

INFLUENCE OF POLYPHARMACY ON THE FUNCTIONAL ABILITY OF PATIENTS WITH RHEUMATOID ARTHRITIS

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Clinical guidelines for the treatment of rheumatoid arthritis (RA) are based on the use of: nonsteroidal anti-inflammatory drugs (NSAIDs), conventional disease-modifying drugs (csDMARDs), immunosuppressants and biological therapies. Unfortunately, a large number of patients have other chronic diseases in addition to RA, which requires additional multiple use of drugs and often leads to polypharmacy. According to the definition of the World Health Organization (WHO), polypharmacy is defined as the routine use of 5 or more drugs, including prescription of over-the-counter drugs, dietary supplements, and traditional medicines. The aim of the study was to examine the impact of polypharmacy on the functional ability of patients with RA estimated based on the HAQ-DI index.

A retrospective study included 131 patients diagnosed with RA. Within the clinical characteristics, attention was focused on the present comorbidities, therapy and the total number of drugs used. The HAQ questionnaire was used to assess health status and functional ability. The obtained data were analyzed and statistically processed using appropriate software and statistical methods.

The study involved 29 males and 102 females mean age 60.25 ± 11.21 years. The analysis of the collected clinical data showed the presence of comorbidities in 80.15% of patients. Synthetic disease-modifying drugs were used 88.55%, while 13.74% of patients were on biological therapy. HAQ-DI values < 1.5 were present in 83.21%, while HAQ-DI ≥ 1.5 values were recorded in 16.79% of respondents. Polypharmacy was present in 75.57% of respondents. Potential interactions were more frequent in the group of respondents who can perform normal physical activities without or with mild restrictions (HAQ-DI < 1.5), while the presence of one serious potential interaction was more pronounced in the group of respondents with reduced functional ability (HAQ-DI ≥ 1.5).

The results of this study show a high frequency of polypharmacy and consequent potential drug interactions in patients with RA. Accordingly, monitoring of polypharmacy in patients with RA is necessary in order to achieve optimal functional status, disease control, minimize drug interactions and side effects.

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Key words: Polypharmacy, Rheumatoid arthritis, HAQ-DI

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Introduction

The incidence of rheumatoid arthritis (RA) is estimated to be 0.5-1% worldwide, while the majority of patients are able-bodied patients (1). The

disease is manifested by joint pain, fatigue, worsening of the emotional state, and if left untreated, there is irreversible structural and functional damage and functional incapacity of patients (2).

With the development and improvement of pharmacotherapy, the success in treatment is much greater compared to the epochs when there were no known drugs that modify the course of the disease (3). The goal of RA treatment is not only based on remission of the disease, but also on minimizing the consequences of the disease in order to increase the functional ability and quality of life of patients (4, 5). In this regard, quality of life is used as a subjective unit of measurement of the condition of patients suffering from this disease (6). The Health Assessment Questionnaire (HAQ) is the most commonly used questionnaire to assess the functional ability of patients with RA. Factors contributing to functional disability include: age, female gender, disease acti-

vity, rheumatoid factor (RF) or anti-citrulline antibodies (AntiCCP), radiological impairment, number of comorbidities present, and socioeconomic status (7-11).

Clinical guidelines for the treatment of RA are based on the use of nonsteroidal anti-inflammatory drugs (NSAIDs), conventional disease-modifying drugs (csDMARDs), immunosuppressants and biological therapies. The use of the mentioned drugs achieves optimal pharmacotherapeutic goals in the treatment of RA. However, patients with RA are significantly burdened by other diseases compared to the general population, which carries a risk of polypharmacy (12, 13). According to the definition of the World Health Organization (WHO), polypharmacy is defined as the routine use of 5 or more drugs, and this including prescription or over-the-counter drugs, as well as dietary supplements and traditional medicines (14). It may be useful to patients if the patient's clinical conditions, comorbidities, allergies, potential drug-drug interactions, drug-disease interactions are taken into account, and if drug prescribing is based on clinical evidence (15). Today, polypharmacy is a major public health challenge, primarily due to the increased likelihood of experiencing side effects that may affect a patient's health (16, 17).

The aim of the study was to examine the impact of polypharmacy on the functional ability of patients with RA estimated based on the value of the HAQ-DI index.

Patients and methods

The research was conducted at the Clinic for Rheumatology of the Military Medical Academy in Belgrade. The conducted retrospective research in-

cluded 131 patients diagnosed with rheumatoid arthritis, treated in the period between 2019 and 2020 by doctors from the Clinic for Rheumatology of the Military Medical Academy. Information on the demographic and clinical characteristics of patients was collected on the basis of medical documentation. As part of the clinical characteristics, attention was focused on the present comorbidities, therapy and the total number of drugs used, while the BNF (British National Formulary) database was used to determine the persistence of potential interactions between prescribed drugs.

The HAQ questionnaire was used to assess the health status and functional status of patients. The questionnaire consists of eight categories of questions that go through the assessment of patients' difficulty in performing normal activities during the day in the previous week. Categories include assessment in performing the following activities: dressing, grooming, getting up, taking food, walking, performing personal hygiene, reaching out, catching, and performing other common activities. Based on the values of the HAQ-DI index, the respondents were divided into two groups (HAQ-DI < 1.5 and HAQ-DI ≥ 1.5). HAQ-DI values < 1.5 indicate that patients can perform normal physical activities without or with mild limitations, while values ≥ 1.5 indicate significant limitations in performing daily activities that can lead to complete inability to perform the same.

Results

The study involved 131 patients, 29 males and 102 females with an average age of 60.25 ± 11.21 years. Demographic and clinical characteristics of the respondents are shown in Table 1.

Table 1. Demographic and clinical characteristics of respondents

Gender (men/women)	29/102 (22.14%/77.86%)
Age	60.25 ± 11.21
Presence of comorbidities (yes/no)	105/26 (80.15%/19.85%)
Synthetic DMARD	116 (88.55%)
Biological DMARD	18 (13.74%)
HAQ-DI	< 1.5: 109 (83.21%) ≥ 1.5: 22 (16.79%)
Presence of polypharmacy	99 (75.57%)
Presence of polypharmacy in relation to HAQ-DI values	< 1.5: 83 (76.15%) ≥ 1.5: 16 (72.73%)
Presence of interactions (yes/no)	86/45 (65.65%/34.35%)
Presence of interactions with respect to HAQ-DI	< 1.5: 69 (80.23%) ≥ 1.5: 17 (19.77%)

The analysis of the collected clinical data showed the presence of comorbidities in 105 (80.15%) patients, and the most common were hypertension (44.27%) and osteoporosis (26.72%). Synthetic disease-modifying drugs were used 88.55%, while 13.74% of patients were on bio-

logical therapy. In the further course of the research, the functional status of the respondents was analyzed. HAQ-DI values < 1.5 were present in 109 (83.21%), while HAQ-DI values ≥ 1.5 were present in 22 (16.79%) respondents.

Polypharmacy was present in 75.57% of respondents, while a total of 164 potential interactions were identified, of which 16 (9.76%) were mild, 27 (16.46%) moderate and 121 (73.78%) severe. Polypharmacy and drug interactions were more pronounced in the group of respondents who could perform normal physical activities without or with mild restrictions (HAQ-DI < 1.5).

Table 2 shows logistic univariate and multivariate regression when the HAQ-DI value is considered as a dependent variable.

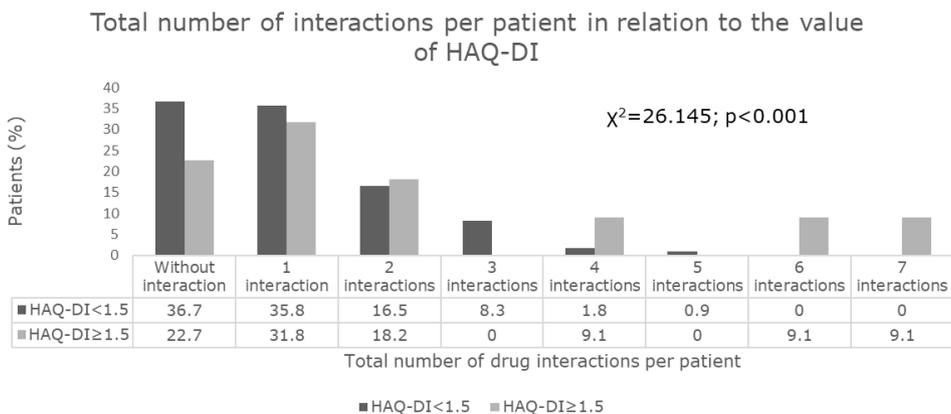
Since a larger number of drugs in therapy is closely related to a larger number of interactions, only one parameter remained significant in the regression analysis.

Graph 1 shows the total number of interactions per patient in relation to the HAQ-DI value.

Table 2. Logistic univariate and multivariate regression when HAQ-DI ≥ 1.5 is observed as a dependent variable

Univariate linear regression						
Independent variable	B	95% CI for B	Beta	R ² (%)	SIG	
Gender (female)	-0.042	-0.246-0.162	-0.036	0.1	0.684	
Age	0.009	0.002-0.017	0.211	4.4	0.016*	
Total number of comorbidities	0.077	0.007-0.148	0.188	3.5	0.032	
Total number of drugs	0.052	0.024-0.081	0.302	9.1	< 0.001*	
Total number of RA drugs	0.026	-0.037-0.088	0.072	0.5	0.414	
Total number of interactions	0.115	0.040-0.191	0.314	9.8	0.003	
DAS28*	0.174	0.130-0.218	0.569	32.3	< 0.001	
Multivariate linear regression						
Independent variable	B	95% CI for B	Beta	SIG par	R ² (%)	SIG mod
Age	0.004	-0.002-0.011	0.089	0.210	40.6	< 0.001
Total number of comorbidities	0.030	-0.039-0.098	0.072	0.390		
Total number of drugs in therapy	0.016	-0.015-0.047	0.094	0.299		
Total number of interactions	0.056	0.001-0.112	0.166	0.046		
DAS28*	0.157	0.114-0.200	0.514	< 0.001		

* DAS28 – Disease Activity Score in 28 Joints

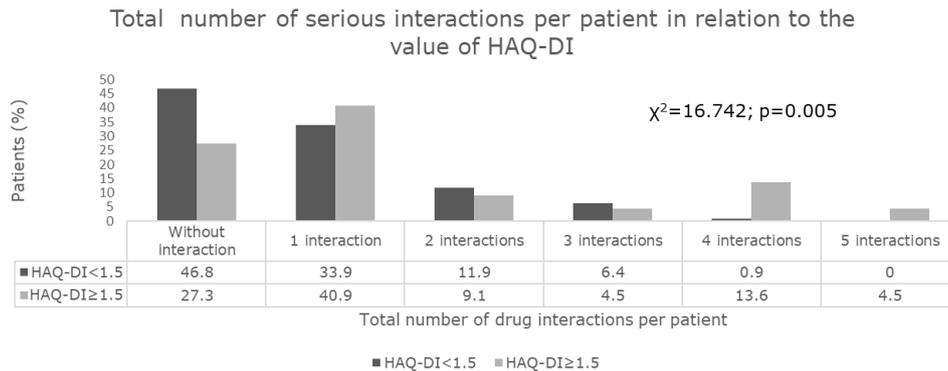


Graph 1. Total number of potential interactions per patient in relation to the HAQ-DI value

The analysis of the obtained results showed that the most frequent presence of one interaction (35.8% of patients whose HAQ-DI value was < 1.5 and 31.8% in patients with HAQ-DI \geq 1.5). A maximum of seven potential interactions (9.1%) were recorded in the group of patients whose HAQ-DI

value was \geq 1.5. Among the examined groups, statistical significance was noted ($\chi^2 = 26.145$; $p < 0.001$).

The total number of serious interactions per patient in relation to the HAQ-DI value is shown in Graph 2.



Graph 2. Total number of potential serious interactions per patient in relation to the HAQ-DI value

Based on the obtained results, it is found that the presence of one serious interaction is more common (40.9%) in patients with HAQ-DI \geq 1.5. The highest number of serious interactions was 5, with 4.5% of patients present. Among the examined groups, statistical significance was noted ($\chi^2 = 16.742$; $p = 0.005$).

Discussion

The course of RA can be mild with spontaneous remissions, which makes it undiagnosed for a long time, but also extremely fast and exhausting for the patient. However, most patients have a moderate form of RA with exacerbation episodes present (18). Early initiation of treatment with regular monitoring of disease activity allows clinicians to adequately identify the most appropriate therapeutic treatment options. This is extremely important to prevent disease progression. By conducting strict control of the disease, doctors can prevent the radiographic development of the disease, improve the performance of physical activities, which ensures a better quality of life for patients (19). By applying the HAQ-DI questionnaire, doctors gain insight into the patient's subjective condition, before starting any therapy, and later it can be used to assess the effectiveness of the therapeutic response, which simplifies the decision on further treatment modalities.

The results of the conducted research show that polypharmacy was present in 75.57% of patients. Polypharmacy can significantly interfere with the treatment and outcome of the disease. The most common consequences of polypharmacy are side

effects and interactions, which lead to increased treatment costs and, in the worst case, death (20). A high rate of polypharmacy within RA patients has been reported in studies conducted in Brazil and the United Kingdom. In a study conducted by Gomides AP et al. (20) in a group of 792 patients with RA, the frequency of polypharmacy was shown depending on the HAQ-DI value, with values in the range of 0-1 being represented in 60.16% of patients, while for values greater than 1 it was present in 78.36% of patients from that subgroup. They also showed that there was an association in a subgroup of patients with HAQ-DI values greater than 1 with polypharmacy (20). The results of the mentioned study are in accordance with the results of the conducted research.

A similar study was conducted by Filkova M et al. (21) in which she showed that the presence of polypharmacy greatly affected HAQ-DI values, with functional ability being reduced most often in patients who had more than 5 drugs in their therapy. A couple of years earlier, the same team dealt with a similar issue and showed that HAQ-DI values increased with the increase in the number of drugs used to treat underlying and other present diseases in patients (22). A study conducted by Treharne GJ et al. (23) also showed a significant correlation of polypharmacy with HAQ-DI values, not only with it but also with age, disease duration and DAS28 values, which is consistent with the results of the study.

Bechman K et al (24) conducted a large study whose results indicated that HAQ-DI values were higher in patients who had 6-9 and more than 9 drugs in the treatment of primary and other chronic

and acute diseases. They have shown that polypharmacy has a great impact on reducing the functional abilities of patients suffering from rheumatoid arthritis (24). As a main conclusion, they stated that any new introduction of the drug with the already existing therapy with modifying drugs could lead to a decrease in the effectiveness of the therapeutic response by 8% at the beginning of biologic therapy, while increasing by 13% the chance of developing serious adverse events (24).

Drug-related problems (DRPs) are events or circumstances related to therapy that may or may not interfere with desired health outcomes, and drug-drug interactions can be classified as DRPs. There is a high incidence of DRP in patients with RA, while the incidence is higher in patients with more comorbidities due to polypharmacy and complex treatment regimens (25). In a study conducted in 65.65% of respondents, possible drug interactions were noted, while the presence of one potential serious interaction was more common in patients with HAQ-DI ≥ 1.5 , whose values indicate that respondents have significant limitations in performing physical activities. In a study conducted by Ma et al., the presence of interactions in patients with RA (33.6%) was significantly less than in the study (25). The results of regression analysis confirm that the total number of interactions is a parameter that statistically significantly affected the functional ability of the respondents (HAQ-DI ≥ 1.5). However, there are currently no available literature data to compare

the results of the study related to the association of potential interactions and functional status of patients with RA.

Polypharmacy can be an important predictor of clinical outcomes in patients with RA and should be considered a "double-edged sword". On the one hand, given the presence of multiple comorbidities, it is inevitable, while on the other hand, the side effects and interactions of the drugs used must be taken into account. In this regard, it is of great importance to consider the impact of polypharmacy on the functional ability of patients with RA.

Conclusion

The results of this study indicate that polypharmacy was present in 75.57% of patients with RA, and the presence of one potential serious interaction was more common in patients with reduced functional capacity (HAQ-DI ≥ 1.5). Monitoring of polypharmacy in patients with RA is necessary in order to achieve optimal functional status, disease control, minimize drug interactions and side effects.

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doi:10.5633/amm.2022.0404**UTICAJ POLIFARMACIJE NA FUNKCIONALNU SPOSOBNOST OBOLELIH OD REUMATOIDNOG ARTRITISA***Nikola Krstić¹, Nikola Stefanović², Valentina Gocić¹, Katarina Ilić¹, Ivana Damjanović²*¹Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija²Univerzitet u Nišu, Medicinski fakultet, Katedra Farmacija, Niš, Srbija

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Kliničke smernice lečenja reumatoidnog artritisa (RA) zasnivaju se na primeni: nesteroidnih, antiinflamatornih lekova (NSAID), konvencionalnih lekova, koji modifikuju tok bolesti (csDMARD), imunosupresiva i biološke terapije. Nažalost, veliki broj bolesnika pored RA ima i druge hronične bolesti, što zahteva dodatnu višestruku primenu lekova i često vodi ka polifarmaciji. Prema definiciji Svetske zdravstvene organizacije (SZO; World Health Organization – WHO; eng), polifarmacija predstavlja rutinsku upotrebu 5 ili više lekova, uključujući lekove sa lekarskim receptom ili bez lekarskog recepta, dijetetske suplemente i tradicionalne lekove. Cilj sprovedenog istraživanja jeste ispitivanje uticaja polifarmacije na funkcionalnu sposobnost bolesnika, koji boluju od RA, procenjenu na osnovu vrednosti HAQ-DI indeksa.

Sprovedeno retrospektivno istraživanje uključivalo je 131 bolesnika sa dijagnozom RA. U sklopu kliničkih karakteristika, pažnja je bila usmerana ka prisutnim komorbiditetima, terapiji i ukupnom broju primenjivanih lekova. Za procenu zdravstvenog stanja i funkcionalne sposobnosti primenjen je HAQ upitnik. Dobijeni podaci analizirani su i statistički obrađeni primenom odgovarajućih softverskih i statističkih metoda.

U sprovedenom istraživanju učestvovao je 131 bolesnik, 29 bolesnika muškog i 102 bolesnika ženskog pola, prosečne starosti 60,25 godina ± 11,21 godina. Analizom prikupljenih kliničkih podataka uočeno je prisustvo komorbiditeta kod 80,15% bolesnika. Lekove koji modifikuju sintetičke bolesti primenjivalo je 88,55%, dok je na biloškoj terapiji bilo 13,74% bolesnika. Vrednosti HAQ-DI < 1,5 bile su prisutne kod 83,21% ispitanika, dok su vrednosti HAQ-DI ≥ 1,5 zabeležene kod 16,79% ispitanika. Polifarmacija je bila prisutna kod 75,57% ispitanika. Potencijalne interakcije bile su učestalije u grupi ispitanika koji mogu obavljati uobičajene fizičke aktivnosti bez ograničenja ili uz blaga ograničenja (HAQ-DI < 1,5), dok je prisustvo jedne ozbiljne potencijalne interakcije bilo izraženije u grupi ispitanika sa smanjenom funkcionalnom sposobnošću (HAQ-DI ≥ 1,5).

Rezultati sprovedenog istraživanja pokazuju veliku učestalost polifarmacije i posledničnih potencijalnih interakcija lekova kod bolesnika sa RA. U skladu sa tim, praćenje polifarmacije kod bolesnika koji boluju od RA neophodno je u cilju postizanja optimalnog funkcionalnog statusa, kontrole bolesti, minimiziranja interakcija i neželjenih efekta lekova.

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