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Assessment of interactions and dosage recommendations of synthetic DMARDs—Evidence-based and consensus-based recommendations based on a systematic literature search

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Abstract

Conventional synthetic (cs) and targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARD) have potential interactions with a multitude of drugs. Furthermore, they sometimes have a lower therapeutic index, particularly in cases of limited organ functions. The aim of this work was to establish evidence-based recommendations on the therapeutic use of DMARDs in the context of drug interactions and dosage recommendations. A systematic literature search was carried out on the issue of drug interactions and dosages in cases of patients with limited kidney function and higher age and suffering from rheumatoid arthritis. A total of 2756 scientific publications were screened and 154 selected of which 68 were scrutinized in detail. Furthermore, the respective product information was also analyzed. A multitude of possible interactions of synthetic DMARDs with different drugs were detected, which were then assessed with respect to the clinical significance and consequences. A consensus process led to making recommendations with which the interactions were classified: A: dangerous combination, B: avoid combination (if possible, pausing DMARD treatment), C: possible combination requiring increased monitoring and potential adjustments in dosage and D: pharmacological interaction without relevance in DMARD standard doses. Apart from that dosage recommendations were established for each csDMARD and tsDMARD depending on kidney function and age. There are 3 primary recommendations and 11 core recommendations on interactions and dosages of csDMARDs and tsDMARDs meant as a practical help for therapeutic decision making and to improve safety in the treatment of rheumatoid arthritis.

Keywords
Rheumatoid arthritis · Disease-modifying antirheumatic drugs · Janus kinase inhibitors · Pharmacology · Drug interactions

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Introduction

Comorbidity and polypharmacy are important contributors to morbidity and hospitalization in patients with rheumatoid arthritis (RA). A retrospective cohort study of 1101 patients with RA showed that among the 173 patients who required inpatient treatment during the observation period, 23% had possible complications associated with the RA drug therapy and predominantly with conventional synthetic (cs) DMARDs [1]. Toxic drug concentrations often play a role. In their development, impaired metabolism or excretion of the substances or their metabolites as a result of impaired organ functions or interactions with other substances may be the cause. In contrast to biologic (b) DMARDs, conventional and targeted synthetic (ts) DMARDs—so-called JAK inhibitors—have narrower therapeutic ranges and, because of their metabolism, potential interactions with other drugs.

The aim of this work is to systematically develop evidence- and consensus-based recommendations for therapy with synthetic DMARDs taking into consideration interactions with other substances and/or reduced renal clearance.

Methods

On January 25, 2022, a systematic literature search in MEDLINE (PubMed) and the Cochrane Library for rheumatoid arthritis using the following search terms: #filgotinib, #tofacitinib, #upadacitinib, #baricitinib, #hydroxychloroquine, #sulfasalazine, #methotrexate, #leflunomide, and #drug interactions, #multidrug interactions, #polypharmacy, #elderly, #age, #renal insufficiency, #dose adjustment.

Both reviews and original publications were screened. The latter contained studies of all levels of evidence including prospective and retrospective studies and evaluations, case reports, and experimental studies.

The search strategies are listed below:

MEDLINE (PubMed)

#1 Arthritis, Rheumatoid[mh] OR (rheumatoid[tiab] AND arthritis [tiab])
#2 filgotinib[tiab] OR tofacitinib[tiab] OR upadacitinib[tiab] OR baricitinib[tiab] OR hydroxychloroquine[tiab] OR sulfasalazine[tiab] OR methotrexate[tiab] OR leflunomide [tiab]
#3 drug interactions[tiab] OR drug interactions [mh] OR multidrug interactions[tiab] OR polypharmacy[tiab] OR polypharmacy[mh] OR elderly [tiab] OR Age[tiab] OR renal insuffciency[tiab] OR dose adjustment[tiab]
#4 #1 AND #2 AND #3
1754 Hits: (after duplicate matching 1745 hits)

Cochrane

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#2 (rheumatoid): ti,ab,kw
#3 (arthritis): ti,ab,kw
#4 #2 AND #3
#5 #1 OR #4
#6 (filgotinib): ti,ab,kw
#7 (tofacitinib): ti,ab,kw
#8 (upadacitinib): ti,ab,kw
#9 (baricitinib): ti,ab,kw
#10 (hydroxychloroquine): ti,ab,kw
#11 (sulfasalazine): ti,ab,kw
#12 (methotrexate): ti,ab,kw
#13 (leflunomide): ti,ab,kw
#14 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15 (drug interactions): ti,ab,kw
#16 (multidrug interactions): ti,ab,kw
#17 (polypharmacy): ti,ab,kw
#18 (elderly): ti,ab,kw
#19 (age): ti,ab,kw
#20 (renal insufficiency): ti,ab,kw
#21 (dose adjustment): ti,ab,kw
#22 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #14 AND #22 AND #5
1277 Hits (after duplicate matching 1203 hits)

After final duplicate matching for MEDLINE and Cochrane as a whole, a total of 2756 references were uploaded in Rayyan (abstract management tool) for further selection by the members of the working group.

The following PICO questions were processed: P (patient): rheumatoid arthritis, I (intervention): administration of a synthetic DMARD, C (control intervention): with and without concomitant medication, renal function impairment or advanced age, O (outcome = outcome criterion): drug-induced toxicity.

A total of 2756 publications were screened and 154 were included in the detailed analysis of which 86 were in abstract form only and 68 as full publications. In addition, data from the product information for the respective substances were included in the analysis.

In a consensus process, the following recommendations were developed. In the process, interactions were classified according to severity: A: dangerous combination, B: avoid combination (if possible DMARD pause), C: possible combination with increased with increased need for monitoring and possible dose adjustment, D: pharmacological interaction without relevance in standard doses of the DMARD.

Dosing recommendations according to renal function and age were given for each cs- and tsDMARD; due to the practical relevance for the tsDMARD, they were also given for hepatic insufficiency, i.e., based on the product information.

Recommendations were classified with a 3-tiered level of recommendation based on the recommendations of the Association of the Scientific Medical Societies in Germany (AWMF; www.awmf.org) into "strong recommendation" = ⇑⇑, "recommendation" = ⇑, or "recommendation open" = ~. In accordance with the recommendations of the AWMF, the relevance of the study endpoints and the strength of the available evidence as well as the feasibility of implementation in everyday life, among other factors, are included in the level of recommendation.

In view of the large number of possible interactions indicated in the csDMARDs product information, a selection had to be made for the development of recommendations, which was primarily based on clinical relevance and the respective availability of publications.

Results

The overarching and core recommendations are summarized in **Table 1**.

Methotrexate

Methotrexate (MTX) is a folate antagonist and plays a central role as a DMARD for the treatment of RA. It is given either orally or subcutaneously and has a plasma protein binding of 42–57% after absorption. In the liver, it is partially converted to the less active metabolite 7-hydroxy-MTX. This and

Table 1 Recommendations. Recommendation levels according to the Association of the Scientific Medical Societies (AWMF), www.awmf.de		
Overall recommendations		
A	Before and during the administration of synthetic DMARDs, liver and kidney function and also blood count are to be monitored	
B	When administering synthetic DMARDs, individual factors such as age, body weight and specific risk factors such as comorbidities and specific risk factors are to be taken into account	
C	Prior to and during therapy with synthetic DMARDs, comedication is to be regularly recorded and checked for possible interactions	
Key recommendation		*Recommendation level*
1	The combination of MTX with higher doses of aspirin (≥ 2 g/day) is not to be used; low-dose aspirin (80–100 mg/day for platelet aggregation inhibition) is unproblematic	↑↑
2	The combination of MTX with therapeutic doses of cotrimoxazole (2 times 960 mg/day) is not to be used; low-dose cotrimoxazole (3 times 960 mg/week for *Pneumocystis jirovecii* prophylaxis) is unproblematic	↑↑
3	MTX should be paused during concomitant administration of penicillins	↑
4	a) The administration of MTX in patients with renal function ≤ 45 ml/min is not recommended	↑
	b) Below 30 ml/min MTX is not be used	↑↑
5	a) The combination of MTX with metamizole in adult patients up to 79 years of age is not recommended	↑
	b) This combination is not be used above the age of 80	↑↑
6	The combination of HCQ with azithromycin is to be avoided due to possible QT time prolongation, with other substances monitoring, e.g., ECG, is recommended	↑↑
7	When combining HCQ with tamoxifen, annual retinopathy monitoring is necessary from the start of therapy	↑↑
8	Leflunomide can be given at the same dose in all stages of renal failure	↑↑
9	Administration of the JAK inhibitors TOF and UPA should be combined with CYP3A4-dependent drugs such as the following: ketoconazole; itraconazole only with special caution and in reduced doses; in combination with rifampicin, there is a risk of decreased efficacy	↑
10	In renal failure, dose adjustment is to be made for the JAK inhibitors TOF (for severe renal failure) and also BAR and FIL (for moderate renal failure)	↑↑
11	The JAK inhibitors BAR and FIL should be halved in initial dose starting at age ≥ 75 years; TOF should be used ≥ 65 years of age only if no suitable treatment alternatives are available	↑
↑↑ = strong recommendation, ↑ = recommendation *HCQ* hydroxychloroquine, *TOF* tofacitinib, *UPA* upadacitinib, *BAR* baricitinib, *FIL* filgotinib, *MTX* methotrexate		

the native MTX are eliminated in the kidney by glomerular filtration and tubular secretion with a short half-life of 2–4 h. Only a small fraction is also excreted in the bile [2]. Dosage recommendations for MTX depend mainly on the renal, but also on the hepatic function. Relevant toxicities that may result from increased exposure are mainly bone marrow toxicity with cytopenias, increase of transaminases, mucositis and general symptoms such as nausea.

Interactions (Table 2)

Drug–drug interactions are a possible cause of MTX-induced pancytopenias. In a database analysis of a British center over 5 years, 18 of 25 MTX-induced pancytopenias were found to have possible drug interactions as a cause. Seven patients (28%) died [3]. A systematic review shows that simultaneous administration of cotrimoxazole as an antibiotic at therapeutic doses of usually 960 mg administered twice daily and MTX is among the most common combinations causing severe pancytopenias [4]. Therefore, due to the large number of case reports with frequently fatal outcome [3, 4], this combination is strictly contraindicated. Importantly, however, low-dose administration of 960 mg cotrimoxazole 3 times/week for prophylaxis of *Pneumocystis jirovecii* pneumonia (PjP) in combination with MTX is not associated with an increased risk of cytopenias according to a case–control study [5]. Thus, this combination is feasible and unproblematic.

Similarly, administration of acetylsalicylic acid (ASA, aspirin) in analgesic doses of 2 g or more/day also has a high risk of interaction with MTX and may lead to potentiation of MTX and pancytopenias [4]. This is shown by retrospective case reports and pharmacological studies summarized in a systematic review [4]. However, such high-dose ASA therapy is rarely used in rheumatology nowadays.

For the frequently given dosage of 80–100 mg/day ASA for platelet aggregation inhibition, no case reports or pharmacological studies which would prove interactions with MTX could be found in the systematic literature search. Although a study focused on this issue is lacking, in the opinion of the consensus group—given the frequency of ASA in comedication—it can be assumed that relevant interactions of MTX in rheumatologic doses and low-dose ASA are very unlikely.

Combinations of MTX with nonsteroidal anti-inflammatory drugs (NSAIDs) have also been observed in association with cytopenias [3, 4, 6]. However, direct pharmacological interactions of NSAIDs, including COX-2 inhibitors, with MTX have not been found [7–9], so that the relationship here is likely to lie primarily in the

Table 2 Methotrexate—mechanisms and evaluation of pharmacological interactions

Substance/substance class	Mechanisms of interaction (selection)	Possible effect	Clinical significance	Reference
Interactions with published evidence[a]				
Acetylsalicylic acid (Analgesic dosages > 2 g/day)	Decreased tubular secretion, displacement from plasma protein binding	Amplification of effect and toxicity	A	[3, 4]
Acetylsalicylic acid (Dosage for platelet aggregation inhibition 80–100 mg/day)		None	D	–
Cotrimoxazole (Therapeutic dosage 2 times 960 mg/day)	Additive folate antagonistic effect and bone marrow toxicity	Amplification of effect and toxicity	A	[3, 4]
Cotrimoxazole (Dosage as pneumocystis prophylaxis 960 mg 3 times/week)		None	D	[5]
Isoniazid (For the treatment of latent tuberculosis at 300 mg/day)	Additive hepatotoxicity	Transaminase elevation	C	[10]
Leflunomide (in the combination csDMARD therapy of RA with 10–20 mg/day)	Additive hepatotoxicity and hematotoxicity	Transaminase elevation and cytopenias	C	[11–13]
NSAID	Decreased tubular secretion, decreased renal perfusion with restriction renal function, displacement from plasma protein binding	Amplification of effect and toxicity	Dependent on kidney function B or C	[6–9]
Penicillins	Displacement from plasma protein binding	Amplification of effect and toxicity	B	[16]
Probenecid	Decreased renal clearance of methotrexate	Amplification of effect and toxicity	B	[15]
Sulfasalazine	Inhibition of folic acid synthesis by sulfasalazine	Amplification of effect and toxicity	D	[14]
Metamizole	Synergistic bone marrow toxicity	Increased rate of agranulocytosis	B (A at age ≥ 80 years)	[17]
Other interactions according to the product information (selection)				
Protein-bound drugs such as salicylates, hypoglycemics, diuretics, sulfonamides, diphenylhydantoins, tetracyclines, chloramphenicol and *p*-aminobenzoic acid and acidic anti-inflammatory substances	Displacement from plasma protein binding	Amplification of effect and toxicity	C	–
Oral antibiotics such as tetracyclines, chloramphenicol and non-resorbable broad-spectrum antibiotics	Influence of the enterohepatic circulation through alteration of the intestinal flora	Amplification of effect and toxicity	C	–
Theophylline	Reduction of theophylline clearance	Increase in theophylline levels	C	–
Bone marrow toxic substances such as azathioprine, chloramphenicol, mercaptopurine, pyrimethamine, retinoids, sulfonamides	Additive bone marrow and hepatotoxicity	Pancytopenias and elevation of transaminases	C	–
Renally active drugs such as loop diuretics	Impairment of the renal excretory function of methotrexate	Amplification of effect and toxicity	C	–
Proton pump inhibitors	Delay in the renal elimination of methotrexate	Amplification of effect and toxicity	D	–

A dangerous combination, *B* avoid combination (if possible DMARD pause), *C* possible combination with increased need for monitoring and possibly, *D* pharmacological interaction without relevance in standard doses of DMARD, *NSAID* non steroidal anti-inflammatory drug

[a]In each case related to the above systematic literature review

potential impairment of renal function by NSAIDs.

The combinations of MTX with the antibiotic isoniazid for the treatment of latent tuberculosis [10] and also the DMARD leflunomide (LEF) [11] can lead to the increase of transaminases. In the case of LEF, cytopenias have also been described [12]. Both drugs have an important role in combination with MTX in the guideline-based management of RA, and life-threatening clinical courses of the interactions are rare. Therefore, under regular monitoring of the appropriate laboratory parameters, the combinations of LEF or isoniazid with MTX are justified. For the combination of MTX and leflunomide, there is also a recent large registry evaluation demonstrating general safety [13].

The combination of MTX with the DMARD sulfasalazine (SSZ) and also hy-

Table 3 Hydroxychloroquine (HCQ)—mechanisms and evaluation of pharmacological interactions

Substance/substance class	Mechanisms of interaction	Possible effect	Clinical significance	Reference
Interactions with published evidence[a]				
Digoxin	Displacement from plasma binding, decreased renal clearance	Increase in digoxin level	C	[22]
Cimetidine[a]	Doubling of the elimination half life	Delay in elimination of HCQ	D	[23]
Azithromycin	Synergistic effect on QT prolongation	Increased risk of cardiovascular mortality, esp. QT prolongation	A	[25]
Trimebutine, tacrolimus, tramadol, rosuvastatin, cyclosporin, sulfasalazine, rofecoxib, diltiazem, piperacillin/tazobactam, isoniazid, clarithromycin, furosemide	Synergistic effect on QT prolongation	Increased risk of QT prolongation	C	[24]
Tamoxifen	Synergistic damaging effect on retina	Increases risk of retinopathy	C	[26]

The product information contains further information for pharmacologically proven interactions with a wide variety of drugs without publications on clinical manifestations in the systematic literature search
[a]Only studied for chloroquine

Table 4 Sulfasalazine (SSZ)—mechanisms and evaluation of pharmacological interactions

Substance/substance class	Mechanisms of interaction	Possible effect	Clinical significance	Reference
Interactions with published evidence				
Digoxin	Inhibition of uptake by SSZ	Reduction of digoxin levels (AUC by 50)	C	[29]
Folic acid	Inhibition of folic acid absorption	Folic acid deficiency, impairment of the combination SSZ + MTX	C	[30]
Iron	Chelating	Resorption inhibition of SSZ	C	[31]
Cyclosporin A (CsA)	Induction of CYP450 enzymes	Enhancement of CsA effect, dose reduction necessary	C	[32]

The product information contains further information for pharmacologically proven interactions with a wide variety of drugs without publications on clinical manifestations in the systematic literature search

droxychloroquine (HCQ) has been shown to be safe with few adverse effects in a prospective study [13]. The gout drug probenecid should not be given in combination with MTX due to toxic drug concentrations and possibly severe side effects due to inhibition of MTX excretion [15].

It is strongly suspected that there are interactions of MTX with penicillins [16]. This may be explained by competition between the two substances for plasma protein binding, which could lead to higher plasma concentrations of MTX. Because antibiotic therapy is transient and MTX can be paused for 2–3 weeks without loss of effect, the consensus group recommends that MTX be paused for the duration of penicillin antibiotic administration.

A relatively new and previously little known fact is that the combination of MTX with metamizole can lead to an approximately 4.5-fold increased rate of agranulocytosis on average, according to an analysis of the EudraVigilance database [17]. The increased risk in this combination is detectable as early as 40 years of age (odds ratio [OR] 2.6), but is highest after 80 years of age (OR 8.1). The rate with fatal outcome is 17% for this complication of combined therapy, pooled in all age groups. Children and adolescents younger than 18 years had no increased risk of agranulocytosis with combination MTX and metamizole in this analysis [17]. The consensus group therefore advises against the combination of MTX and metamizole in adult patients up to 79 years of age. Above 80 years of age, it should not be administered at all. It should be noted that this interaction is not listed in the product information of MTX, but of metamizole.

It should be mentioned that no safety evidence for interactions in controlled clinical trials has been observed for the combination of MTX with both biologic (b) and tsDMARDs (JAK inhibitors).

Dosage in old age and renal insufficiency (Tables 6 and 7)

Various studies have shown that it is not age per se but organ function and comedications in old age that are decisive for the tolerability and thus dose of MTX [18]. The common adverse effect of nausea with MTX even occurs more frequently in younger than in old people [19]. Because renal function may be labile in the elderly, the consensus group recommends cautious dosing of MTX starting at ages older than 75 years. However, the approach is highly dependent on the biological age of the patient.

Pharmacologic studies show that with a glomerular filtration rate (GFR) of < 45 ml/min, the concentration of MTX

Table 5 Leflunomide—mechanisms and evaluation of pharmacological interactions

Substance/substance class	Mechanisms of interaction (selection)	Possible effect	Clinical significance	Reference
Interactions with published evidence				
Warfarin	Unknown	Enhancement of warfarin effect	C	[34, 35]
MTX	Effect on OAT-3 and BCRP substrates	Increase liver toxicity	C	[11]
Other interactions according to the product information (selection)				
Drugs that are metabolized via CYP2C8, e.g., repaglinide, paclitaxel, pioglitazone or rosiglitazone	Inhibition of CYC2C8	Amplification of the effect and toxicity by increasing of the effect levels	C	–
Drugs that are metabolized via CYP1A2, e.g., duloxetine, , alosetron, theophylline and tizanidine	Weak induction of CYP1A2	Reduction of the effect due to a drop in the active substance level	C	–
Drugs that are metabolized via OAT-3 e.g., cefaclor, benzylpenicillin, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, zidovudine	Effect on OAT-3 substrates	Amplification of the effect and toxicity by increasing of the effect levels	C	–
Drugs that are metabolized via BCRP, e.g., topotecan, sulfasalazine, daunorubicin, doxorubicin	Effect on BCRP substrates	Amplification of the effect and toxicity by increasing of the effect levels	C	–
Drugs that are metabolized via OATP1B1/B3, e.g., rosuvastatin simvastatin, atorvastatin, pravastatin, nateglinide, repaglinide, rifampicin	Effect on OATP1B1/B3 substrates	Amplification of the effect and toxicity by increasing of the effect levels	C	–

OAT organic anion transporters, *OATP1B1/B3* organic anion transporters polypeptides B1 and B3, *BCRP* breast cancer resistance protein, *CYC* cytochrome C

Table 6 csDMARD dosage recommendation by age

	< 65 years	65 to75 years	> 75 years	> 80 years	Reference
Methotrexate	No restriction	No restriction	Depending on biological age, comorbidities and body weight reduced starting dose if necessary consider gradual dose adjustment	Depending on biological age, comorbidities and body weight 10 mg/week as starting dose with gradual dose adjustment if necessary	[18]
Sulfasalazine[a]	2000–3000 mg/day	1000–1500 mg/day			Product information
Hydroxychloroquine	≤ 5 mg/kg body weight				[27]
Leflunomide	10–20 mg/day				[33]

[a]Source product information; "elderly patients" (not further defined)

in plasma increases 1.3- to 1.6-fold and the half-life of MTX nearly doubles. In contrast, very little change is seen at a GFR of 45–60 ml/min [20]. Accordingly, the consensus group recommends dose adjustment as described in **Table 7** and discourages the administration of MTX at a GFR of 45 ml/min or less. Below a GFR of 30 ml/min, MTX is contraindicated. Potential rapid changes in renal function due to changes in comedication or concomitant disease must always be factored into the dose decision. In addition, it must be noted that determination of estimated glomerular filtration rate (eGFR) may lead to over- or underestimation of renal function depending on age, body weight, and the dynamics of renal failure. The latter two points are also the reason why the consensus recommendation differs from the recommendations in the MTX product information to halve the MTX dose at a GFR of 30–45 ml/min.

Hydroxychloroquine

Hydroxychloroquine (HCQ) is an antimalarial drug used as an antirheumatic agent and undergoes extensive metabolism after intestinal absorption. There is an exceptionally long half-life of 40–50 days and high binding capacities of the molecules to pigmented tissue, but also mononuclear cells, muscles, etc. Plasma protein binding is 30–40% [21].

Interactions (**Table 3**)

HCQ is one of the DMARDs for which interaction problems only recently have come into focus. In an early study, a case report postulated displacement of digoxin from plasma binding and reduced renal clearance resulting in an increase in digoxin levels [22]. Since no further studies on this followed later, the clinical significance remains unclear. This also applies to an interaction with cimetidine, which is hardly used today and doubles the elimination half-life of HCQ [23].

In a retrospective Korean case–control study, the risk of QT prolongation by HCQ due to interaction with other drugs was investigated; a total of 118 substances were tested. For 12 of them, an addi-

Table 7 csDMARD dosage recommendations according to renal function						
GFR (ml/min)	**< 15/dialysis**	**15–30**	**30–45**	**45–60**	**> 60**	**Reference**
Methotrexate	Contraindicated		not advised	Initial dose maximum 10 mg/week with gradual adjustment consider	15–25 mg/week	[20]
Hydroxychloroquine	≤ 3 mg/kg body weight		≤ 5 mg/kg body weight			[27]
Sulfasalazine	Contraindicated		"With caution"		Full dosage	Product information
Leflunomide	10–20 mg/day					[33]
Attention must be paid to other medication with influence on renal function *GFR* glomerular filtration rate						

tive effect of HCQ and the respective substance on QT time was found: trimebutine, tacrolimus, tramadol, rosuvastatin, cyclosporin, sulfasalazine, rofecoxib, diltiazem, piperacillin/tazobactam, isoniazid, clarithromycin, furosemide [24]. The practical significance of this effect is unclear. Another retrospective cohort study compared the cardiovascular risk of HCQ, sulfasalazine, HCQ + azithromycin, and HCQ + amoxicillin in approximately 2 million RA patients [25]. For the combination HCQ + azithromycin, a significant doubling of 30-day cardiovascular mortality (HR 2.19), and also to a lesser extent of risk for chest pain/angina (HR 1.15) and heart failure (HR 1.22) were found.

A relevant functional interaction (with no pharmacologically known mechanism) exists between HCQ and the estrogen antagonist tamoxifen, which itself can also cause retinopathy. Here, concomitant administration is known to significantly increase the risk of toxic retinopathy with an odds ratio of 4.59 [26]. The current safety recommendations for therapy with antimalarials therefore provide for annual ophthalmologic screening examinations already from the first year of therapy when HCQ and tamoxifen are combined [27].

Dosage in old age and in renal insufficiency (■ Tables 6 and 7)

HCQ can be given regardless of the age. In renal insufficiency with GFR of 30 ml/min or less, the dose should be reduced to 3 mg/kg body weight.

Sulfasalazine

Sulfasalazine (SSZ) is partially absorbed natively, but predominantly cleaved in the small intestine by bacterial azoreductases into sulfapyridine and mesalazine, which are then also absorbed. It is likely that both sulfasalazine and the cleavage products have anti-inflammatory activity. They are each further metabolized in the hepatic system [28].

Interactions (■ Table 4)

Interactions are also rarely a clinical problem with SSZ. In a study conducted in 1976 (later not replicated by any other study), a reduction in digoxin levels of up to 50% was observed in 10 subjects when SSCs and digoxin were administered simultaneously [29]. A Dutch in vitro study revealed a relevant inhibition of folate transporter 1 mediated by SSZ and thus a potential relevance in the use of the combination SSZ + MTX [30]. Since MTX is hardly ever used today without folic acid substitution anyway, the practical consequence is probably minor.

The concomitant use of iron preparations and SSZ can lead to resorption inhibition of SSZ via chelation, as was reported as early as 1973 [31]. Therefore, they should be taken separately over time. SSC can lead to an increase in the effect of cyclosporin A (CsA) via induction of CYP450 enzymes like many other substances—this was first described by a case report [32]. When both substances are used simultaneously, the CsA dose should therefore be reduced; in the case described, the reduction was approx. 40%.

Dosage in old age and in renal insufficiency (■ Tables 6 and 7)

The technical information recommends a dose reduction from 65 years of age. With a GFR of 30 ml/min or less, SSZ is contraindicated.

Leflunomide

Leflunomide (LEF) inhibits dihydroorotate dehydrogenase, thereby inhibiting the formation of pyrimidine. Leflunomide is administered orally and is converted in the liver to its racemate teriflunomide (A771726) as the active metabolite. Teriflunomide is almost completely excreted biliarily, with only a very small portion eliminated renally after glucuronidation. Teriflunomide undergoes enterohepatic recirculation and has a long half-life of usually 1–4 weeks. Teriflunomide is > 99% bound to plasma proteins. Diseases associated with decreased plasma protein levels (e.g., liver cirrhosis, nephrotic syndrome) result in increased levels of the active metabolite in serum [33], and drugs that affect enterohepatic circulation reduce the active level.

Interactions (■ Table 5)

Warfarin as well as drugs metabolized via CYP2C8 (e.g., repaglinide, paclitaxel, pioglitazone, or rosiglitazone) may be enhanced in their effect by LEF [34, 35]. Therefore, there is an increased need for monitoring of the respective laboratory parameters influenced by the substance. The combination with MTX has been discussed previously. Under therapy with LEF, the appearance of alveolitis in association with concurrent MTX therapy was postulated in a small case series [36]. Evidence for interactions of LEF with biological DMARDs does not exist; this was also not found in clinical studies with adalimumab and rituximab in combination with LEF [37–39].

Dosage in old age and renal insufficiency (■ Tables 6 and 7)

There is no information on any restriction to the administration of LEF in older age. LEF can be administered without restriction in all stages of renal function including patients requiring dialysis. Although the molecule is comparatively small, the high plasma protein binding protects against elimination by standard

Table 8 Tofacitinib—mechanisms and evaluation of pharmacological interactions of JAK inhibitors

Substance/substance class	Mechanisms of interaction (selection)	Possible effect	Clinical significance	Reference
Interactions with published evidence				
Fluconazole, ketoconazole, rifampicin, cyclosporin A	CYP3A4 inhibition	Possible enhancement of effect and toxicity of TOF	B	[45–47]
Rifampicin	CYP3A4 induction	Possible weakening of the effect	B	[45–47]
The following additional substances with potential pharmacologic interactions are listed in the product information and publications with minor pharmacokinetics, but without clinically relevant effects: oral contraceptives levonorgestrel and ethinylestradiol, MTX, and midazolam				

Table 9 Baricitinib (BAR)—mechanisms and evaluation of pharmacological interactions

Substance/substance class	Mechanisms of interaction (selection)	Possible effect	Clinical significance	Reference
Interactions with published evidence				
Probenecid	Strong inhibitor of OAT3	Significant enhancement of effect and toxicity of BAR	B	[50]
Cyclosporin	P-gp inhibitor	Slight enhancement of effect and toxicity of BAR	C	[62]
Simvastatin	CYP3A inhibitor	Slight decrease in the absorption of simvastatin	D	[62]
Leflunomide	Inhibitor of OAT3	Possible enhancement of effect and toxicity of BAR	C	Product information
The following additional substances with potential pharmacologic interactions are listed in the product information with minor effects on pharmacokinetics, but without clinically relevant effects: ibuprofen, diclofenac, ketoconazole, fluconazole, rifampicin, oral contraceptives, digoxin				
P-gp P-glycoprotein				

Table 10 Filgotinib (FIL)—mechanisms and evaluation of pharmacological interactions

Substance/substance class	Mechanisms of interaction (selection)	Possible effect	Clinical significance	Reference
Interactions with published evidence				
Itraconazole[a]	P-gp modulation	Significant enhancement of effect and toxicity of FIL	B	[54]
Rifampicin	P-gp inducer	Moderate weakening of the effect of FIL	C	[54]
Atorvastatin	Inhibition OATP	Slight enhancement of the effect of atorvastatin	D	[55, 56]
Pravastatin	Inhibition OATP	Slight enhancement of effect and toxicity of pravastatin	D	[55, 56]
Rosuvastatin	Inhibition OATP and BCRP	Moderate amplification of effect and toxicity of rosuvastatin	D	[55, 56]
P-gp P-glycoprotein, *BCRP* breast cancer resistance protein				
[a]By analogy, probably also ketoconazole (not studied)				

hemodialysis [40–42]. A similar situation has been described casuistically with peritoneal dialysis [43].

tsDMARDs (JAK inhibitors)

tsDMARDs (Janus kinase [JAK] inhibitors) are small molecules and are given orally. They differ not only in their specificity with regard to inhibition of the various JAKs, but also how they are metabolized.

Tofacitinib

Tofacitinib (TOF) is eliminated primarily by hepatobiliary secretion (approximately 70%) and to a smaller extent renally (approximately 30%). TOF is metabolized primarily by CYP3A4 and to a lesser extent by CYP2C19 [44]. Concomitant use of the CYP3A4 inhibitors fluconazole, ketoconazole, and also cyclosporin A leads to an increase in the concentration of tofacitinib. When administered concomitantly with rifampicin, a strong CYP3A4 inducer, TOF exposure decreases ([45–47]; ◘ **Table 8**).

Baricitinib

Baricitinib (BAR) is predominantly eliminated by renal secretion (approximately 75%) and to a lesser extent by fecal excreted (approximately 20%) [48, 49]. Probenecid, a potent OAT3 inhibitor, increased the area under the curve (AUC) of BAR 2-fold in vivo and decreased renal clearance to 69% [50]. LEF, which is a weak OAT3 inhibitor via the metabolite teriflunomide, can also affect BAR concentrations ([51]; ◘ **Table 9**). The practical significance of this interaction is still unclear.

Filgotinib

Filgotinib (FIL) is predominantly metabolized in the intestine to the active metabolite GS-829845, which is approximately 10-fold less potent than the parent compound and accounts for the majority of substances circulating in plasma. Approximately 87% of the administered dose is excreted as native FIL or its metabolites and only about 15% is excreted in the feces [52, 53]. Because FIL and GS-829845 are substrates of the drug transporter P-glycoprotein (P-gp), administration of P-gp inhibitors such as itraconazole results in an increase in FIL and its metabolite, whereas concomitant administration with rifampicin as a P-gp in-

Table 11 Upadacitinib (UPA)—mechanisms and evaluation of pharmacological interactions

Substance/substance class	Mechanisms of interaction (selection)	Possible effect	Clinical significance	Reference
Interactions with published evidence				
Ketoconazole	Strong CYP3A inhibitor	Significant enhancement of effect and toxicity of UPA	C	[58]
Rifampicin	CYP3A inducer	Significant weakening of the effect of UPA	C	[58]
Other interactions according to the product information				
Itraconazole, posaconazole, voriconazole and clarithromycin	Strong CYP3A inhibition	Enhancement of effect and toxicity of UPA	C	–
Phenytoin	Strong CYP3A induction	Attenuation of the effect of UPA	C	–
The following additional substances with potential pharmacologic interactions are listed in the product information and publications with minor pharmacokinetics, but without clinically relevant effects: oral contraceptives levonorgestrel and ethinylestradiol, rosuvastatin and atorvastatin, midazolam, methotrexate				

Table 12 Recommended dosage of JAK inhibitors by age

	< 65 years	65 to 75 years	> 75 years	> 80 years
Tofacitinib	2 times 5 mg (or 11 mg sustained release)	[a]	[a]	[a]
Baricitinib	4 mg		2 mg	–
Upadacitinib	15 mg			
Filgotinib	200 mg		100 mg	

Dose information per day; indications: tofacitinib and upadacitinib: rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS); baricitinib and filgotinib: RA
[a]Use according to product information only if no suitable treatment alternatives are available are available (as of November 2022)

Table 13 Dosage recommendations according to renal function as per product information (daily dose)

GFR (ml/min)	< 30 ml		30–45	45–60	> 60
	< 15	15–29			
Tofacitinib	5 mg		10 mg		
Baricitinib	(–)	(–)	2 mg		
Upadacitinib	15 mg				
Filgotinib	(–)	100 mg			200 mg

(–) not recommended

ducer results in a moderate reduction [54]. Substrates of OATP such as atorvastatin, pravastatin, and rosuvastatin can affect the concentrations of FIL [55]. However, the effect was not found to be relevant in a recent study ([56]; ◘ **Table 10**).

Upadacitinib

Approximately 53% of upadacitinib (UPA) is excreted fecally and approximately 43% in the urine (mainly unchanged approximately 62% and metabolized approximately 34%). The major CYP enzyme involved in the metabolism of UPA is CYP3A4 [47, 57]. Accordingly, the CYP3A4 inhibitors fluconazole or ketoconazole may enhance the efficacy of UPA, whereas rifampicin attenuates it ([57]; see ◘ **Table 11**). No relevant effect of TOF, BAR, FIL, or UPA on the pharmacokinetics of ethinylestradiol or levonorgestrel has been demonstrated. Thus, the substances do not influence the effect of these most commonly used oral contraceptives [47, 59–61].

Dosing in the elderly, liver and kidney insufficiency (◘ **Tables 12 und 13**)

According to the product information, TOF should be given from the age of 65 years only if no suitable treatment alternatives are available. BAR and FIL should be halved in dose to 2 mg/day and 100 mg/day, respectively, starting at age 75 (status November 2022). Although hepatobiliary elimination of tofacitinib and upadacitinib is comparatively higher than that of baricitinib and filgotinib, the recommendations regarding dosing in hepatic dysfunction are identical for all JAK inhibitors according to the product information: administration is possible in mild (Child Pugh A) and moderate hepatic dysfunction (Child Pugh B) at the standard doses approved for RA and PsA, but either not recommended or contraindicated in severe hepatic dysfunction (Child Pugh C). Conversely, renal elimination is more significant with baricitinib and filgotinib, which is why the product information recommends dose reduction in impaired renal function (eGFR of ≤ 60 ml/min).

Discussion

Drug–drug interactions of synthetic DMARDs with other substances can lead to both undesirable effects due to an enhancement of the effect of the DMARDs or the combination partners and also to the respective weakening of the effect. In addition, attention to the renal excretory function of many DMARDs is important for the safety of therapy. This is very important for the practice of rheumatologic therapy. However, the pharmacological data are complex and potential pharmacologically detectable interactions may vary widely in clinical practice. Therefore, in the work presented, an evidence- and consensus-based expert recommendation based on a systematic literature review was prepared to assist the rheumatologist in daily practice to evaluate potential

interactions and dose finding in the elderly and in renal insufficiency. To our knowledge, this is the first systematic evaluation based on clinical criteria in the international literature.

The relevance and thus also the consequences of pharmacologically described interactions according to the evaluation of the literature and the consensus of the experts were classified in a 4-level grading from A to D. The classification was made according to the strength of the pharmacologically described interactions. In addition to the strength of the pharmacological interaction, we also considered whether DMARD therapy can be paused without problems, for example, in the case of temporary antibiotic therapy (level B). In contrast, despite relevant interactions, it may be clinically important to continue combination therapy on a permanent basis, but this should then be particularly monitored (level C). Some of the interactions described concern substances that are very rarely used nowadays (and for which there are good treatment alternatives), such as probenecid, on the one hand, and substances that are frequently used in Germany, such as metamizole, on the other hand, for which knowledge of interactions with MTX was not generally known until now. When making recommendations on dosage in renal insufficiency, it must be emphasized that renal function may quickly change in some patients. Therefore, special attention is required when administering potentially nephrotoxic drugs, such as NSAIDs with renally eliminated cs- or tsDMARDs.

It should be mentioned that for the csDMARDs, most of which have been used for many decades, a large number of case reports and series on clinically manifest interactions have been published, whereas for the JAK inhibitors only papers with pharmacological analyses have been predominantly published so far. This has been taken into account in the recommendations.

We have completed the results of the systematic literature search in each case in the tables with data taken only from the product information. However, this part makes no claim to completeness, since a large number of interactions, some of them weak and some of them rarely clinically relevant, have still been pharmacologically proven, especially in the case of csDMARDs.

The aim of the recommendations was to consider as many aspects as possible and at the same time to summarize the complex field of interactions to a manageable number of clinically relevant recommendations. However, the decision on the clinical use and dosage of a synthetic DMARD, e.g., also with comedication of substances with potential interactions, is still incumbent on the treating physician and may well deviate from the recommendations presented here. The product information remains the legally binding document.

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Declarations

Conflict of interest. The authors point out the following. C. Fiehn, J. Leipe, and K. Krüger: lecture and/or consulting fees from Abbvie, Galapagos, Lilly, Medac, and Pfizer. R. Bergner: lecture and/or consulting fees from Abbvie and Galapagos. C. Weseloh declares that she has no competing interests.

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Zusammenfassung

Bewertung von Wechselwirkungen und Dosierungsempfehlungen von synthetischen DMARDs – Evidenz- und konsensbasierte Empfehlungen auf Basis einer systematischen Literatursuche

Konventionelle synthetische („conventional synthetic" [cs]) und gezielte synthetische („targeted synthetic" [ts]) DMARDs haben potenzielle Wechselwirkungen mit einer Vielzahl von Medikamenten. Darüber hinaus haben sie insbesondere bei eingeschränkten Organfunktionen teilweise eine geringe therapeutische Breite. Ziel der Arbeit war eine systematische Erarbeitung von evidenzbasierten Empfehlungen zur Therapie mit DMARDs im Kontext von Arzneimittelinteraktionen und Dosierungsempfehlungen. Es wurde eine systematische Literaturrecherche zur Frage nach Wechselwirkungen sowie Dosierungen bei eingeschränkter Nierenfunktion und höherem Lebensalter bei rheumatoider Arthritis durchgeführt. Insgesamt wurden 2756 wissenschaftliche Publikationen gescreent und 154 ausgewählt, wobei 68 Publikationen in eine detaillierte Analyse eingingen. Darüber hinaus wurden die Informationen der jeweiligen Fachinformationen analysiert. Es fand sich eine Vielzahl von möglichen Wechselwirkungen von synthetischen DMARDs mit verschiedenen Medikamenten, welche bezüglich klinischer Bedeutung und Konsequenz bewertet wurden. In einem Konsensprozess wurden Empfehlungen erarbeitet, wobei eine Graduierung der Wechselwirkungen erfolgte: A: gefährliche Kombination, B: Kombination meiden (wenn möglich DMARD-Pause), C: mögliche Kombination mit erhöhtem Überwachungsbedarf und evtl. Dosisanpassung, D: pharmakologische Interaktion ohne Relevanz in Standarddosierungen des DMARD. Es wurden darüber hinaus Dosierungsempfehlungen nach Nierenfunktion und Alter für jedes cs- und tsDMARD erarbeitet. Drei übergeordnete Empfehlungen und 11 Kernempfehlungen zu Wechselwirkungen und Dosierung von cs- und tsDMARDs sollen praktische Hilfestellung für therapeutische Entscheidungen geben und die Sicherheit der Therapie der rheumatoiden Arthritis verbessern.

Schlüsselwörter
Rheumatoide Arthritis · Disease-modifying antirheumatic drugs · Januskinaseinhibitoren · Pharmakologie · Arzneimittelinteraktionen

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