Potential drug interactions in patients with rheumatoid arthritis

Fabíola Bagatini[1], Carine Raquel Blatt[2], Gabriela Maliska[3], Gunter Voges Trespash[3], Ivânio Alves Pereira[4], Adriana Fontes Zimmermann[5], Bernd Heinrich Storb[6], Mareni Rocha Farias[7]

ABSTRACT

Introduction: The term polypharmacy, meaning the concomitant use of multiple medications by one individual, has been widely reported in institutionalized or elderly patients. It can, however, occur in patients with chronic diseases, such as rheumatoid arthritis (RA). **Objective**: To quantify polypharmacy in a group of RA patients and to assess the risk of potential undesirable interactions between medications used for managing RA and those used for non-chronic diseases. **Methods:** A cohort study was carried out with 103 RA patients registered at the Strategy of Access to Medications from the Brazilian Health Ministry, at the School of Pharmacy of the city of Florianópolis, state of Santa Catarina. Patients were monthly followed up by use of form completion. Drug interactions were identified by use of the Drugdex System - Thomson Micromedex® - *Interactions* database. **Results:** Polypharmacy was found in 95.1% of the patients, and 19 potential undesirable interactions were observed between the drugs used by 74 patients (mean of 3.0 ± 1.2 interactions/ patient). All potential interactions were related to methotrexate. Omeprazole was the major representative, accounting for 29.3% of the interactions, followed by diclofenac sodium (17.6%), and metamizole sodium (13.2%). **Conclusion:** Considering that this study confirms that polypharmacy is a common therapeutic practice in RA patients, it is worth emphasizing the need for greater surveillance regarding the adverse effects or effectiveness reduction of certain drugs due to drug interaction.

Keywords: rheumatoid arthritis, drug interaction, polypharmacy, antirheumatic drugs.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease, characterized by progressive symmetric polyarticular impairment, and, in some cases, extra-articular manifestations.[1,2]

Rheumatoid arthritis is estimated to affect 0.5% to 1% of the world population, women being three to four times more affected than men.[3,4]

Ideal therapy varies according to the patient's individual characteristics, such as disease stage, activity, and severity, in addition to the response to previous treatment regimens.[5,6] Currently, the following five classes of drugs that benefit RA patients are available: analgesics; non-steroidal anti-inflammatory drugs (NSAID); corticosteroids; disease modifying anti-rheumatic drugs (DMARD); and biological drugs.

As the prevalence of comorbidities and risk factors, such as dyslipidemias, diabetes mellitus, hypertension, obesity, and osteoporosis, increases with age,[7] the prescription of concurrent medications is frequent in RA patients. In addition, the use of medications for symptomatic treatments and/or self-medication can further increase the number of drugs used by RA patients.

Polypharmacy deserves special attention, because medications are chemical substances that can interact with each

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Universidade Federal de Santa Catarina – UFSC, Brazil.
1. Pharmacist – UFSC
2. Pharmacist – M.Sc., UFSC
3. Undergraduate student in Pharmacy, UFSC; Pharmacy Professor of UniSul
4. Chief physician of the Service of Rheumatology, UFSC - Doctor in Rheumatology, USP
5. Assistant physician of the Service of Rheumatology, UFSC - Candidate for Doctor's Degree in Medical Sciences, UFSC
6. Collaborative researcher - Doctor in Production Engineering, UFSC
7. Pharmacist, Professor of the Post-Graduation Program in Pharmacy, UFSC - Doctor in Natural Sciences by the Pharmazeutisches Institut - Universitat Bonn, Germany
Correspondence to: Mareni Rocha Farias. Universidade Federal de Santa Catarina. Departamento de Ciências Farmacêuticas. Campus Universitário, Trindade. CEP: 88040-970. Florianópolis, SC, Brazil. Phone.: +55 48 3721-9567. Email: marenif@yahoo.com.br

other, with nutrients, or with environmental chemical agents and trigger undesirable or iatrogenic responses.[8,9] Despite the lack of consensus about what number of medications expresses polypharmacy, many authors define it as the association of six or more medications or as the administration of a greater number of medications than that clinically indicated.[10,11]

The term polypharmacy has been associated with institutionalized and elderly patients, but it can occur in other groups of patients with chronic diseases, such as RA. Thus, this study aimed at quantifying polypharmacy in RA patients and at assessing the risk of potential undesirable interactions between medications used for managing RA and those used for treating non-chronic affections.

METHODOLOGY

Our data were obtained from a cohort study of RA patients registered at the Strategy of Access to Medications from the Brazilian Health Ministry, at the School of Pharmacy of the UFSC/PMF, in the city of Florianópolis, state of Santa Catarina, from August 2008 to February 2010.

The sample comprised adult RA patients of both sexes, living in the city of Florianópolis and registered at the Strategy of Access to Medications from the Brazilian Health Ministry to receive the following medications: adalimumab, infliximab, etanercept (biologic agents), and leflunomide (DMARD).

Patients who did not want or could not participate in the study were excluded (20), and the following patients were considered as losses: those who did not sign the written informed consent (4); those who abandoned the study (8); and a deceased patient (1). The total sample comprised 103 patients. Total follow-up included one month of initial assessment and monthly follow-up for 12 months.

Data were collected by the major author during monthly interviews with patients, at the occasion of drug dispensation, by using previously validated follow-up forms. The following variables were collected: sex, age, medications used for RA treatment, and other medications used during the study period with or without medical prescription.

Considering the maximum number of drug associations used, the patients were classified according to the presence or absence of polypharmacy. In this study, polypharmacy was defined as the association of six or more medications, regardless of the duration. Topical medications, domestic formulations, and eye solutions were not included in the evaluation.

This study assessed the existence of possible interactions between the medications used for treating non-chronic affections and those used for treating RA. The medications used for treating non-chronic affections were those used by patients at any time of the study and that had no indication to be used in chronic diseases. The drugs used in the symptomatic RA treatment were included in the group of drugs for non-chronic affections.

Those medications used for non-chronic diseases during the follow-up of the RA patients were classified according to the Anatomical Therapeutic Chemical (ATC) Classification[12] into their therapeutic groups.

The ATC Classification is an international classification recommended by the World Health Organization. It consists in classifying medications into different groups and subgroups (levels) according to the organ or system upon which the medications act and according to their chemical, pharmacological, and therapeutic properties. There are five levels, the fifth level being the active chemical substance.[12]

The Drugdex System - Thomson Micromedex® - Interactions[13] database was used to assess reports of possible interactions between the drugs previously cited.

An association of the presence of potential interactions was observed with the variables sex, age bracket, presence of polypharmacy, and therapeutic schemes including methotrexate, by using the chi-square ($\chi 2$) and Fisher's Exact tests, with 95% confidence interval.

The associations showing potential drug interaction were classified and presented according to their severity, scientific evidence available, and time for the beginning of the adverse effect, according to that same database.

Regarding severity, the drug associations were classified as follows: *contra-indicated*, when the concomitant administration of drugs is not recommended; *major*, when the association represents a threat to life, requiring immediate medical intervention; *moderate*, when the patient's clinical findings get worse, requiring alteration of the medicamentous therapy instituted; *minor*, when the patient's clinical findings change, but alterations in the medicamentous therapy are not required.[13]

The scientific evidence available about drug interactions was classified as follows: *excellent*, when controlled clinical trials confirm the existence of drug interaction; *good*, when documents about the interaction exist, but controlled clinical trials lack; *fair*, when documents about the interaction are scarce, but pharmacological considerations of the occurrence of the interaction exist; *unknown,* when no document in the literature confirms the drug interaction.[13]

Regarding the time for the beginning of adverse effects, interactions were classified as follows: *rapid*, when the adverse effects resulting from the interaction occur within less than 24 hours; *slow*, when the adverse effects resulting

from the interaction do not occur within the first 24 hours; *nonspecified*, when there is no report in the literature about the time for the beginning of adverse effects after the simultaneous administration of the drugs.[13]

This study was approved by the Committee on Ethics in Research with Human Beings of the Universidade Federal de Santa Catarina (protocol 103/2008).

RESULTS

Regarding the sample, the female sex represented 89.7% of the patients, and the age ranged from 22 to 83 years (median, 57.4 years; mean, 56.9 ± 13.1 years).

Figure 1 shows the therapeutic regimens used by patients on study occasions T0, T4, T8, and T12, corresponding to 0, 4, 8, and 12 months, respectively. The combinations of DMARDs (49%, 44%, 39%, and 36% at T0, T4, T8, and T12, respectively) and of DMARDs and biological agents (35%, 37%, 35%, and 35% at T0, T4, T8, and T12, respectively) predominated, and methotrexate was present in approximately 60% of the therapeutic regimens. Throughout the study, a reduction in the association of DMARDs and an increase in the use of a biological agent in isolation (from 3% at T0 to 8% at T12) and of a DMARD in isolation (from 15% at T0 to 24% at T12) were observed.

The association of leflunomide and methotrexate was the predominant therapeutic regimen throughout the study.

The presence of polypharmacy was observed in 95.1% of the patients (Table 1). The means of the minimum and maximum numbers of medications associated per patient were 7.5 ± 3.2 and 12.2 ± 4.1, respectively.

Of the medications used by the patients studied, only those for treating non-chronic diseases were selected for assessing the risk of drug interaction, and they corresponded to 105 different active substances of 19 therapeutic groups.

Figure 2 shows the percentage frequency of the therapeutic groups used in the RA patients for treating their non-chronic diseases during the period studied. The three most frequently used therapeutic groups were the anti-inflammatory products (17.6%), analgesics (17.6%), and corticosteroids (15.8%). In such groups, the most used drugs were diclofenac sodium (36.4%), paracetamol (43.2%), and prednisone (72.3%), respectively.

The literature consulted evidenced 19 potential interactions, all related to methotrexate (Chart 1). Drug associations with potential interactions were used by 74 patients, in a total of 205 potential interactions and mean of 3.0 ± 1.2 potential interactions per patient. Nine patients showed only one potential interaction (Chart 2).

The literature also shows three potential drug interactions referring to chloroquine diphosphate and four others related to methotrexate, but no patient studied reported the use of such associations.

Of the variables assessed, only the presence of polypharmacy showed a positive correlation with the existence of drug interactions (Table 2).

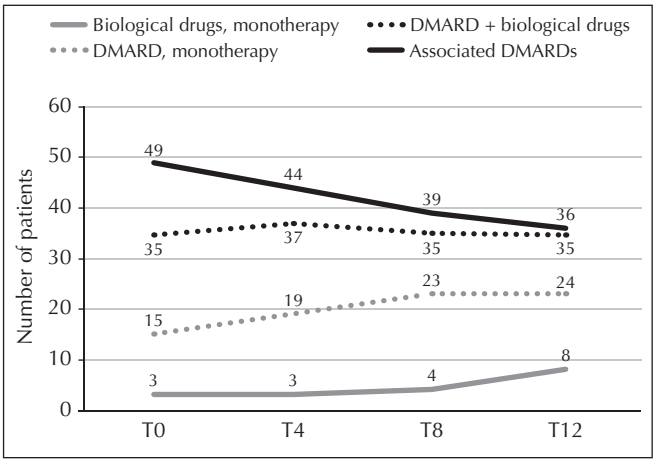

Figure 1
Therapeutic regimens used by patients undergoing treatment for RA.

Table 1
Presence of polypharmacy, means of the minimum and maximum numbers of medications used by patients undergoing treatment for RA.

Variables	Frequency or Mean ± SD*
Total number of medications used	1,836
Mean of the total number of medications used per patient	17.8 ± 6.9
Mean of the minimum number of medications associated per patient	7.5 ± 3.2
Mean of the maximum number of medications associated per patient	12.2 ± 4.1
Presence of polypharmacy	**% (n)**
Yes	95.1%
Male	9.2% (9)
Female	90.8% (89)
No	4.9%
Male	20.0% (1)
Female	80.0% (4)

* SD: standard deviation.

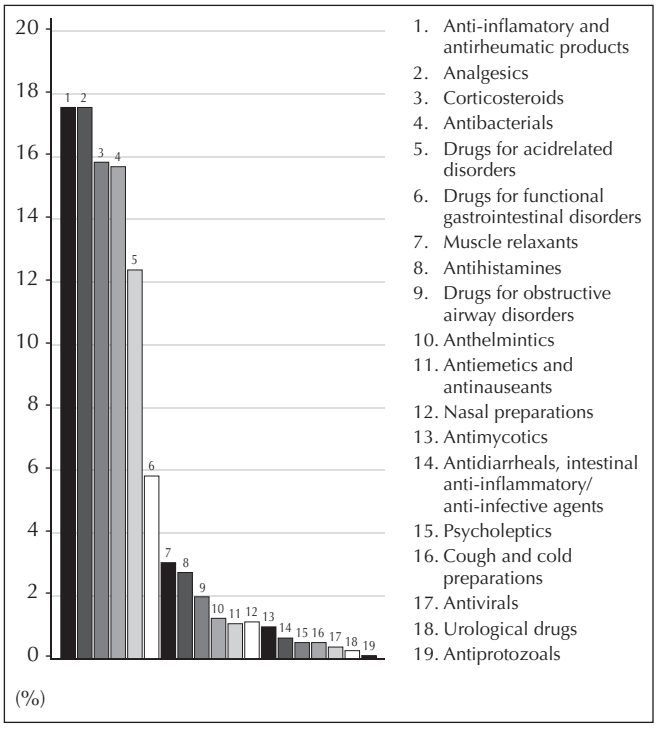

Figure 2
Percentage frequency of the therapeutic groups used for treating non-chronic diseases of patients undergoing RA treatment.

Table 2

Association of the variables sex, age, presence of polypharmacy, and therapeutic regimen including methotrexate with the presence of interaction of medications used for treating non-chronic diseases and those used by patients undergoing treatment for severe RA.

Variables	With interaction (N = 74)	No interaction (N = 29)	Relative risk (95% CI*)	P-value
Sex				
Male	6	3	0.92 (0.57-1.49)	0.7177
Female	68	26		
Age bracket				
< 60 years	39	18	0.90 (0.71-1.14)	0.3898
≥ 60 anos	35	11		
Presence of polypharmacy				
Yes	73	25	3.72 (0.64-21.58)	0.0214
No	1	4		
Therapeutic regimen for RA including methotrexate				
Yes	74	3	-	-
No	0	26		

* CI: Confidence interval.

Chart 1

Distribution of medications used for non-chronic diseases according to their therapeutic group, ATC classification, number of patients, and potential interactions with medications used in the RA treatment.

			Number of patients using the association and presence of potential interaction								
Therapeutic group	**Medications**	**ATC**	**LEF[1]**	**MTX[2]**	**CQN[3]**	**HCQ[4]**	**ABA[5]**	**ADA[6]**	**ETA[7]**	**INF[8]**	**RIT[9]**
Drugs for acid-related disorders	Esomeprazole magnesium	A02BC05	4	3	0	0	0	1	0	2	0
	Famotidine	A02BA03	1	0	1	0	0	0	0	0	0
	Lansoprazole	A02BC03	1	2	0	0	0	1	0	0	0
	Omeprazole	A02BC01	54	60*	3	5	1	18	8	9	1
	Pantoprazole sodium	A02BC02	2	3*	0	0	0	1	0	0	0
	Rabeprazole sodium	A02BC04	1	1	0	0	0	0	0	0	0
	Ranitidine, hydrochloride	A02BA02	1	2	0	0	0	1	0	1	0
Drugs for functional gastrointestinal disorders	Bromopride	A03FA04	2	2	0	1	0	0	0	1	0
	Domperidone	A03FA03	2	1	0	0	0	0	0	0	0
	Scopolamine, butylbromide	A03BB01	3	8	0	0	0	3	0	1	0
	Isometheptene mucate	A03AX10	5	7	0	0	1	6	0	1	0
	Metoclopramide hydrochloride	A03FA01	10	13	2	0	1	5	0	2	0
	Octylonium bromide	A03AB06	1	0	0	0	0	0	0	0	0
	Papaverine hydrochloride	A03AD01	2	2	0	0	0	0	0	0	0
	Pinaverium bromide	A03AX04	1	1	0	0	0	0	0	1	0
Antiemetics and antinauseants	Dimenhydrinate	A04AD	2	3	0	0	0	1	0	0	0
	Ondansetron hydrochloride	A04AA01	3	4	1	0	0	1	0	2	0

Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	Loperamide hydrochloride	A07DA03	1	0	0	0	0	0	0	0	0
	Nystatin	A07AA02	3	3	0	0	0	0	0	0	0
	Racecadotril	A07XA04	0	1	0	0	0	1	0	0	0
Urological drugs	Phenazopyridine hydrochloride	G04BX06	2	0	0	1	0	0	0	0	0
Corticosteroids	Betamethasone	H02AB01	9	8	0	0	0	5	0	1	0
	Deflazacort	H02AB13	6	4	0	0	0	1	0	2	0
	Dexamethasone	H02AB02	4	4	1	0	0	0	0	1	0
	Prednisolone	H02AB06	4	6	0	1	0	3	1	0	0
	Prednisone	H02AB07	62	65	5	6	3	19	7	11	1
	Triamcinolone acetonide	H02AB08	0	1	1	0	0	0	0	0	0
Antibacterials	Amoxicillin	J01CA04	10	14*	0		0	2	3	2	0
	Amoxicillin + potassium clavulanate	J01CE30	5	3*	0	0	0	0	0	1	0
	Dihydrate azithromycin	J01FA10	14	10	1	0	0	2	2	2	0
	Benzathine benzylpenicillin	J01CE08	1	2*	0	0	0	1	0	0	0
	Cefalexin monohydrate	J01DB01	8	8	0	0	0	2	1	0	0
	Cefepime hydrochloride	J01DE01	1	1	0	0	0	0	0	0	0
	Ceftriaxone disodium	J01DD04	1	1	0	0	0	0	0	0	0
	Cefuroxime sodium	J01DC02	2	1	0	0	0	0	0	0	0
	Ciprofloxacin hydrochloride	J01MA02	13	19*	0*	2	1	5	2	5	1
	Clarithromycin	J01FA09	2	2	0*	0	0	0	0	0	0
	Doxycycline hydrochloride	J01AA02	1	1*	0	0	0	0	0	0	0
	Fosfomycin trometamol	J01XX01	0	1	0	0	0	1	0	0	0
	Gentamicin sulfate	J01GB03	1	1	0	0	0	0	0	0	0
	Levofloxacin hemihydrate	J01MA12	7	5	0	1	0	0	0	3	0
	Metronidazole	J01XD01	2	1	0	0	0	0	0	0	0
	Minocycline hydrochoride	J01AA08	1	0	0	0	0	0	0	0	0
	Moxifloxacin hydrochloride	J01MA14	2	1	0	0	0	0	0	0	0
	Nitrofurantoin	J01XE01	4	3	0	0	0	0	0	0	0
	Nitrofurantoin + sulfamethoxypyridazine + phenylzodiamine piridine	J01ED20	1	0	0	1	0	0	0	0	0
	Norfloxacin	J01MA06	9	4	1	0	1	0	0	0	0
	Sulfamethoxazole trimethoprim	J01EE01	3	1*	0	2	0	1	0	0	0
	Tetracycline hydrochloride	J01AA07	0	1*	0	0	0	0	0	1	0
Antimycotics	Ketoconazole	J02AB02	1	1	0	0	0	0	0	0	0
	Fluconazole	J02AC01	5	3	0*	0	0	2	0	1	0
Antivirals	Aciclovir	J05AB01	1	1	0	0	0	0	0	1	0
	Oseltamivir phosphate	J05AH02	1	1	0	0	0	0	0	0	0
Anti-inflamatory products	Celecoxib	M01AH01	2	2	0	1	0	1	0	0	0
	Ketoprofen	M01AE03	5	3*	1	0	0	1	0	0	0
	Chondroitin sulfate + glucosamine sulfate	M01AX25	3	0	1	0	0	1	0	0	0
	Diclofenac potassium	M01AB05	1	0*	0	0	0	0	0	0	0
	Diclofenac sodium	M01AB05	32	36*	2	3	1	12	3	10	1
	Etodolac	M01AB08	1	1*	0	0	0	0	0	1	0
	Etoricoxib	M01AH05	3	1	0	0	0	1	0	0	0
	Phenylbutazone calcium	M01AA01	2	1*	0	0	0	0	0	0	0
	Ibuprofen	M01AE01	6	4*	3	0	0	2	1	0	0
	Mefenamic acid	M01AG01	2	0*	0	0	0	0	0	0	0
	Meloxicam	M01AC06	5	6	3	0	0	1	1	2	0
	Naproxen sodium	M01AE02	3	3*	0	0	1	2	0	0	0
Anti-inflamatory products	Nimesulide	M01AX17	27	**22***	3	1	0	2	3	3	0
	Piroxicam	M01AC01	1	**0***	1	0	0	0	0	0	0
	Tenoxicam	M01AC02	3	**0***	1	0	0	0	0	0	0
Muscle relaxants	Carisoprodol	M03BA02	9	6	2	1	0	2	1	1	0

Muscle relaxants	Cyclobenzaprine hydrochloride	M03BX08	5	3	2	0	0	0	0	0	0
	Orphenadrine citrate	M03BC51	5	4	0	0	0	1	0	0	0
Analgesics	Acetylsalicylic acid	N02BA01	5	3*	0	0	0	0	0	1	0
	Lysine clonixinate	N02BG61	1	1	0	0	0	0	0	0	0
	Codein phosphate	N02AA08	12	8	1	1	0	2	1	4	0
	Dihydroergotamine mesylate	N02CA01	2	0	1	0	0	0	1	0	0
	Metamizole sodium	N02BB02	28	27*	0	1	2	11	2	4	0
	Naratriptan hydrochloride	N02CC02	1	1	0	1	0	0	0	0	0
	Paracetamol	N02BE01	38	38	4	5	1	10	5	11	0
	Tramadol hydrochloride	N02AX02	3	2	1	0	0	0	0	2	0
Psycholeptics	Hydroxyzine hydrochloride	N05BB01	1	2	1	0	0	2	0	1	0
Antiprotozoals	Secnidazole	P01AB07	1	0	0	0	0	0	0	0	0
Anthelmintics	Albendazole	P02CA03	3	1	0	0	0	2	0	0	0
	Ivermectin	P02CF01	4	3	0	0	0	2	0	0	0
Nasal preparations	Oxymetazoline hydrochloride	R01AA05	1	0	0	0	0	0	0	0	0
	Phenylephrine hydrochloride	R01BA03	5	1	2	0	0	0	0	0	0
	Pseudoephedrine sulfate	R01BA03	1	1	0	1	0	0	1	0	0
Drugs for obstructive airway diseases	Acebrophylline	R03DA	1	1	0	0	0	0	0	0	0
	Beclomethasone dipropionate	R03BA01	2	2	0	0	0	0	0	0	0
	Budesonide	R03BA02	4	2	0	0	0	0	0	0	0
	Phenoterol hydrobromide	R03AC04	2	2	0	0	0	0	0	0	0
	Fluticasone furoate	R03BA05	1	0	0	0	0	0	0	0	0
	Formoterol fumarate	R03AC13	1	0	0	0	0	0	0	0	0
	Ipratropium bromide	R03BB01	3	2	0	0	0	0	0	0	0
	Salbutamol sulfate	R03AC02	2	2	0	0	0	0	0	0	0
	Theophylline	R03DA04	1	1*	0	0	0	0	0	0	0
Cough and cold preparations	Acetylcysteine	R05CB01	2	3	0	0	0	0	1	0	0
	Ambroxol	R05CB06	1	0	0	0	0	0	0	0	0
Antihistamines	Carbinoxamine maleate	R06AA08	1	0	1	0	0	0	0	0	0
	Chlorpheniramine maleate	R06AB04	7	5	1	0	1	1	1	0	0
	Desloratadine	R06AX27	1	0	0	0	0	0	0	0	0
	Dexchlorpheniramine maleate	R06AB02	2	1	0	0	0	0	0	0	0
	Epinastine hydrochloride	R06AX24	0	0	0	0	0	0	0	1	0
	Fexofenadine hydrochloride	R06AX26	1	2	0	0	0	0	0	1	0
	Loratadine	R06AX13	3	2	1	0	0	0	0	1	0
	Promethazine hydrochloride	R06AD02	1	1	0	0	0	0	0	0	0

[1]LEF: Leflunomide; [2]MTX: Methotrexate; [3]CQN: Chloroquine diphosphate; [4]HCQ: Hydroxychloroquine sulfate; [5]ABA: Abatacept; [6]ADA: Adalimumab; [7]ETA: Etanercept; [8]INF: Infliximab; [9]RIT: Rituximab
* Existence of potential drug interaction reports.

Omeprazole was the major representative of the risk for potential drug interaction identified in the study, corresponding to 29.3% of them, followed by diclofenac sodium (17.6%), and metamizole sodium (13.2%).

Regarding the potential interactions identified in the study, 78.9% were classified as major, 21.0% had fair scientific evidence, and, in 21.0%, the beginning of adverse effects was rapid (Chart 2).

DISCUSSION

This study aimed at providing information about the risk of potential drug interactions in RA patients, considering that, in Brazil, that type of information is rare.

Studies have shown that combinations of DMARDs are more effective than monotherapy.[14,15,16] In addition, biological agents are more effective when combined with DMARDs, in particular methotrexate.[17,18,19] This justifies the strategy of combining DMARDs or biological agents found in most patients in this study.

The means of the minimum and maximum numbers of medications used per patient in this study were 7.5 ± 3.2 and 12.2 ± 4.1, respectively. In a survey about medications used by retired elderly, the mean number of medications used was 4.1 ± 3.0.[20] In 2006, Loyola Filho *et al.*,[21] studying the prevalence of medication consumption in 1,598 elderly, reported that the mean number of medications used was 2.18.

Chart 2

Distribution of medications reported as having a potential interaction with methotrexate according to the number of users, severity of the interaction, scientific evidence available, and time for the beginning of adverse effects. N = 103 patients.

Medications	Number of patients using the MTX association[1]	Severity	Evidence	Time for the beginning of adverse effects
Acetylsalicylic acid	3	Major	Good	Rapid
Amoxicillin	14	Major	Good	Slow
Amoxicillin + potassium clavulanate	3	Major	Good	Slow
Benzathine benzylpenicillin	2	Major	Good	Slow
Ketoprofen	3	Major	Good	Slow
Diclofenac sodium	36	Major	Good	Slow
Metamizole sodium	27	Major	Good	Slow
Doxycycline hydrochloride	1	Major	Good	Rapid
Etodolac	1	Major	Fair	Slow
Phenylbutazone calcium	1	Major	Fair	Slow
Ibuprofen	4	Major	Good	Slow
Naproxen sodium	3	Major	Good	Slow
Nimesulide	22	Major	Good	Slow
Omeprazole	60	Major	Good	Rapid
Sulfamethoxazole + Trimethoprim	1	Major	Excellent	Slow
Ciprofloxacin hydrochloride	19	Moderate	Fair	NS [2]
Pantoprazole sodium	3	Moderate	Good	Rapid
Tetracycline hydrochloride	1	Moderate	Fair	NS [2]
Theophylline	1	Moderate	Good	Slow

[1] MTX: Methotrexate, [2]NS: Noy specified.

The mean number of medications used and the frequency of polypharmacy in our study were higher than those found in other national studies.[22,23] However, studies about medication use and the term polypharmacy are usually associated with institutionalized and/or elderly patients, hindering the comparison of the results obtained with those of other studies.

According to Prybys *et al.*[24], in elderly patients, the risk of adverse effects, including drug interactions, increases 13% with the use of two medications, 58% with the use of five medications, reaching 82% in the presence of seven or more medications.

Polypharmacy is associated with an increase in the risk and severity of adverse reactions, in the risk of triggering drug interactions, of causing cumulative toxicity and mistakes during medication administration, and of reducing adherence to treatment. Therefore, it is directly related to health care costs, which include medications and the repercussions of their use, such as costs of visits to specialists, emergency health care, and hospital admission.[22,25]

In this study, the most frequently used therapeutic groups were the anti-inflammatory products (17.6%), analgesics (17.6%), and corticosteroids (15.8%). These groups and their representatives are used for treating RA, and, in more severe cases, their full doses can be administered,[6,26] which explains their greater frequency of use.

It is worth noting that, in this study, the detection of potential drug interactions was based in an information technology tool included in the Drugdex System - Thomson Micromedex® - Interactions[13] database, which cannot consider aspects related to patients, dosages, and sequence and time of medication administration. This, thus, may overestimate the incidence and risk of potential drug interactions.

All potential drug interactions found in this study were related to methotrexate. In the literature consulted, no potential interaction of the medications selected in this study with those used for RA management (abatacept, adalimumab, etanercept, infliximab, leflunomide, and hydroxychloroquine sulfate) has been reported.[13,27,28]

Methotrexate is the most used initial therapy in RA patients, except for those with liver disease.[26] Despite its excellent efficacy and tolerability profiles, in addition to its low cost,[29] methotrexate can interact with other medications, resulting in toxicity.

In this study, 19 types of potential interactions with methotrexate were observed, 15 of which were classified as major and four as moderate. This emphasizes the need for being cautious when prescribing and dispensing other medications to patients already using methotrexate in their treatment regimens, as well as the need for instructing patients regarding self-medication.

The interactions related to methotrexate and classified as major can result in an increase in the serum concentrations of its active metabolite, potentiating its adverse effects, such as leukopenia, thrombocytopenia, anemia, liver toxicity, nephrotoxicity, and mucosal ulcerations.[1,13,27,28]

An increase in the serum concentrations of methotrexate, with signs and symptoms of toxicity, was observed when the drug was coadministered with a variety of penicillins, such as amoxicillin, benzylpenicillin, mezlocillin, piperacillin.[30,31] Because of the structural similarity between penicillins and methotrexate, a competitive inhibition of methotrexate tubular secretion can occur, increasing its half-life.[28,32,33]

According to the Drugdex System - Thomson Micromedex® - Interactions[13] database, tetracyclines and other oral antibiotics can reduce the effectiveness of methotrexate by reducing its intestinal absorption or interfering with its enteropathic circulation, inhibiting the intestinal flora and suppressing the drug metabolism by bacteria. However, other authors believe that tetracyclines and their derivatives increase methotrexate serum concentrations.[27,34,35]

The association of high doses of methotrexate with doxycycline can result in gastrointestinal and hematologic toxicity.[34] The interaction mechanism remains unknown, but it is believed to be related to the removal of methotrexate from its binding sites in serum proteins, the competition for renal tubular secretion, or the inhibition of the renal synthesis of prostaglandins.[13,27,34,35]

No potential interaction between minocycline and methotrexate has been reported, but as minocycline is a tetracycline derivative, its association with methotrexate should be monitored.

Pancytopenia and myelotoxicity have been reported after the concomitant administration of methotrexate and sulfamethoxazole + trimethoprim.[36,37,38] The literature suggests the following two mechanisms of interaction: 1) sulfonamides can remove methotrexate from its binding site to serum proteins or reduce its renal excretion; and 2) additive inhibition of dihydrofolate reductase by methotrexate and trimethoprim.[36,39]

In addition to pancytopenia and myelotoxicity, that association can increase the risk of megaloblastic anemia because methotrexate and sulfonamides can produce a folate deficiency by suppressing dihydrofolate reductase.[1,13,27,28]

The concomitant use of methotrexate and ciprofloxacin can result in an increase in the serum concentrations of the former due to the inhibition of its renal tubular transportation caused by the latter.[1,13,27,28] Two cases of severe toxicity have been reported, and, thus, the association of high doses of methotrexate and ciprofloxacin should be avoided.[40]

The association of methotrexate and NSAIDs can cause several complications, such as severe hematologic and gastrointestinal toxicity.[13,35] In addition, preexisting renal dysfunctions (or NSAID-induced renal dysfunctions) potentiate the risk for adverse reactions.[13,27,28] That interaction can occur through four different mechanisms: 1) competition between methotrexate and NSAIDs for renal tubular secretion; 2) removal of methotrexate, or its active metabolite, from the binding site to serum proteins; 3) a reduction in the liver metabolism of methotrexate caused by NSAIDs; and 4) NSAIDs inhibit the synthesis of prostaglandins (vasoconstrictors of renal capillaries), which results in a decrease in renal blood flow, and, thus, in the glomerular filtration of methotrexate.[41,42]

Some studies have reported that the coadministration of methotrexate, piroxicam, naproxen, ketoprofen, and ibuprofen in RA patients did not affect the pharmacokinetic profile of methotrexate.[43,44]

Although the concomitant administration of NSAIDs and methotrexate can potentially cause severe toxicity, low doses of that association are considered well tolerated, but the appearance of severe adverse effects should always be cautiously monitored.[13,35]

Although metamizole sodium and acetylsalicylic acid have been classified as analgesics according to the ATC Classification, in the literature consulted, their mechanisms of interaction with methotrexate have been compared with the general mechanism of NSAIDs.[13,27,28,45,46]

The major representative of the potential drug interactions identified was omeprazole, accounting for 29.3% of them. Its interaction was classified as major and the beginning of adverse effects was rapid. The concomitant use of methotrexate and omeprazole can increase the risk of toxicity of the former,[13,27,28,47] because, according to Suzuki *et al.*,[48] the coadministration of proton pump inhibitors can delay the excretion of methotrexate and

potentiate its adverse effects.Omeprazole serum concentrations decrease rapidly after interruption of its use.[13,27,28,47] Thus, patients receiving that association should be strictly monitored to avoid possible damage resulting from the high concentration of methotrexate in their bodies.[13,27,28]

The interaction between pantoprazole and methotrexate is less severe due to the degree of activation of pantoprazole according to the pH of the medium. With a pH of approximately 5, as that found in the renal tubules, pantoprazole is less active than omeprazole, having, thus, a lower inhibitory effect on methotrexate tubular secretion.[49]

A double-blind, placebo-controlled study with 15 adult asthmatic patients was carried out to assess the effects of the concomitant use of theophylline and methotrexate.[50] Eight patients received methotrexate and seven received placebo for six weeks. After six weeks, theophylline excretion reduced from 48 to 38.9 mL/h/kg in patients treated with methotrexate. The serum concentrations of theophylline should be monitored when methotrexate is introduced, discontinued, or has its dosage altered.[13,50]

Patients with RA undergo treatment protocols with multiple medications and for prolonged time. Those are important factors, which, when combined, can contribute to the occurrence of adverse reactions and undesirable drug interactions, which can worsen the pathophysiological scenario already installed and/or require the suspension or change of the therapeutic regimen.

It is worth emphasizing the need for assessing the risk-benefit relation of each drug association, as well as the adoption of measures that can reduce negative effects, such as changing the time of drug administration and monitoring adverse effects related to drug association.

The practice of self-medication, mainly for pain control, is common among RA patients, which puts them at greater risk for drug interactions, adverse effects, and toxicity. The therapeutic group with the highest potential of interaction with the medications used for RA treatment was that of the anti-inflammatory drugs.

To minimize or prevent the potential risk of adverse reactions and drug interactions, contributing to the rational use of medications and improvement of the health conditions of RA patients, the following is recommended: multidisciplinary teams; pharmacotherapeutic follow-up; and education of patients regarding the practice of self-medication.

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