Drug interactions: a contribution to the rational use of synthetic and biological immunosuppressants

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ABSTRACT

Drug interaction is a clinical event in which the effects of a drug are altered by the presence of another drug, phytochemical drug, food, beverage, or any environmental chemical agent. The incidence of adverse reactions caused by drug interactions is unknown. This lack of information is compounded by not knowing the number of patients who are prescribed combinations of drugs that can potentially interact. Patients who will or will not experience an adverse drug interaction cannot be clearly identified. Those with multiple diseases, with kidney or liver dysfunction, and those on many drugs are likely to be the most susceptible. Patients with autoimmune diseases are at higher risk for drug interactions. In addition to representing a risk for the patient and jeopardizing the health care provided by professionals, drug interactions can increase dramatically health care costs. This review article approached the clinically relevant interactions between the most used drugs in rheumatology (except for non-steroidal anti-inflammatories and corticosteroids) aiming at helping rheumatologists to pharmacologically interfere in the disease processes, in the search for better outcomes for patients and lower costs with the complex therapy of chronic diseases they deal with.

Keywords: drug interactions, drug therapy, antirheumatic agents, rheumatic diseases.

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INTRODUCTION

Drug interaction is a clinical event in which the effects of a drug are altered by the presence of another drug, phytochemical drug, food, beverage, or any environmental chemical agent. When two drugs are administered concomitantly to a patient, they can act independently or interact with each other, increasing or reducing the therapeutic or toxic effect of one and/or the other. Sometimes, the drug interaction can reduce the efficacy of a drug, and be as harmful as the increase in its toxicity. Some interactions can be beneficial and useful, justifying the concomitant deliberate prescription of two drugs.[1]

The incidence of adverse reactions caused by drug interaction is unknown and varies from study to study, depending on its design, population assessed (elderly, children), and the outpatient or hospitalized patient condition, the latter usually using a greater number of drugs. This lack of information is compounded by not knowing the number of patients who are prescribed combinations of drugs that can potentially interact.

A pharmacological and epidemiological study[2] of drug interactions carried out in a Brazilian university-affiliated hospital has assessed 1,785 prescriptions of adult wards and has found the following: each patient received, on average, seven drugs (ranging from two to 26); 49.7% of the prescriptions comprised drug interactions, 23.6% being considered moderate and 5%, severe; 17.9% of the prescriptions had more than one drug interaction. The study has assessed 33 medical records containing prescriptions with severe drug interactions and evidenced the presence of adverse reactions due to drug interaction in 51.5% of the patients. The authors compared their results with those of other three studies also performed in Brazil, which assessed prescriptions for psychiatric patients (22% of the prescriptions with drug interactions), pediatric patients (33%

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of the prescriptions with drug interactions), and hospitalized patients (38% of the prescriptions with drug interactions).[2]

Patients who will or will not experience an adverse drug interaction cannot be clearly identified. Those with multiple diseases, with kidney or liver dysfunction, and those on many drugs are likely to be the most susceptible. The elderly population often fits that description; therefore, many cases reported involve elderly individuals on several drugs.[1]

The magnitude of the problem of drug interactions increases significantly in certain populations in parallel with the increase in the number of drugs used. The interactions that can be of lesser clinical significance in patients with less severe forms of a disease can significantly worsen the clinical condition of patients with more severe forms of the disease. According to Brown,[3] the following conditions put patients at high risk for drug interactions:

1. High risk associated with the severity of the disease being treated: aplastic anemia, asthma, cardiac arrhythmia, diabetes, epilepsy, liver disease, hypothyroidism, or intensive care.
2. High risk associated with the potential for drug interaction of the therapy: autoimmune diseases, cardiovascular diseases, gastrointestinal diseases, infections, psychiatric disorders, respiratory disorders, and convulsions.

Patients with rheumatic diseases usually have a higher number of comorbidities and usually undergo complex therapeutic regimens. The hypothesis that the use of a large number of drugs relates to the advanced age of those patients, long disease duration, disease activity, functional deficit, and large number of comorbidities seems reasonable. Treharne *et al.*,[4] assessing 348 patients undergoing treatment for rheumatoid arthritis (RA), have reported that the total number of drugs prescribed to each patient was, on average, 5.39, reaching a maximum of 16 drugs for the same patient. Of the drugs prescribed, only 2.4 were for the specific treatment of the disease. Longer duration of the disease and more advanced age of the patients were predictors of a higher total number of drugs, which was explained by the elevated number of comorbidities in the most elderly patients with longer disease duration. The authors recommend the regular review of the treatment plan of RA patients by health professionals specialized in rheumatology to assess the risk/benefit ratio of each drug and their interactions.

In addition to representing a risk for the patient and jeopardizing the health care provided by professionals, drug interactions can increase dramatically health care costs, because of both the increase in the number of hospitalization days and the higher need for laboratory tests to monitor the outcomes of hospitalizations.[5]

The search for review articles in English, French, and Spanish in the PubMed database (1998-2008) with the keywords *drug interactions* and *DMARDs* (disease-modifying anti-rheumatic drugs) in human beings revealed 568 references. We chose to look for review articles, because the search without that filter resulted in 3,224 articles comprising isolated studies for each drug or studies related to their prescription by dermatologists, nephrologists, or oncologists. Other studies reported the use of immunosuppressants in transplanted patients, who, by receiving different doses of some immunosuppressants intended to treat rheumatic diseases, are exposed to different conditions of potential interactions.

This review article approached the clinically relevant interactions between the most used drugs in rheumatology (except for non-steroidal anti-inflammatories and corticosteroids) aiming at helping rheumatologists to pharmacologically interfere in the disease processes, in the search for better outcomes for patients and lower costs with the complex therapy of chronic diseases they deal with. This article approaches the potential drug interactions of the following drugs: azathioprine, chloroquine/hydroxychloroquine, cyclophosphamide, methotrexate, mycophenolate mofetil, adalimumab, etanercept, and infliximab. The drug interactions reported in this study are cited in the following sources:

National Therapeutic Form (*Formulário Terapêutico Nacional*) – 2008[6]

Micromedex® Drugdex® – consultation on December 2008[7]

Text book: Stockley Drug Interactions – 2006[8]

Text book: Tatroo, D S – Drug interaction facts – 2007[9]

Haagsma CJ. Clinically important drug interactions with Disease Modifying Antirheumatic Drugs – 1998[10]

Lacaille D. Rheumatology: 8. Advanced Therapy – 2000[11]

UpToDate – www.uptodate.com – consultation on December 2008[12]

In the literature consulted, there is consensus regarding neither the drugs that interact with each of the antirheumatic drugs, nor the severity degree of the interaction. This review was aimed at reporting the maximum number of possible drug interactions according to the above-cited publications.

This study approached neither the intentional combination of drugs in the search for beneficial synergic effects, nor the interactions between drugs and vaccines. However, it reviewed the interactions that reduce the efficacy or increase the toxicity of one or both drugs, and those of greater clinical relevance were selected. The presentation order of the drugs did not follow a specific order of preference, but an alphabetical order/group:

non-biological DMARDS and biological agents. The drugs and their possible interactions are shown in Charts 1, 2, 3, 4 and 5.

AZATHIOPRINE

Chart 1
Drugs that interact with azathioprine*

Increase the azathioprine effect	Reduce the azathioprine effect	Effect altered by azathioprine
Allopurinol[6-11] B	Warfarin[6] I	Atracurium[8,9] E
Captopril[6,7,11] A		Cyclophosphamide[8] F
Enalapril[6,7,11] A		Cyclosporine[6,7,9] G
Leflunomide[8] BC		Clozapine[6] H
Mercaptopurine[7] CD		Pancuronium[8,9] E
Methotrexate[7,9] B		Warfarin[6-9] I
Mycophenolate mofetil[7,8] C		
Sulfasalazine[8,9]		
Trimethoprim[6,8]		
Myelosuppressive drugs[11]		

*According to the previously cited sources.
A) increased risk of myelosuppression: anemia and leukopenia – there are reports about the increase in the risk of myelosuppression, anemia, and leukopenia for other inhibitors of the angiotensin-converting enzyme, such as benazepril, cilazapril, fosinopril, lisinopril, perindopril, quinapril e ramipril (contraindicated);[7] B) associated use not recommended; C) increased risk of liver and hematological toxicity with myelosuppression; D) increased risk of kidney dysfunction; E) reduction in or reversion of the neuromuscular blocking effect; F) increased cyclophosphamide liver toxicity (liver necrosis); G) reduction in the pharmacological effect of cyclosporine and increased risk of cyclosporine-related infections and neoplasias; H) increased risk of clozapine agranulocytosis; I) reduction in the anticoagulant effect of warfarin.

CHLOROQUINE/HYDROXYCHLOROQUINE

If the QT interval on the electrocardiogram (ECG) is excessively prolonged, ventricular arrhythmias, particularly polymorphic ventricular tachycardia, known as *torsades de pointes*, can occur. On ECG, that arrhythmia can appear as intermittent series of spikes, during which a failure in heart ejection occurs, blood pressure drops, and the patient feels dizzy and can lose consciousness. It is usually a self-limiting condition, but can degenerate into ventricular fibrillation, which can cause sudden death. There are innumerous causes for prolonged QT interval, such as congenital conditions, heart disease, some metabolic disorders (hypokalemia, hypomagnesemia), but the most likely major cause of such alterations is drug use. The risk for prolonging the QT interval is uncertain and unpredictable, and, thus, several pharmaceutical laboratories and regulating agencies currently contraindicate the concomitant use of drugs with a known potential for prolonging the QT interval due to the additive potential of that property. The University of Arizona, aware of the relevance of the issue, provides up-to-date lists of drugs that can prolong the QT interval,[13] classifying those drugs as follows:

RISK OF TORSADES: drugs generally accepted to carry a risk of *torsades de pointes*: amiodarone,[7,8] amitriptyline,[7] clarithromycin,[7,8] chlorpromazine,[7,8] disopyramide,[7] erythromicin,[7,8] haloperidol,[7,8] imipramine,[7,8] nortriptyline,[7] pentamidine,[7,8] pimozide,[7,8] quinidine,[7,8] sotalol,[7,8] thioridazine.[7]

POSSIBLE RISK OF TORSADES: drugs that can prolong the QT interval, but at this time lack substantial evidence for causing *torsades de pointes*: dolasetron,[7] gatifloxacin,[8] isradipine,[7] moxifloxacin,[8] octreotide,[7] quetiapine,[7] risperidone,[7] tacrolimus,[8] tamoxifen,[8] telithromycin,[7] ziprasidone.[7]

CONDITIONAL RISK OF TORSADES: drugs whose use should be avoided in patients diagnosed with or suspected of having the congenital long QT syndrome: fluconazole,[7] fluoxetine,[7] trimethoprim.[7]

The drugs that do not fit to any of the three classifications above, but that are reported in the above-cited sources of this review study as drugs that can interact with chloroquine resulting in an increased risk for prolonging the QT interval were classified as of UNDETERMINED RISK: enflurane,[7] spiramycin,[7,8] halothane,[7] isoflurane,[7] propafenone,[7] trifluoperazine,[7] vasopressin,[7,8] zolmitriptan.[7]

Chloroquine is accepted by the QTdrugs.org Advisory Board of the Arizona CERT to carry a risk of *torsades de pointes* and, thus, its use is not recommended in association with other drugs with potential for the same alteration, thus increasing its cardiotoxicity unpredictably. Other drug interactions of chloroquine are shown in Chart 2.

Chart 2
Drugs that interact with chloroquine and hydroxychloroquine*

Increase the effect of chloroquine	Reduce the effect of chloroquine	Effect altered by chloroquine
Ampicillin[6]	Kaolin[6,8,9] D	Ampicillin[8] D
Cimetidine[6-8,10] A	Calcium carbonate [8]	Carbamazepine[6] F
Hydroxyzine[8] B	Cholestyramine[8]	Cyclosporine[6-9] G
Ranitidine[10] C	Praziquantel[6]	Ciprofloxacin[7]
Antiarrhythmic drugs[6]	Aluminum salts[9] D	Chlorpromazine[7,8] H
	Magnesium salts[7-9] E	Clozapine[8] I
	Antacids[6]	Digoxin[6,8,10] J
		Hydroxyzine[8] B
		Leflunomide[8] K
		Levothyroxine[7] L
		Methotrexate[8,10] M
		Praziquantel[7,8] N

		Sodium valproate[1] O
		Anticholinesterase drugs[8] P
		Neuromuscular blockers[8]
Increase the effect of hydroxychloroquine	**Reduce the effect of hydroxychloroquine**	**Effect altered by hydroxychloroquine**
Leflunomide[8] K	Rifampicin[8] R	Carvedilol[7-9] S
NSAIDs[6]		Digoxin[6-10] T
		Leflunomide[8]
		Labetalol[9] S
		Metoprolol[6-9] S
		Methotrexate[8] U
		Propranolol[8,9] S
		Timolol[4] S
		Beta-blockers[6-9] S

* According to the previously cited sources.
A) the following can occur: agitation, convulsions, cardiac arrest (contraindicated);[7] B) at high doses can cause ECG alterations, which add to the cardiotoxicity potential of chloroquine (potential of arrhythmias and cardiac arrest); C) when concomitantly used, reduce the dose of chloroquine; D) administer the drugs 2-4 hours apart; E) the associated use is contraindicated;[7] F) reduction in antiepileptic effects; G) increase in the pharmacological and toxic effects of cyclosporine [paresthesia, cholestasis, nephrotoxicity (kidney dysfunction even at low doses of both drugs)]; H) increase in the serum concentration of chlorpromazine for several days (increased sedation) (contraindicated);[8] I) increased risk of myelosuppression; J) increase in the serum concentration of digoxin; K) increased risk of liver and hematological toxicity (contraindicated);[8] L) elevation in the thyroxine levels and reduction in "levothyroxine efficacy"; M) reduction in the peak serum concentration and bioavailability of methotrexate; N) reduction in the bioavailability of praziquantel; O) reduction in the effect of valproate; P) reduction in the effects of anticholinesterase drugs in the treatment of *miastenia gravis*; Q) increased risk of hematological and liver toxicity (not recommended);[8] R) can result in uncontrolled course of disease; S) can result in increased serum concentration of beta-blocker – in the case of metoprolol, bradycardia can occur; T) elevation in digoxin serum levels; U) increased bioavailability of methotrexate and reduction in its peak serum concentration (increased efficacy and reduced acute liver toxicity).

CYCLOPHOSPHAMIDE

Chart 3
Drugs that interact with cyclophosphamide*

Increase the effect of cyclophosphamide	Reduce the effect of cyclophosphamide	Effect altered by cyclophosphamide
Allopurinol[6-10] A	Cyclosporine[6]	Amiodarone[8] B
Amiodarone[8] B	Chloramphenicol[6-8]	Carbamazepine[8] H
Bendroflumethiazide[9] C	Nevirapine[6,7] F	Cyclosporine[7,8] I
Ketoconazole[9] D	Prednisolone[8,9] E	Ciprofloxacin[8,9] J
Cimetidine[8,10]	Prednisone[8,9] E	Dexamethasone[8] K
Chlorthalidone[9] C	Ondansetron[6-9]	Digoxin[7-9] L
Dexamethasone[8] D	Rifampicin[8] G	Sparfloxacin[9] J
Fluconazole[8,9] D	Trimethoprim[8]	Etanercept[6,7] M
Itraconazole[8,9] D		Fenitoin[8] H
Fenitoin[8,9]		Indometacin[7,8] N
Hydrochlorothiazide[7,9] C		Insulin[8] O
Indapamide[9] C		Levofloxacin[9] J
Prednisolone[8,9] E		Metronidazole[8] P
Prednisone[8,9] E		Ofloxacin[8,9] J
Rifampicin[8]		Paclitaxel[8] Q
Myelosuppressive drugs[12]		Propofol[8] R
		Suxamethonium[7-9] S
		Tamoxifen[6-8] T
		Trastuzumab[6,7] U
		Warfarin[7-9] V
		Verapamil[8] W

* According to the previously cited sources.
A) increased effect and toxicity of cyclophosphamide (nausea, vomiting, and myelosuppression); increased risk of bleeding; increased risk of infection; reduction in hematopoiesis (contraindicated);[7] B) increased pulmonary toxic effect of both substances; C) prolongation of the cyclophosphamide-induced leukopenia; D) increased serum concentration of the cyclophosphamide active metabolite (adverse effects); E) conflicting data: reduction or increase related to the metabolic activation of cyclophosphamide in the presence of corticoids; F) not recommended;[7] G) alteration in the metabolism regarding formation of both active and inactive metabolites of cyclophosphamide with an unpredictable clinical effect; H) reduction in the serum concentration of the anticonvulsant (loss of control over convulsions); I) increased serum concentration of cyclosporine (convulsions); J) reduction in the effect of oral quinolone; K) increased serum concentration of dexamethasone; L) reduction in the absorption of digoxin tablets, but not of liquid digoxin (deterioration of the cardiac function, uncontrolled ventricular rhythm) - increase the digoxin tablet dosage; M) increased incidence of non-cutaneous solid tumors (contraindicated);[7] N) increased fluid retention (water intoxication); O) hypoglycemia or development of diabetes; P) case report: encephalopathy; Q) the administration order seems to influence the incidence of toxic effects (neutropenia and thrombocytopenia), which are higher when cyclophosphamide is administered after paclitaxel; R) pain increase (venous congestion in the administration of propofol to patients who received cyclophosphamide previously); S) increases and prolongs the effect of suxamethonium - reduce the suxamethonium dose; T) increased risk of thromboembolism - use anticoagulants prophylactically (contraindicated);[7] U) increased risk of cardiac dysfunction (contraindicated);[7] V) increased INR and increased risk for bleeding with high doses of cyclophosphamide combined with antineoplastic drugs (contraindicated);[7] W) a reduction in verapamil absorption can occur.

METHOTREXATE

Chart 4
Drugs that interact with methotrexate*

Increase the effect of methotrexate	Reduce the effect of methotrexate	Effect altered by methotrexate
Mefenamic acid[7,9] A	Acetazolamide[8]	Adapalene[7] B
Adapalene[7] B	Aminophylline[8]	Carbamazepine[8] P
Amiodarone[7-9] C	Caffeine[9]	Digoxin[8,9] Q
Amoxycillin[7-9] D	Carbamazepine[8] O	Fenitoin[7,9] P
Ampicillin[9]	Activated charcoal[9]	Fluorouracil[8] R
Amphotericin [8] B	Chloramphenicol[7]	Isotretinoin[7] B
Aspirin[7-10] E	Chloroquine[9,10]	Mercaptopurine[7-9] S
Azathioprine[7] B	Cholestyramine[7,8,10]	Propofol[8] T
Benzylpenicillin[8] C	Nystatin[10]	Tamoxifen[6-8] U
Carbenicillin[8,9] F	Polymixin B[10]	Theophylline[7] V
Ketoprofen[7-9] G	Potassium (citrate and acetate)[9]	Sodium valproate[8] P
Ketorolac[7,9] A	Sodium salts[9]	Warfarin[7,8] W
Cyclosporine[7-10] C	Theophylline[8]	
Ciprofloxacin[7] C	Tromethamine[9]	

Cisplatin[8] C	Urine alkalinizing agents[8]
Chlortalidone[9] H	Aminoglycosides[8,9] X
Dexamethasone[8] I	
Diclofenac[7-9] A	
Dicloxacillin[8] C	
Doxycycline[6-9] A	
Etodolac[7-9] G	
Fenitoin[6,7,9,11] G	
Fenoprofen[7,9] A	
Flurbiprofen[7-9] G	
Haloperidol[9] J	
Hydrochlorothiazide[9] H	
Ibuprofen[7-9] A	
Indapamida[9] H	
Indomethacin[7-9] A	
Isotretinoin[7] B	
Lansoprazole[8]	
Leflunomide[6,7] K	
Methicillin[9]	
Naproxen[7-9] A	
Nimesulide[7] A	
Omeprazole[6-9] D	
Oxacillin[8,9] L	
Nitrous oxide[8]	
Pantoprazole[7-9]	
Penicillins[6-9]	
Piperacillin[7-9] G	
Pyrimethamine[6]	
Piroxicam[7]	
Prednisolone[8]	
Probenecid[6-11] GN	
Sulfadiazine[9]	
Sulfamethoxazole + trimethoprim[6-10] M	
Tenoxicam[7] G	
Tetracycline[7-9] N	
Ticarcillin[8,9]	
Tolbutamide[8]	
Triamterene[6-8] G	
Vancomycin[8-10] N	
NSAIDs [6,8-10] Y	
Thiazide diuretics[9] H	

* According to the previously cited sources.
A) increased toxicity of methotrexate at high doses and at doses used for treating RA and other inflammatory diseases: leukopenia, thrombocytopenia, anemia, nephrotoxicity, and mucosal ulcers (contraindicated);[7-9] B) increased hepatotoxic effects; C) increased risk of methotrexate toxicity: leukopenia, thrombocytopenia, anemia, nephrotoxicity, and mucosal ulcers; D) contraindicated;[7] E) increased risk of methotrexate toxicity: leukopenia, thrombocytopenia, anemia, nephrotoxicity, and mucosal ulcers; associate leukovorin (contraindicated);[7-9] F) increased risk of methotrexate toxicity, replace carbenicillin with ceftazidime;[9] G) increased risk of methotrexate toxicity at high doses: leukopenia, thrombocytopenia, anemia, nephrotoxicity, and mucosal ulcers (contraindicated);[7] H) can prolong methotrexate-induced leukopenia; I) can increase the toxicity of high doses of methotrexate (contraindicated);[8] J) increased risk of dermatological toxicity of methotrexate; K) increased risk of myelotoxicity, pancytopenia, and hepatotoxicity (contraindicated);[7] L) case report: 53-times increase in methotrexate serum level = kidney failure + aplastic anemia + death (contraindicated);[8] M) trimethoprim increases the risk of methotrexate toxicity even at low doses (myelotoxicity and pancytopenia) - contraindicated;[7,9] N) contraindicated;[9] O) increased excretion of methotrexate at high doses – low doses seem not to be affected; P) reduction in the serum levels of the anticonvulsant; Q) reduction in the absorption of digoxin tablets, but not of liquid digoxin; R) topical adverse reactions in the use of topical associations; S) increased pharmacological and toxic effects of mercaptopurine (nausea, vomiting and late leukopenia) - reduce the mercaptopurine dose; T) increased pain due to propofol injection; U) increased risk of thromboembolism - use anticoagulants prophylactically (contraindicated);[7] V) increased theophylline toxicity; W) increased warfarin effect, increased risk of bleeding (increased INR) - contraindicated;[7] X) reduced methotrexate absorption, use parenteral methotrexate; Y) there is no pharmacokinetic interaction with methotrexate used at low doses, but effects should be monitored in kidney dysfunction, hypovolemia, cardiovascular disease or concomitant use of diuretics (reduced methotrexate excretion).

MYCOPHENOLATE MOFETIL

Chart 5
Drugs that interact with mycophenolate mofetil*

Increase the effect of mycophenolate mofetil	Reduce the effect of mycophenolate mofetil	Effect altered by mycophenolate mofetil
Azathioprine[8] A	Activated charcoal[7]	Acyclovir[7-9] F
	Cyclosporine[7-9]	Azathioprine[8] G
	Cholestyramine[7,8] B	Gancyclovir[7,8] F
	Metronidazole[7,9] C	Valacyclovir[7-9] F
	Norfloxacin[7,9] B	Valganciclovir[8] F
	Rifampicin[7] B	Oral contraceptives[6-8] H
	Aluminum salts[6-8] BD	
	Iron salts[6-9] DE	
	Magnesium salts[6-8] D	
	Antacids[8]	
	Oral contraceptives[6-8]	

* According to the previously cited sources.
A) increased potential for myelosuppression (contraindicated);[8] B) contraindicated;[8] C) reduced mycophenolate effect when norfloxacin is also associated (contraindicated);[7] D) reduced efficacy of mycophenolate mofetil (do not use simultaneously);[8] E) contraindicated;[9] F) increase in the therapeutic and toxic effects of the antiviral (significant only in kidney dysfunction); G) increased potential for myelosuppression (contraindicated);[8] H) reduced efficacy of the contraceptive (use an additional method due to mycophenolate teratogenicity).

BIOLOGICAL DRUGS (ADALIMUMAB, ETANERCEPT, AND INFLIXIMAB)

The drug interactions related to the use of the biological agents adalimumab, etanercept, and infliximab should be considered, because there is an increase in the risk of severe infections when those agents are administered in association with abatacept,[7,12] anakinra[7,12] or rilonacept.[7,12] Based on such interactions, the associated use of such drugs is not recommended. In addition, the concomitant use of etanercept and cyclophosphamide has been reported to be associated with an increase in the risk of

developing non-cutaneous solid tumors, contraindicating the simultaneous use of those drugs. Although the clinical significance of the interaction has not yet been well assessed, an increase in the risk of neutropenia as an adverse effect of etanercept used simultaneously with sulfasalazine has been reported.[12]

DRUGS THAT DO NOT ALTER THE EFFECT OF ANTIRHEUMATIC DRUGS AND WHOSE EFFECTS ARE NOT ALTERED BY ANTIRHEUMATIC DRUGS

Safety reports on the simultaneous administration of drugs are scarce. Most of them are pharmacokinetic studies with a small number of patients, and assess the existence of an alteration in the safety profile of each drug when concomitantly used. The sources consulted suggest the concomitant use of the following drugs as safe:

- *Chloroquine*: oral contraceptives;[8] hypoglycemic agents;[8] ranitidine.[8]
- *Cyclophosphamide*: barbiturates,[8] benzodiazepines,[8] docetaxel,[8] etoposide,[8] famotidine,[8] megestrol,[8] ranitidine,[8,10] sulfonamides,[9] sulfadiazine,[9] sulfamethoxazole.[9]
- *Methotrexate*: acetaminophen,[8] celecoxib,[8] etoposide,[8] meloxicam.[8]
- *Mycophenolate mofetil*: allopurinol,[8] gancyclovir (the simultaneous use of mycophenolate mofetil and gancyclovir is not safe in the presence of kidney dysfunction),[7] methotrexate,[8] voriconazole.[8]
- *Etanercept*: digoxin.[8]

DISCUSSION AND CONCLUSION

It is almost impossible to remember all known drug interactions, even when referring to the drugs used within a specialty, such as rheumatology. According to the WHO's Guide to Good Prescribing: a practical manual[14], a treatment to be applied should be chosen based on efficacy, safety, applicability, and cost. That manual teaches how to choose and not what to choose. This study approaches not the efficacy of the drugs, but the second criterion for choosing the drugs, safety. In reality, this study assesses the safety of drug combination. Not all damage caused by drugs or drug combination can be avoided, but, since most harm results from the inadequate selection of the combinations, it can be prevented. For several inadequate associations, high risk groups can be identified. Usually, those are exactly the groups of patients who should be carefully considered: elderly, children, pregnant women, and individuals with kidney or liver disease. Such patients can have alterations in both the pharmacodynamics and pharmacokinetics of the drugs administered.

According to the Guide to Good Prescribing, step 5, information, instructions, and warnings should be provided to patients. This study highlights the need for providing the patient with information about the signs and symptoms of possible drug interactions, considering that drug interaction is unpredictable. A practical solution would be to choose an alternative with no interaction, but, if none is available or possible, sometimes drugs that interact with each other can be prescribed when adequate precautions are taken. If the effects of the interactions are well monitored, they can often be allowed, usually with dose adjustment. Many interactions are dose-related, as can be observed with the drugs approached in this study: the use of the same drug for oncological purpose and its use at reduced doses for antirheumatic purposes differ. For example, dipyrone can increase the toxicity of high doses of methotrexate, but does not seem to have a similar effect on the methotrexate doses used for rheumatic diseases. Low doses of methotrexate do not seem to interact with carbamazepine, while high doses seem to do so.[8]

Some drug interactions can be prevented by using another member of the same group of drugs, such as chloroquine and hydroxychloroquine. The potential of the former to prolong the QT interval on ECG, causing consequent life-threatening arrhythmias, does not recommend its use in association with other drugs with the same potential (antiarrhythmic drugs, anti-infectious agents, azole antifungals, quinolones, aminoglycosides, tricyclic antidepressants and SSRI, antipsychotics).[13] Cimetidine and ranitidine, both H2 receptor antagonists, have a very different interaction profile.

It is worth emphasizing the following: immunosuppressants are drugs with a low therapeutic index; several frequently used drugs are enzyme inducers or inhibitors, and, thus, can alter the serum concentration of other substances or metabolites (active-toxic); and, finally, elderly patients, those with cardiac, liver or kidney dysfunction, and those submitted to polypharmacy are more susceptible to drug interactions.

Thus, a large number of drugs with potential for interaction can be safely administered when precautions are taken. That is step 6 of the Guide to Good Prescribing: monitor the treatment. The next step is: keep up-to-date about drugs!

For preventing adverse reactions consequent to drug interactions, the following is proposed:

- Know the interaction potential of the drugs (be it with other drugs, foods, tobacco or alcohol) most commonly prescribed in a specialty.
- Establish a way of gathering information about the drugs used by the patient (prescribed by other professionals or used in the form of self-medication). Would it not be useful if each patient were educated to carry along a prescription card that would be presented and whose filling should be required to every professional involved with the patient's care?

One limitation of our study is the number of sources researched. The study was not aimed at fully covering the issue, but at providing a contribution to rheumatology professionals involved with the responsible health care of patients with chronic diseases that require complex therapies.