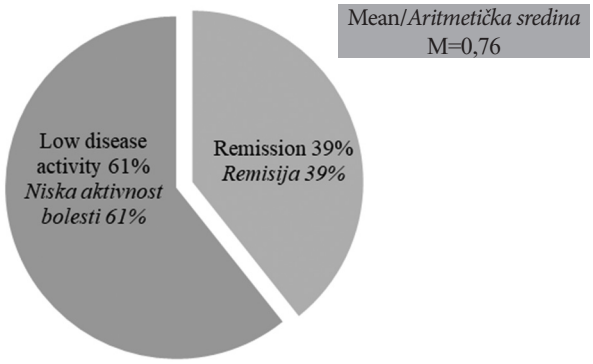
56 patients with rheumatoid arthritis treated with biological therapy participated in the study. The average age of the participants is 56 years. The sample comprised of 26.8% male and 73.2% female patients. The majority (64.3%) live in urban and 25% live in rural areas. The majority of the participants (73.2%) live with their families, 17.9% are single, while 8.9% of the participants live in multigenerational households. 48.2% of the participants are employed, 16.1% are unemployed, and 35.7% are retired. Up to 5 years have passed since the diagnosis of RA in 7.1% of patients, the duration of RA from 6 to 10 years is present in 46.4% of patients, while 46.4% of the examined patients have suffered from RA for more than 10 years. Positive rheumatoid factor (RF) was recorded in 92.9% of patients, and negative in 7.1%. Positive anti-CCP antibody was recorded in 26.8% of the participants, and negative in 73.2%. 28.6% of the patients

do not experience morning stiffness, 66.1% experience stiffness for 2 hours after rising, whereas 5.4% experience stiffness for more than 2 hours after rising. 35.7% of the participants have had current therapy for under a year. 23.2% of the participants have had current therapy for 1-3 years, 7.1% for 3-5 years, whereas 33.9% of the participants have received current therapy for more than 5 years. Of the total number of the participants, 91.9% are on methotrexate, while the other 8.1% are on hydroxychloroquine. Glucocorticoids are taken by 14.3% of the participants, 7.1% are occasionally on glucocorticoids, while 78.6% of the patients have never taken corticosteroids.

The HAQ-DI values range from Min=0.00 to Max=2.25, with the mean M=0.76. Observed by category, 39.3% of the participants are in remission, while the rest (60.7%) have low disease activity **(Graph 1)**.

The HAQ-DI has a statistically significant correlation with the place of residence ($p<0.05$). The highest percentage of the participants from urban areas is in remission (86.4%), whereas the percentage of the participants from rural areas is significantly lower (13.6%). Low disease activity is found in 50.0% from urban areas, 32.4% from rural areas and 17.6% from the suburbs. The HAQ-DI does not have a statistically significant correlation with other disease data **(Table 1)**.

The duration of morning stiffness has a statistically significant correlation with the HAQ-DI ($p<0.01$). Of the total number of participants in remission, about a half (54.5%) do not have morning stiffness, while most of those with low disease activity (79.4%) have stiffness that lasts for 2 hours. The HAQ-DI does not have a statistically significant correlation with other disease data.



Graph 1. HAQ-DI in patients with rheumatoid arthritis treated with biological therapy
Grafikon 1. *Health Assessment Questionnaire-disability index kod pacijenata sa reumatoidnim artritisom lečenih biološkom terapijom*

The therapy data do not have statistically significant correlation with the HAQ-DI. The statistical significance of the χ^2-test is above the threshold of 0.05 **(Table 2)**.

Discussion

The majority of the participants in our study were female (73.2%), which is expected as RA is the most common disease in women; three times more common than in men [14]. The average age of the participants was 56, which corresponds to the period of onset of the disease, between the ages of 35 and 50 [14]. The obtained data showing that 46.4% of patients have suffered from RA for 6-10 years and the same percentage

Table 1. General data on participants and HAQ-DI
Tabela 1. *Opšti podaci o ispitanicima i Health Assessment Questionnaire-disability index*

		HAQ-DI						p/*p*
		Remission *Remisija*		Low disease activity *Niska aktivnost bolesti*		Total *Ukupno*		
		F	%	f	%	f	%	
Average age *Prosečna starost*	56	22	100%	34	100%	56	100%	
Sex *Pol*	Male/*Muški*	6	27.3%	9	26.5%	15	26.8%	0.947
	Female/*Ženski*	16	72.7%	25	73.5%	41	73.2%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
Place of residence *Mesto stanovanja*	Urban/*Grad*	19	86.4%	17	50%	36	64.3%	0.014
	Rural/*Selo*	3	13.6%	11	32.4%	14	25%	
	Suburban/*Prigradsko naselje*	0	0%	6	17.6%	6	10.7%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
I live with *Živim sa*	Family (spouse and children) *Porodicom (suprug/a i deca)*	17	77.3%	24	70.6%	41	73.2%	0.150
	Multigenerational household *U široj zajednici*	0	0%	5	14.7%	5	8.9%	
	Alone/*Sam/sama*	5	22.7%	5	14.7%	10	17.9%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
Employment *Radni odnos*	Yes/*Da*	11	50%	16	47.1%	27	48.2%	0.870
	No/*Ne*	4	18.2%	5	14.7%	9	16.1%	
	Retired/*Penzioner/ka*	7	31.8%	13	38.2%	20	35.7%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	

Table 2. Disease and therapy data and HAQ-DI
Tabela 2. *Podaci o bolesti i terapiji i Health Assessment Questionnaire-disability index*

		HAQ-DI						
		Remission *Remisija*		Low disease activity *Niska aktivnost bolesti*		Total *Ukupno*		p/*p*
		f	%	f	%	f	%	
Duration of RA disease *Dužina trajanja bolesti RA*	1-5 years/*1-5 godina*	0	0%	4	11.8%	4	7.1%	0.211
	6-10 years/*6-10 godina*	10	45.5%	16	47.1%	26	46.4%	
	+10 years/*+10 godina*	12	54.5%	14	41.2%	26	46.4%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
RF	RF+	21	95.5%	31	91.2%	52	92.9%	0.544
	RF-	1	4.5%	3	8.8%	4	7.1%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
Anti-CCP antibody *Anti-CCP antitela*	Anti-CCP antibody+ *Anti-CCP antitela+*	6	27.3%	9	26.5%	15	26.8%	0.947
	Anti-CCP antibody– *anti-CCP antitela–*	16	72.7%	25	73.5%	41	73.2%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
How long does morning stiffness last? *Koliko dugo traje jutarnja ukočenost zglobova?*	Not present/*Nema*	12	54.5%	4	11.8%	16	28.6%	0.002
	Up to 2h/*Do 2 h*	10	45.5%	27	79.4%	37	66.1%	
	+2 h/*+2 h*	0	0%	3	8.8%	3	5.4%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
When was the current biological drug therapy introduced? *Kada je uvedena sadašnja terapija biološkim lekom?*	<1 year/*<1 godine*	5	22.7%	15	44.1%	20	35.7%	0.244
	1-3 years/*1-3 godina*	6	27.3%	7	20.6%	13	23.2%	
	3-5 years/*3-5 godina*	3	13.6%	1	2.9%	4	7.1%	
	+5 years/*+5 godina*	8	36.4%	11	32.4%	19	33.9%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	
Therapy *Terapija*	Methotrexate/*Metotreksat*	11	84.6%	23	95.8%	34	91.9%	0.233
	Sulfasalazine/*Sulfasalazin*	0	0%	0	0%	0	0%	
	Hydroxychloroquine *Hidroksihlorohin*	2	15.4%	1	4.2%	3	8.1%	
	Total/*Ukupno*	13	100%	24	100%	37	100%	
Glucocorticoids *Glukokortikoidi*	Yes/*Da*	2	9.1%	6	17.6%	8	14.3%	0.137
	No/*Ne*	20	90.9%	24	70.6%	44	78.6%	
	Occasionally/*Povremeno*	0	0%	4	11.8%	4	7.1%	
	Total/*Ukupno*	22	100%	34	100%	56	100%	

for more than 10 years speak in favour of the fact that the participants' age fits into the most common period of the disease onset. These results are similar to the results of the study by Al-Jabi et al. who investigated the impact of socio-demographic characteristics of RA patients on functional disability and quality of life. The study included 300 RA patients, most of whom were female (76.3%) with an average duration of the disease of 6 years [15]. Similarly, in their study, Direskeneli et al. looked into the quality of life, disease activity and whether there is a preference for administration routes by doctors and RA patients. Their study included a larger number of women (76%), with an average age of 50 [16]. In their study, Tipsing et al. looked into the influence of general data – age, sex, comorbidities, as well as data related to RA, including disease duration, treatment methods and lab results with the level of disease activity. The average age in that study was 52.33, while RA duration was 7.65 years [17].

The study results show that 35.7% of participants have been on current therapy for less than a year and 33.9% of participants have been receiving current therapy for more than five years. For most participants, this was the first therapy with a biological drug (76.8%). A study conducted in the territory of Vojvodina in 2018 showed that the average elapsed time from the RA diagnosis to the application of biotherapy in participants who received Etanercept was 6.12±5.62 years, while it was 7.54±7.15 years in patients who received Adalimumab, which indicated the necessity of increasing the availability of treatment with biotherapy in order to prevent the development of deformities and contractures and preserve the functional status and work ability of the patients [18]. The average duration of the disease before the commencement of biotherapy is not surprising because the official application of biotherapy for RA treatment in Serbia began in 2006, and in the Special Hospital for Rheumatic Diseases in Novi Sad in 2007 [7]. A ten-

year French study showed that although access to biological drugs in France was available, less than one-third of patients with early RA detection started treatment with biological drugs during the ten-year research [19]. Machado-Alba et al. collected information on the time from the initiation of conventional treatment in RA patients to the initiation of biological therapy. After 5 years of cDMARD therapy, 6% of RA patients started bDMARD therapy [20].

Analysing the impact of biological therapy on the quality of life and functional status of RA patients measured by the HAQ-DI questionnaire, it was found that patients treated with biological drugs were in remission (39.3%) or had low disease activity (60.7%), which is consistent with the results of other studies. Direskeneli et al. proved in their study that RA patients who are on biological therapy have better disease control and health status compared to patients who met the requirements for biotherapy but did not receive it [16]. In their study, Azevedo et al. followed 30 patients diagnosed with RA before and after the introduction of the first biological drug over the period of 6 months. Their study showed that there was a significant improvement in quality of life and functional status in just 3 months of biological drug administration [10]. In their study, Boyadzieva et al. followed 124 patients who were transferred from cDMARDs to bDMARDs for 1 year and assessed the quality of life using a questionnaire. The assessment was carried out at the beginning of therapy, 6 months and 1 year after the therapy. Their study confirmed that the quality of life rapidly improved after the introduction of biological therapy [21]. Boyadzhieva et al. did a similar study in 2022. In the prospective study, they concluded with use of the HAQ-DI and the 36-item short form health survey questionnaires that the application of biological therapy in RA patients led to improvement in the quality of life and functional capacity of RA patients. Intensity of RA activity and pain sensation were lower among the patients treated with cDMARDs and bDMARDs compared to the patients treated only with cDMARDs [22]. Bogojević et al. looked at whether there were any differences between the impact of biological therapy and conventional treatment on productivity and quality of life in patients suffering from RA. The HAQ-DI showed that the level of difficulty in daily functioning was higher with patients treated with cDMARDs compared to the ones treated with biological drugs. They also obtained results that health status, emotional status and quality of life are better in patients treated with biological therapy [23].

The results in our study showed that the HAQ-DI has a statistically significant correlation with the place of residence. The largest percentage of participants from urban areas (86.4%) is in remission as compared to a significantly smaller percentage of participants from rural areas (13.6%). Pinarosa et al. studied whether there was any difference in the distribution of RA disease and lack of health services in rural areas compared to urban areas. They came to the conclusion that the prevalence of RA is not increased in rural areas but that it is more difficult to provide adequate access to health services in such an environment. The problem occurs due to untimely visit to the doctor after the onset of symptoms, leading to late diagnosis, as well as due to frequent discontinuity in disease and therapy monitoring [24]. In their study, Hollick et al. showed that there are greater functional disability and disease activity in patients living in rural areas [25]. Study conducted in Taiwan showed that lower socioeconomic status or living in a rural area may be a risk factor for the development of RA and that it also may influence disease activity [26]. Movahedi et al. obtained results that a higher RA disease activity, measured by the number of swollen joints, was observed in patients living in rural areas [27]. Iltchev et al. showed that morbidity in residents of rural areas of Poland is higher than in residents of urban areas [28]. Codreanu et al. evaluated the influence of socioeconomic factors on the availability of biological therapy in RA patients in Romania. They found that people living in rural areas have difficulty in accessing biological drugs [29].

Study conducted at the Special Hospital for Rheumatic Diseases in Novi Sad in 2022 showed that the duration of morning stiffness has a statistically significant correlation with the HAQ-DI, which is also shown by the results of our study [30]. Of the total number of participants in remission, about a half (54.5%) do not have morning stiffness, while most of the ones with low disease activity (79.4%) have stiffness lasting up to 2 hours. These results coincide with the results of the study showing that the presence of morning stiffness was associated with higher HAQ-DI scores and thus significantly influenced the degree of disability, as well as a low level of the quality of life [15]. The authors of the Polish study compared the level of the life quality in patients with RA during cDMARD therapy and in combination with bDMARDs. They concluded that the intensity of the disease activity, pain and duration of morning stiffness were significantly lower in patients from the group that used biological drugs [31].

Conclusion

Patients suffering from rheumatoid arthritis who are treated with biological therapy have low disease activity and are in remission. Compared to the ones living in rural areas, respondents who live in urban areas have better quality of life and almost 1/3 of them do not have the feeling of morning stiffness.

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