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INFLUENCE OF BIOLOGICAL THERAPEUTICS ON PATIENT-REPORTED QUALITY-OF-LIFE OUTCOMES (WHOQOL-BREF), FUNCTIONAL SCORES AND DISEASE ACTIVITY AMONG CROATIAN PATIENTS WITH RHEUMATOID ARTHRITIS: OUR EXPERIENCE

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SUMMARY

Background: *Rheumatoid arthritis (RA) is a chronic and disabling disease with a great impact on the quality of life (QOL). The aim of this study was to assess QOL and health in RA patients treated with biological disease-modifying drugs (bDMARDs) as opposed to those treated with conventional synthetic DMARDs (csDMARDs). We analysed four domains of QOL: physical health (D1), mental health (D2), social relationships (D3) and one's surroundings (D4); as well as general quality of life (W1), general state of health (W2), and disease activity and physical disability.*

Subjects and methods: *Seventy-seven RA patients (group A=29 on bDMARDs, group B= 48 on csDMARDs) were enrolled in the study. QOL was evaluated using WHO questionnaire (WHOQOL-BREF), disease activity using Disease ActivityScore28C-reactive protein (DAS28CRP) and functional status using Health Assessment Questionnaire (HAQ).*

Results: *There was no statistically significant difference of mean values in the four domains of QOL, nor in the general QOL, between groups A and B. There was also no statistically significant difference regarding RA activity (3.51 vrs 3.54, p=0.56). However, we have found that the variable of the general state of health domain was statistically significantly higher in group B (2.66 vrs 2.89, p=0.001), while HAQ was statistically significantly higher in group A (1.19 vrs 1.07, p=0.018), as well as the duration of RA (6.25vrs 3.75 years, p=0.0006). Statistically significant correlation was found between HAQ and W2, disease duration and D3 in group A and DAS28CRP and D1, D2, W2 and HAQ and D1 and D2 in group B.*

Conclusion: *These findings suggest that the inclusion of bDMARDs in the treatment regimen was overdue, with RA already advancing with developed functional disability, which prevented the achievement of the primary goals of treatment: low disease activity or remission and the improvement of patient's QOL.*

Key words: *rheumatoid arthritis - quality of life – QOL - biological therapy - bDMARDs*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune disease of unknown etiology characterized by systemic inflammation, synovitis and joint destruction (Lee et al. 2001). RA patients, especially those undertreated or untreated experience pain, increased disability and impaired health-related QOL (HRQOL) (Scott et al. 2007, Strand et al. 2010). Most of the research conducted so far in relation to RA patients has been focused on HRQOL that is determined by clinical symptoms and also by physical and social functioning (Kvien et al. 2005). HRQOL questionnaires include domains of QOL that bear significance to a particular disease. The World Health Organization QOL assessment group has defined QOL as individuals' perception of their position in life in the context of the culture and the value system in which they live and in relation to their goals, expectations, standards and concerns (Kuyken et al. 1995). Literature lacks research on QOL in consideration to four domains with the general QOL and general state of health relevant to RA patients. By reviewing literature, only data on QOL using WHOQOL-BREF in diabetes mellitus patients undergoing different treatment plans has been noted (Pibernik-Okanović et al. 1998). It is well known that the relationship between medical health and subjective quality of health is not unambiguous, furthermore defining QOL as all encompassing state of well-being, influenced by not only objective indicators, but also by subjective perception. Early diagnosis and effective treatment is very important in RA (Curtis et al. 2011). The choice of therapies depends upon several

factors, including the severity of disease activity and the response of the patient to prior therapeutic interventions. The goals in RA treatment are reduction of inflammation (Matcham et al. 2014), achieving low disease activity or remission and improving patient's QOL. The European League against Rheumatism (EULAR) recommends the use of csDMARDs; methotrexate (MTX) or combination therapy with other csDMARDs e.g. sulfasalazine, hydroxychloroquine and leflunomide as the first-line therapy for RA (Smollen et al. 2014). Biologic DMARDs (bDMARDs) are monoclonal antibodies or antibody derivatives that block specific cytokines. bDMARDs have revolutionized RA treatment improving symptoms, and inhibiting structural damage with a safely profile and high cost (van der Velde et al. 2011). They change the course of the disease, improving the QOL and functional capacityand decrease mortality in RA patients (Felson et al. 2011). bDMARDs are recommended for use in RA patients who have previously failed csDMARDs treatment. QOL in RA patients is influenced by the degree of disease activity and functional ability that is dependent on the efficiency of applied therapy. The aim of this study is to assess the QOL in respect to four domains: physical health, mental health, social relationships and one's surroundings; along with the general QOL and general state of health, disease activity and functional scores in Croatian RA patients undergoing bDMARDs in contrast to those undergoing cs DMARDs.

SUBJECTS AND METHODS

Subjects

An observational, real-life study was conducted on 77 RA patients treated with different therapeutic options: bDMARDs and csDMARDs. The study site was the Department of clinical immunology, allergology and rheumatology at the University Hospital Dubrava. RA diagnosis was established according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria (Aletaha et al. 2010). Patients were assessed for QOL, disease activity and functional disability. All patients signed an informed consent form. The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Ethics Commutte of the University Hospital Dubrava.

Methods

For the purpose of this research, a QOL questionnaire by the WHO, WHOQOL-BREF, has been used (Perera et al. 2018). As a result, a profile of QOL in respect to four domains: physical health, mental health, social relationships and one's surroundings; has been ascertained. The patient was to retrospectively assess QOL in two weeks period. The results of the domains were attained by a combination of 24 questionnaire items. Results are expressed in each domain as an average of answers to the items that are used in its description. Answers for each item are given on a Likert type scale from 1 to 5, whereas 1 signifies the lowest degree of agreement with the corresponding item, and 5 signifies the highest degree of agreement. The answers were transformed to a scale from 0 to 100. Items of general QOL and general state of health were observed separately on a scale from 1 to 5**.** Results of the domains and overall satisfaction with life were expressed in a positive direction, determining a higher score as an indicator of a higher QOL. DAS28CRP was used to determine the disease activity, where DAS28CRP $\geq$5.1 was considered as high, DAS28CRP 3.2-5.1 was considered as moderate, DAS28CRP 2.6-3.2 as low disease activity and DAS28CRP $\leq$2.6 as RA remission. DAS28CRP is a standardized, composite outcome measure of disease activity calculated using a four variable formula (C-reactive protein, 28 joint count for tenderness, 28 joint count for swelling and patient global health assessment on a 0-10 numeric rating scale). The degrees of disability (functional score) based on the health assessment questionnaire (HAQ) score are categorized into four grades: HAQ:0 (no disability), HAQ: 0.1-0.99 (mild to moderate difficulty), HAQ: 1-1.99 (moderate to severe disability), HAQ: 2-3 (severe to very severe disability). HAQ is a questionnaire composed of questions that seek to understand the level of difficulty the patient has to perform such activities, as well as the need for assistance to perform them (Fries et al. 1980).

Statistical analyses

Descriptive statistics were used to describe categorical and continous variables. Relative frequencies were computed for all variables, and medians and ranges were determined for continous variables. Fisher's F test of independence was used as we have two nominal variables and we wanted to see whether the proportions of one variable are different depending on the value of the other variable. Statistical significance implies the decision that the prime link between two or more variables is the result of an incident or is caused by the action of an experimental factor. The decision whether to accept or reject the null hypothesis is based on the contrast between the results obtained and those that would be expected to be a true hypothesis true. The decision is made to use an adequate statistical test. A value of $p<0.05$ was statistically significant. If probability $p>0.05$ the hypothesis is not rejected, because it is probable that the relationship between the variables generated by the case action is more than 5%. If probability $p<0.05$ the null hypothesis is rejected, because it is probable that the relationship between variables is less than 5%. Statistical analyses were done using XLSTAT 2019.1.2.57072 program.

RESULTS

Seventy-seven RA patients (9 men, 68 women) were included in the study. Patients demographics and disease characteristics are presented in Table 1. There were 29 patients on biologics (Group A), and 48 patients on conventional therapy (group B). Biologic therapy included: TNF inhibitors (adalimumab (7), etanercept (7), infliksimab (4), golimumab (2), certolizumab (2)), interleukin-6 inhibitors (tocilizumab (5)), and interleukin-17-inhibitors (secukinumab (2)). The median of the duration of disease in group A was 6.25 years, and in group B was 3.75 years, which shows significant statistical difference (p=0.0006). The average DAS28CRP in group A is 3.51, and 3.54 in group B, without a statistically significant difference (p=0.56). The average HAQ in group A is 1.19, as opposed to 1.07 in group B, with a statistically significant difference (p=0.018). The mean value in the domain of D1 in group A was 52.31, and in group B 48.62, without a statistically significant difference (p=0.370). The mean value in D2 in group A was 68.84, and in group B 63.41, without a statistically significant difference (p=0.195). The mean value in D3 in group A was 72.29, and in group B 68.79, without a statistically significant difference (p=0.0.343). The mean value in D4 in group A was 69.63, and in group B 66.93, without a statistically significant difference (p=0.524). The mean value of W1 in group A was 3.55, and in group B 3.52, without a statistically significant difference (p=0.954). The mean value of W2 in group A was 2.66, whereas in group B it was 2.89, with a statistically significant difference (p=0.001) (Table 2). Statistically significant correlation was found between HAQ and W2, disease duration and D3 in group A and DAS28CRP and D1, D2, W2 and HAQ and D1 and D2 in group B (Table 3).

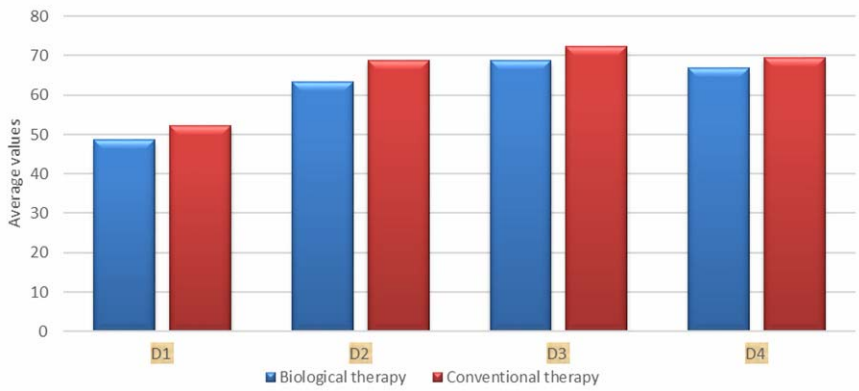

Figure 1. Four domains of the quality of life in RA patients on different therapies; D1-physical health, D2-mental health; D3-social relationships; D4-one's surroundings; W1-general quality of life; W2-general state of health

Table 1. Patient and disease characteristics

	Biological therapy	Conventional therapy	p value
Number of patients	29/77	48/77	
Age (years)	62	62	
Range	37-80	35-79	
Gender			
Male	7/29 (24%)	2/48 (4%)	0.712
Female	22/29 (76%)	46/48 (96%)	0.964
Duration of disease (years)	6.25	3.75	0.0006*
DAS28-CRP	3.51±1.55	3.54±1.05	0.560
HAQ	1.19	1.07	0.018*
DAS28-CRP			
remission	9/29 (31%)	8/18 (17%)	0.595
low disease activity	3/29 (10%)	9/48 (19%)	0.096
moderate discease activity	11/29 (38%)	28/48 (58%)	0.241
high disease activity	6/29(21%)	3/48 (6%)	0.383
HAQ			
no functional damage	1/29 (3%)	4/48 (8%)	0.001*
mild to moderate difficulty	11/29 (38%)	17/48 (35%)	0.918
moderate to severe disability	12/29 (41%)	23/48 (48%)	0.646
severe to very severe disability	5/29 (17%)	4/48 (8%)	0.187

DAS28-CRP - Disease Activity Score 28-C-reactive protein; HAQ - Health Assessement Questionaire;
* statistically significant p<0.05

Table 2. Mean values and standard deviation of four domains of the quality of life with the general quality of life and general state of health in RA patients on different therapies

	D1	D2	D3	D4	W1	W2
Biological therapy	52.31±18.42	68.83±17.85	72.29 ± 22.76	69.63±18.01	3.55±0.78	2.66±0.94
Conventional therapy	48.62±16.76	63.41±17.47	68.79±21.83	66.93±17.81	3.52±0.74	2.89±0.92
p-value	0.370	0.195	0.343	0.524	0.954	0.001*

D1 - physical health; D2 - mental health; D3 - social relationships; D4 - one's surroundings; W1 - general quality of life; W2 - general state of health; *statistically significant p<0.05

Table 3. Relationship between disaese activity, functional disability and domains of the quality of life in RA patients on different therapies

Pearson correlations, Pairwise two-sided p-values						
	D1	D2	D3	D4	W1	W2
Biological therapy						
DAS28CRP	0.913	0.204	0.471	0.195	0.179	0.142
HAQ	0.092	0.308	0.276	0.999	0.729	0.009*
Disease duration	0.165	0.249	0.004*	0.058	0.991	0.808
Conventional therapy						
DAS28CRP	0.031*	0.041*	0.107	0.437	0.379	0.043*
HAQ	0.002*	0.003*	0.197	0.608	0.210	0.103
Disease duration	0.515	0.811	0.396	0.893	0.807	0.902

DAS28-CRP - Disease Activity Score 28-C-reactive protein; HAQ - Health Assessment Questionnaire; D1 - physical health; D2 - mental health; D3 - social relationships; D4 - one's surroundings; W1 - general quality of life; W2 - general state of health; * statistically significant p<0.05

DISCUSSION

In this research, we focused on QOL in respect to four domains: physical health, mental health, social relationships and one's surroundings; as well as the general QOL and general state of health, disease activity and functional scores in Croatian RA patients on bDMARDs in comparison to those on csDMARDs. To the best of our knowledge this is the first national study from one center of the QOL of RA patients on different therapeutic options that used WHOQOL-BREF questionnaire. In our study there was no statistically significant difference of mean values in the four domains of QOL, as well as the general QOL between the two groups of RA patients. The mean value in the domain of general state of health was statistically significantly higher in RA patients treated by csDMARDs, in contrast to bDMARDs. Our results are not in accordance with some of the previously conducted studies, which have shown a favourable effect of biological therapy in the improvement of HRQOL while using a short-form health survey (SF-36) questionnaire, highlighting the social aspects, pain, physical functioning, emotional issues, vitality and physical aspects (Azevedo et al. 2015, Gerhold et al. 2015). The HRQOL and WHOQOL-BREF questionnaires are based on different aspects of perception of quality of life. HRQOL questionnaires, namely SF-36 and EuroQoL Group (EQ-5D) encompass domains of quality of life that are of relevance to a particular disease such as the medical outcome (Marra et al. 2005, Pollard et al. 2005). WHOQOL-BREF questionnaire assesses the subjective evaluation of quality of life in the frame of one's culture, social surroundings and environment, and is used significantly more rarely in research related to RA patients' QOL. RA is a heterogeneous chronic disease, and it is difficult to predict clinical outcomes, natural disease course and select the most efficient treatment option. Moreover, the quality of life in RA patients is impacted by fatigue, which is present in 80% of RA patients according to the results of the research conducted by Chauffier K. et al (Chauffier al. 2012). It is also affected by depression, appearing as a common co-morbidity with a prevalence approximately two to three times higher than the one in the general population (Frank et al. 1988, Lu et al. 2016). We found predominance of female participants (88%), it is known that women with RA are affected three times more than men (Turesson et al. 2009). bDMARDs in Croatia are recommended for use in RA patients who have previously failed csDMARDs treatment and who have high RA activity (Mitrović et al. 2017). In our study, the duration of RA was statistically significantly longer in patients treated by bDMARDs than those treated by csDMARDs. If bDMARDs are included in the therapy at a later time, when RA is already advanced with a developed functional disability, there is an inability to achieve the primary goals of treatment, which are low disease activity or remission and the improvement of QOL. Patients in both groups had on average a moderately high activity disease score RA without a statistically significant difference, which is not in accordance with the results of studies

conducted to assess the efficiency of bDMARDs (Wells et al. 2008, Minnock et al. 2015, Felson et al. 2011, Larmore et al. 2018). Out of the patients who were treated by bDMARDs, 31% were in remission, whereas 10% had a low activity disease score, in contrast to the group of patients treated by csDMARDSs, in which 17% of patients were in remission, and 19% had a low activity disease score. According to the results of a recent study Žagar et al. (Žagar et al. 2018) RA patients with higher disease activity and disability experience more pain, fatigue and have lower HRQOL. In our study, physical disability was moderate to severe, statistically significantly higher in patients treated by bDMARDs in comparison to those treated by csDMARDs. The underlying reason might be the significantly longer duration of RA and the later inclusion pf bDMARDs in the treatment. As reported by the study of Miwa et al. (2016) functional remission on bDMARDs is achieved in RA patients with a low HAQ and low depression scores. The lower mean variables in the domain of physical health, in comparison to those in the domains of mental health, social relationships and one's surroundings, are in support of the advanced physical disability of our patients. Statistically significant correlation in RA patients on bDMARDs was found between HAQ and W2, disease duration and D3 and between DAS28CRP and D1, D2, W2 and HAQ and D1 and D2 in RA patients on csDMARDs.

Our study has several limitations. First; small number of RA patients, especially RA patients on bDMARDs which may limit its applicability. Second; small number of male patients, 88% of patients were female. Third; this was an observational real-life study and for the effect of biological therapy to be ascertained, a longer observation is needed. Further, larger analysis with long-term follow up should be done.

CONCLUSION

These findings suggested that there is no difference in QOL in respect to four domains: physical health, mental health, social relationships and one's surroundings; as well as the general QOL and disease activity in RA patients treated by bDMARDs in comparison to those treated by scDMARDs. bDMARDs are included in the therapy at a later time, when RA is advanced with a developed functional disability, which prevents from achieving the primary goals of treatment; low disease activity or remission and improving patient's QOL. In support of the latter are the results of the longer duration of RA, a higher HAQ and the lower mean values of the general state of health in patients treated by bDMARDs. Our intention is to continue this study to clarify what else we should do for further improvement of QOL in RA patients.

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Conflict of interest: None to declare.

Contribution of individual authors:

Ana Gudelj Gračanin: designed the study, collected the data, drafted the manuscript and approved the final version.

Aldenita Matić: designed the study, collected the data and approved the final version.

Tea Mikula: collected the data, drafted the manuscript and approved the final version.

Jasminka Dobša: performed the statistical analysis, drafted the manuscript and approved the final version.

Iva Žagar: drafted the manuscript and approved the final version.

Lana Mužinić Marinić: conceptualized and designed the study, drafted the manuscript and approved the final version.

Jadranka Morović-Vergles: conceptualized the study, drafted the manuscript and approved the final version.

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