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Original article

Polypharmacy and the Risk of Drug-Drug Interactions in Patients with Rheumatoid Arthritis

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SUMMARY

Introduction/Aim. Polypharmacy can increase the risk of side effects and cause adverse drug interactions with a significant impact on the course of the basic disease. The aim of the study was to determine the frequency of polypharmacy and examine its impact on the risk of drug-drug interactions in patients with rheumatoid arthritis (RA). The research was conducted in the form of a retrospective cross-sectional study. Material and methods. The study included 131 patients diagnosed with RA, treated during 2019 and 2020. Demographic data and clinical characteristics of the subjects were collected from the medical documentation (presence of comorbidities, prescribed therapy and number of drugs). In the study, polypharmacy was defined as the use of more than five drugs, regardless of the length of therapy. Results. The data analysis of the therapy used by patients showed that 84 subjects (64.12%) used 5 - 9 drugs, both for the treatment of primary and for the treatment of other present acute and chronic diseases. The analysis of the collected results identified potential interactions in 86 respondents (65.65%), while the total number of potential interactions was 164. The most common potential interactions were serious (73.78%). Analyzing the obtained results, it appears that aceclofenac is the drug that has the potential to enter into the largest number of interactions with the drugs used in the therapy of RA. Conclusion. Given the wide range of available drugs and therapeutic modalities used in the treatment of RA, it is necessary to choose the right combination of drugs in order to achieve the desired therapeutic outcomes and minimize potential drug-drug interactions.

Keywords: **polypharmacy, drug-drug interactions, rheumatoid arthritis**

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune, chronic and systemic disease of unknown etiology, characterized by changes in the joints with a tendency to deform if the therapy is not carried out adequately (1, 2). Modern pharmacotherapy of RA relies on the use of combinations of the following groups of drugs: analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids (GC), conventional synthetic drugs that modify the course of the disease (csDMARD) and biological drugs that modify the course of the disease (bDMARD) (3). The choice of RA therapy depends on a large number of factors, and the most important are: sex, age, degree of disease activity and the presence of comorbidities (4).

It is widely known that comorbid conditions play a key role in achieving optimal therapeutic outcomes during the treatment of RA, bearing in mind that a large number of patients suffering from RA often have two or more comorbidities associated with them (3). The presence of comorbidities significantly influences the choice of therapeutic modalities in patients with RA, which implies the simultaneous use of several drugs, consequently leading to polypharmacy. Polypharmacy is defined as a simultaneous use of 5 or more drugs in the treatment of one disease or for the treatment of more than one disease (5, 6). Polypharmacy can increase the risk of side effects and cause adverse drug interactions with a significant impact on the course of the basic disease (7). In addition, polypharmacy may reduce compliance with prescribed therapy, especially in elderly patients (8 - 10).

The aim of the study was to determine the prevalence of polypharmacy and examine its impact on the risk of drug-drug interactions in patients with RA.

PATIENTS AND METHODS

A retrospective study was conducted according to the principle of cross-sectional study at the Clinic for Rheumatology of the Military Medical Academy in Belgrade. The study included 131 patients diagnosed with RA, treated during 2019 and 2020. Demographic data and clinical characteristics of the subjects were collected from the medical documentation (presence of comorbidities, prescribed therapy and number of drugs). Within the therapeutic protocols, the drugs used in the treatment of RA were considered, as well as additional therapy, which includes drugs used to treat other present diseases. In the study, polypharmacy was defined as the use of more than five drugs, regardless of the length of therapy, and the BNF (British National Formulary) database was used to determine the persistence of potential interactions between prescribed drugs. The established interactions are divided into three groups: mild - which do not cause life-threatening side effects; moderate – interactions that can cause more serious side effects and which can also partially incapacitate the patient (the effect is more present in long-term interactions); serious - interactions that have a life-threatening effect on the patient that will depend on the exposure and dose of drugs used in the interaction.

Statistical methods

Within the descriptive statistics, the frequency (%), arithmetic mean with standard deviation and median with interquartile difference for the examined parameters are presented. Univariate and multivariate logistic regression analysis was used to examine the association between demographic characteristics, total drug numbers and comorbidities, including specific drugs (independent determinants) and the existence of interaction as dependent variables. Statistical analyses were performed using the SPSS software package (version 20) at the significance level $p < 0.05$.

RESULTS

Twenty-nine male subjects (22.14%) and 102 female subjects (77.86%) took part in the study. Table 1 shows the demographic characteristics and data on the present comorbidities in patients. The average age of the respondents was 60.25 ± 11.21 years (32 - 90 years, median 61 years).

In the conducted research, 80.15% of respondents had comorbidities, while 19.85% of respondents suffered only from RA. The most common comorbidities were hypertension (44.27%) and osteoporosis (27.48%). The obtained results show that 1.57 comorbidities per patient (in relation to all patients) and 1.97 comorbidities per patient (in relation to patients with comorbidities) were present.

The data analysis of the therapy used by patients showed that 84 subjects (64,12%) used 5 - 9

Table 1. *Demographic characteristics of respondents and the prevalence of comorbidities*

Gender	
Men	29 (22.14%)
Women	102 (77.86%)
Age	60.25 ± 11.21 61 (53.5 - 68)
Comorbidities	
Yes	105 (80.15%)
No	26 (19.85%)
Comorbidities (distribution)	
1	41 (31.30%)
2	36 (27.48%)
3	19 (14.50%)
4	8 (6.11%)
5	1 (0.76)
Total comorbidities per patient	1.58 (all patients) 1.97 (patients with comorbidities)
The most common comorbidities in patients	
Hypertension	58 (44.27%)
Osteoporosis	35 (26.72%)
Hypothyroidism	18 (13.74%)
Diabetes mellitus	13 (9.92%)
Osteopenia	12 (9.16%)
Lumbar syndrome	7 (5.34%)
Sjogren's syndrome	7 (5.34%)
Arrhythmias	7 (5.34%)
Lung fibrosis	6 (4.58%)
Anemia	6 (4.58%)

drugs, both for the treatment of primary and for the treatment of other present acute and chronic diseases (Table 2). The average number of drugs in the treatment of RA was 3.96 ± 1.36 (median: 4). The most common drugs in the treatment of RA in the study are corticosteroids (87.02%) and methotrexate (56.49%). The use of four drugs in the treatment of RA was the least common (5.34%), while the regimen of 2 drugs in the treatment of RA was the most common (48.1%) and referred to the combination of GC/scDMARD or GC / bDMARD (Table 2).

The distribution of interactions is shown in Table 3. The analysis of the collected results identified potential interactions in 86 respondents (65.65%), while the total number of potential interactions was 164. The most common were serious (73.78%), while the lowest percentage was recorded as mild interactions (9.76%). Each patient with drug interactions had two interactions.

Table 4 shows logistic univariate and multivariate regression when the presence of interaction is considered as a dependent variable.

In the logistic univariate regression shown in Table 4, the significance for the occurrence of the interaction was shown if more than five drugs were present in the therapy (OR = 6.19; 95% CI = 2.806 - 13.658; $p < 0.001$). Statistical significance was also observed when taking into account the total number of drugs used specifically in the treatment of RA (OR = 2,198; 95% CI = 1,544 - 3,131; $p < 0,001$). When it comes to the drugs used in the treatment of RA, significance for the occurrence of interactions was observed in patients receiving GC, methotrexate and NSAIDs (Table 4).

Table 2. *Characteristics of the subjects' therapy*

Total number of drugs	
< 5	**32 (24.43%)**
5 - 9	**84 (64.12%)**
≥ 10	**15 (11.45%)**
RA drugs	3.96 ± 1.36 4 (3 - 5)
Drugs for RA – distribution	
Corticosteroids	114 (87.02%)
Methotrexate	74 (56.49%)
Hydroxychloroquine/chloroquine sulphate	50 (38.17%)
Sulfasalazine	12 (9.16%)
Leflunomide	22 (16.79%)
NSAIL	52 (39.69%)
Biological catherapy	18 (13.74%)
Bisphosphonates	17 (12.98%)
Folic acid	76 (58.02%)
Vitamin D	108 (77.86%)
Representation of therapeutic regimens	
1 drug (GC or DMARD)	21 (16.03%)
2 drugs (GC/scDMARD or GC/bDMARD)	63 (48,1%)
3 drugs (GC/scDMARD / bDMARD)	40 (30.53%)
4 drugs (GC/multi scDMARD/bDMARD)	7 (5.34%)

Table 3. *Distribution of interactions*

Interactions	
Yes	86 (65.65%)
No	45 (34.35%)
Total identified interactions	**164**
Mild interactions (number of patients, total identified)	14 (10.69%), 16 (9.76%)
Moderate interactions (number of patients, total identified)	25 (19.08%), 27 (16.46%)
Serious interactions (number of patients, total identified)	74 (56.49%), 121 (73.78%)
Average number of interactions per patient	1.25 (all patients) 1.91 (patients with interaction)
Average number of interactions per drug (only patients with interaction)	0.27 ± 0.14 0.22 (0.17 - 0.33)
Average number of interactions per RA drugs (only patients with interaction)	0.43 ± 0.25 0.33 (0.25-0.50)
Average number of drugs per interactions (only patients with interaction)	4.84 ± 2.74 4.5 (2 - 4)
Average number of RA drugs per interactions (only patients with interaction)	2.94 ± 1.31 3 (2 - 4)

Table 4. *Logistic univariate and multivariate regression when the presence of interaction is considered as a dependent variable*

Logistic univariate regression				
Independent variable	B	OR	95% CI	SIG
Gender (female)	-0.192	0.825	0.340 - 2.000	0.670
Age	-0.015	0.985	0.954 - 1.018	0.378
HTA	-0.010	0.990	0.479 - 2.045	0.977
DM	-0.899	0.407	0.128 - 1.295	0.128
Total no. of comorbidity	0.052	1.053	0.774 - 1.432	0.742
Number of drugs > 5	1.823	6.190	2.806 -13.658	**< 0.001**
Total number of RA drugs	0.788	2.198	1.544-3.131	**< 0.001**
GC	1.462	4.314	1.476 - 12.609	**0.008**
MTX	1.175	3.237	1.529 - 6.856	**0.002**
CQ/HCQ	-0.401	0.670	0.321-1.399	0.286
SSZ	1.040	2.829	0.592-13.511	0.192
LEF	0.396	1.486	0.538 - 4.107	0.445
NSAID	2.266	9.641	3.469 - 26.791	**< 0.001**
Logistic multivariate regression				
Independent variable	B	OR	95% CI	SIG
Number of drugs > 5	1.393	4.029	1.579 - 10.278	**0.004**
GC	1.786	5.963	1.575 - 22.580	**0.009**
MTX	1.745	5.726	2.087-15.713	**0.001**
NSAID	2.473	11.863	3.482 - 40.418	**< 0.001**
Constant	-3.280	0.038	/	**< 0.001**

HTA - Arterial hypertension; DM - diabetes mellitus; MTX – methotrexate; CQ/HCQ – chloroquine/hydroxychloroquine; SSZ – sulfasalazine; LEF - leflunomide

While observing multivariate logistic regression, a statistically significant presence of interaction in all important parameters from univariate analysis was observed, except for the total number of drugs (Table 4).

While observing multivariate logistic regression, a statistically significant presence of interaction was observed .

Table 5 shows the distribution of drugs used in the treatment of acute and chronic diseases according to their therapeutic group, number of patients and potential interactions with drugs used in the treatment of RA.

Analysing the obtained results, it can be seen that aceclofenac is the drug that has the potential to enter into the largest number of interactions with drugs used in the therapy of RA. The potential interactions of aceclofenac are serious in nature. Their frequency is high, as shown by the fact that they make up 31.71% of the total interactions present, while in terms of serious interactions present, they make up 42.97%. Pantoprazole also showed a frequency of being able to interact (Table 5). Acetylsalicylic acid is the drug that gives the most common interactions of the moderate type (12). When the drugs used in the treatment of RA are taken into account, MTX stands out as the drug that enters into the largest number of interactions (56.09%).

Table 5. *Distribution of drugs used in the treatment of acute and chronic diseases according to their therapeutic group, number of patients and potential interactions with drugs used in the treatment of RA*

Anatomical Therapeutic Chemical Classification System (ATC)	Drug	sDMARDs					bDMARDs		Type of interactions		
		MTX[1]	PRE[2]	HCQ[3]	CQ[4]	SSZ[5]	GOM[6]	RIX[7]	Mild	Moderate	Severe
Antibiotics	Amoxicillin + clavulanic acid	1	0	0	0	0	0	0	0	0	1
	Ceftibuten	1	0	0	0	0	0	0	1	0	0
	Ciprofloxacin	1	0	0	0	0	0	0	0	0	1
	Clarithromycin	0	1	0	0	0	0	0	0	0	1
	Isoniazid	2	0	0	0	0	0	0	2	0	0
Analgesics	Aceclofenac	20	32	0	0	0	0	0	0	0	52
	Diclofenac	4	6	0	0	0	0	0	0	0	10
	Acetylsalicylic acid	10	12	0	0	0	0	0	0	12	10
	Ibuprofen	1	2	0	0	0	0	0	0	0	3
	Dexketoprofen	1	2	0	0	0	0	0	0	0	3
	Paracetamol	2	0	0	0	2	0	0	4	0	0
	Coxibs	1	1	0	0	0	0	0	0	0	2
	Meloxicam	0	3	0	0	0	0	0	0	0	3
Anticoagulants	Warfarin	0	2	0	0	0	0	0	0	2	0
Antiarrhythmic	Amiodarone	0	2	0	0	0	0	0	0	0	2
Proton pump inhibitors	Pantoprazole	33	0	0	0	0	0	0	0	0	33
Antineoplastic and immunomodulator	Leflunomide	7	0	0	0	0	0	0	0	7	0
Antianemic	Folic acid	0	0	0	0	6	0	0	0	6	0
AntiCD20	Rituximab	1	0	0	0	0	0	0	1	0	0
AntiTNFα	Golimumab	1	0	0	0	0	0	0	1	0	0
COPD therapy	Formoterol, budesonide	0	1	0	0	0	0	0	1	0	0
Anti-inflammatory	Sulfasalazine	6	0	0	0	0	0	0	6	0	0
		92	64	0	0	8	0	0	16	27	121

MTX[1]: metotrexate; PRE[2]: prednisolone; HCQ[3]: hydroxychloroquine; CQ[4]: chloroquine; SSZ[5]: sulfasalazine; GOM[6]: golimumab; RIX7: rituximab

DISCUSSION

With aging, most patients have an increase in the number of comorbidities. As a consequence of the manifestation of new comorbidities, the number of drugs that the patient uses increases, which consequently leads to polypharmacy. In most cases, polypharmacy is present in older patients, but it should be noted that the age limit has shifted today, and that polypharmacy is becoming more and more present in middle-aged patients. The main cause of shifting this limit is reflected in bad life habits, stress and improper diet (11 - 13).

The presence of polypharmacy is associated with frequent adverse events such as drug interactions, prolonged hospitalization, and death (14 - 16). In order to avoid potential side effects of polypharmacy, it is necessary to consider their po-

tential for interactions before introducing new drugs into therapy. By doing so, the possibility of interactions can be minimized (17).

The conducted research is a continuation of the research in which we studied the impact of polypharmacy on the functional ability of RA patients (18). The results of the conducted research show that polypharmacy was present in more than two thirds of patients, where 64.12% of patients in therapy had 5 - 9 drugs, while 11.45% of patients used more than 10 drugs at the same time. The obtained results are in accordance with other conducted studies which also show a high prevalence of polypharmacy in patients suffering from RA (19, 20). A study conducted by Bagatini F et al. (19) indicates that the prevalence of polypharmacy was in 95.1% of patients, while the average minimum and maximum number of drugs per patient was 7.5 ± 3.2 and 12.2 ± 4.1, respectively. It should be taken into account that the conducted study included 103 patients and that the total number of drugs used for their treatment was 1,836, which is significantly more when compared to our group. A multicenter study conducted by Gomides AP et al. (20) showed that the presence of polypharmacy in the study group of patients with RA was 67.9% and referred to patients who had five or more drugs in their therapy. Based on the results obtained, it was concluded that the percentage of polypharmacy increased in patients older than 70 years, who were positive for rheumatoid factor and had MTX, GC and NSAID in their therapy. Gomides AP et al. also showed that the maximum number of drugs prescribed in the treatment of RA was five, while the total number of drugs for the treatment of RA and other comorbidities was a maximum of 11 (20), while the most common comorbidity was hypertension in 47% of patients, which is in line with the results obtained in our study. In a study conducted by Bagatini F et al. (19), drugs from the group of proton pump inhibitors and NSAIDs showed the highest potential for interactions, primarily with MTX. Similar results were obtained by Ma et al. (21) in their study. Both studies showed that the use of NSAIDs can cause potential serious interactions in patients, which is in line with the results of the study.

In the conducted research, prednisolone was used as part of the RA treatment, which has the potential to enter into serious interactions with NSAIDs. Pflugbeil S et al. (22) also studied potential interactions in patients treated for RA in their study. Based on the database program, they identified and classified potential interactions. By studying drug metabolism, they came to the conclusion that polypharmacy can significantly contribute to faster manifestation of interaction. The analysis of the results of the conducted research showed potential interactions in MTX and prednisolone, primarily with NSAIDs and proton pump inhibitors. The results obtained are consistent with the Cochrane systematic review (23) which included 8,621 studies where only 17 studies showed no clinical interactions.

Methotrexate is a synthetic DMARD that has great potential for interactions with NSAIDs and leflunomide. In the conducted research, there were subjects who used leflunomide and MTX at the same time. Previous studies (24 - 28) have shown that leflunomide shows hepato- and hematotoxicity, and it is recommended to avoid the simultaneous use of these two drugs in order to minimize the harmful effects of drugs on hematopoiesis and liver. If it is necessary to combine them, it is desirable to monitor transaminases and blood parameters (leukocytes, erythrocytes, hemoglobin, platelets, differential blood count) at certain time intervals in order to prevent side effects that concomitant use of MTX and leflunomide may lead to. Interactions of MTX were also observed during simultaneous administration of bDMARDs, but in our case, they were not significant, which was also confirmed by the results of other authors (29, 30). The Canadian Association of Rheumatologists studied the interactions between MTX and the drugs most commonly used in the treatment of RA and other chronic diseases (31). They showed that the use of NSAIDs (31, 32), proton pump inhibitors (31,33) in combination with low doses of MTX (≤ 25 mg) will not lead to clinically significant interactions, while the use in combination with trimethoprim may lead to side effects even at low doses of MTX. As a safe alternative to trimethoprim in patients with rheumatoid arthritis, the use of amoxicillin, erythromycin and quinolone is recommended for bacterial infections (31). Clinically significant interactions and side effects of methotrexate are most common in cancer patients on high doses of the drug (> 500 mg) (34).

The presence of polypharmacy carries with it the risk of developing potential interactions, while also increasing the cost of patient care (35). In some situations, the presence of polypharmacy is almost

inevitable, however, efforts should be made to fully justify it.

CONCLUSION

A high prevalence of polypharmacy was noted in the conducted research. GC and MTX have been singled out as drugs used in the treatment of RA with the greatest potential for interactions, and the possibility of serious interactions was noted when NSAIDs and/or pantoprazole are co-administered with RA drugs. The greatest significance for the occurrence of interactions was shown in the subjects who had more than five drugs in the therapy. Given the wide range of available drugs and therapeutic modalities used in the treatment of RA, it is necessary to choose the right combination of drugs, while minimizing the number of potential interactions in that therapy. A detailed overview of the patient's therapy prescribed by a physician and/or clinical pharmacists is an important procedure to enable safe and effective RA treatment and prevent side effects and drug-drug interactions.

Contributions

All authors were involved in the preparation of the article, and all authors approved the final version to be submitted for publication.

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All authors have contributed significantly to the publication.

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Polifarmacija i rizik od lek–lek interakcija kod bolesnika sa reumatoidnim artritisom

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SAŽETAK

Uvod/Cilj. Polifarmacija može povećati rizik od nastanka neželjenih efekata i prouzrokovati neželjene interakcije lekova, imajući pritom značajan uticaj na tok osnovne bolesti. Cilj ove studije bio je da se utvrdi učestalost polifarmacije i da se ispita njen uticaj na rizik od lek–lek interakcija kod bolesnika sa reumatoidnim artritisom (RA).

Materijal i metode. Istraživanje je sprovedeno u vidu retrospektivne studije preseka. Studijom je bio obuhvaćen 131 bolesnik sa dijagnozom RA lečen u toku 2019. i 2020. godine. Demografski podaci i kliničke karakteristike bolesnika preuzeti su iz medicinske dokumentacije (prisustvo komorbiditeta, propisana terapija i broj lekova). Polifarmacija je u ovoj studiji definisana kao upotreba više od pet lekova, bez obzira na dužinu trajanja terapije.

Rezultati. Analiza podataka o terapiji koju su bolesnici primenjivali pokazala je da su 84 ispitanika (64,12%) primenjivala od pet do devet lekova, kako za lečenje primarnih, tako i za lečenje drugih prisutnih akutnih i hroničnih bolesti. Analizom prikupljenih rezultata identifikovane su potencijalne interakcije kod 86 ispitanika (65,65%), dok je ukupan broj potencijalnih interakcija bio 164. Najčešće potencijalne interakcije bile su ozbiljne (73,78%). Analiza dobijenih rezultata ukazala je na to da je aceklofenak lek koji ima potencijal da ostvari najveći broj interakcija sa lekovima koji se koriste u terapiji RA.

Zaključak. S obzirom na širok spektar dostupnih lekova i terapijskih modaliteta koji se koriste u lečenju RA, neophodno je odabrati pravu kombinaciju lekova kako bi se ostvarili željeni ishodi terapije, a potencijalne lek–lek interakcije svele na najmanju moguću meru.

Ključne reči: **polifarmacija, lek–lek interakcije, reumatoidni artritis**