REVIEW

Drug interactions in the treatment of rheumatoid arthritis and psoriatic arthritis

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Received: 10 December 2019 / Accepted: 25 January 2020 / Published online: 12 February 2020
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Abstract

Background Treating patients with inflammatory joint diseases (rheumatoid arthritis, psoriatic arthritis) according to established treatment algorithms often requires the simultaneous use of three or more medications to relieve symptoms and prevent long-term joint damage as well as disability.

Objective To assess and give an overview on drug-drug interactions in the pharmacotherapy of inflammatory joint diseases with regards to their clinical relevance.

Methods All possible drug combinations were evaluated using three commercially available drug interaction programs. In those cases where only limited/no data were found, a comprehensive hand search of Pubmed was carried out. Finally, the drug–drug interactions of all possible combinations were classified according to evidence-based medicine and a specifically generated relevance-based system.

Results All three interaction software programs showed consistent results. All detected interactions were combined in clearly structured tables.

Conclusion A concise overview on drug-drug interactions is given. Especially in more sophisticated cases extensive knowledge of drug interactions supports optimisation of therapy and results in improved patient safety.

Keywords Drug interaction · Pharmacotherapy · Drug combination · Rheumatoid arthritis · Psoriatic arthritis

Introduction

When treating inflammatory joint diseases [e.g., rheumatoid arthritis (RA), psoriatic arthritis (PsA)] one therapeutic goal is to reach and maintain remission or low disease activity. Over time a reduction in functional loss as well as radiographic progression and an improved social integration for patients should be achieved. Meanwhile broad evidence supports the early use of aggressive therapy for patients with active inflammatory arthritis. According to the EULAR

treat-to-target recommendations antirheumatic therapy contains conventional (c), biologic (b) and targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARDs) as well as corticosteroids used to attenuate the inflammatory process. In addition, non-steroidal-antirheumatic drugs (NSAIDs) in combination with proton-pump inhibitors (PPIs) as well as analgesics are part of the therapeutic armamentarium [1, 2]. This mandatory long-term polypharmacy can result in potentially harmful drug–drug interactions (DDIs). A considerable amount of literature is available on the risk of potential interactions of single drug combinations [3–8] but to our knowledge there is no detailed review on the whole range of drugs used for managing inflammatory joint diseases.

RA and PsA were singled out on the fact that in these two inflammatory joint diseases there is an especially large variety of medication involved in the treatment. The aim of this paper is to provide a current and detailed overview on DDIs and their clinical relevance to support safety and consequently also optimise pharmacotherapy.

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Methods

Search strategy

To overcome limitations of separate online sources and comprehensively cover scientific information, three different databases as well as Pubmed and SciFinder were applied. Based on the three drug interaction screening programs (Apotronic, mediQ, and Micromedex Solutions [9–11]), a comprehensive literature research (PubMed, SciFinder) was performed to evaluate possible interactions especially for drugs new to the market (up to Feb. 27th 2019). Apotronic contains drugs available in Austria, mediQ is a Swiss software and Micromedex includes drugs available at European level. Apotronic and mediQ classify the severity of DDIs with a colour code and Micromedex with a coloured symbol code. The severity of interactions is graded in three categories in the Apotronic and mediQ database: (1) minor risk/unlikely to be clinically significant; (2) moderate risk/clinically relevant/monitoring recommended; (3) major risk/potentially severe or life-threatening interaction. The Micromedex program uses the four categories mild, moderate, major and contraindicated. It should be noted that this paper only focuses on major risks and contraindications. All programs provide information about DDIs on 1:1 interaction.

The following search strategy was applied and included English and German literature: If appropriate data for a drug were available from the three interaction databases (Apotronic, mediQ, Micromedex), PubMed was used for searching clinical trials, reviews and case reports. In case of no or limited data available for a drug, an extensive search regarding general interactions was performed via PubMed and SciFinder. To identify all suitable articles, the following keywords were applied: drug AND drug (e.g., MTX AND pantoprazole) OR drug AND group of drugs (e.g., MTX AND PPIs) AND interaction OR combination AND rheumatoid (Fig. 1). If further little/no data were obtained with this procedure the terms were omitted stepwise from behind. Finally, if no results were found with this strategy, a specific search with regard to CYP-enzymes and transport systems was carried out to ascertain theoretically possible interactions. This procedure was mainly applied with regards to tsDMARDs.

Main outcome variable

Evaluation and classification of the results were performed with the system of evidence-based medicine (EBM) and a specifically generated relevance-based system (RBS). RBS

Fig. 1 Flow chart of search procedure strategy

was developed as a decision-making tool for helping identify potential DDIs. In a first step, the RBS differentiates between clinically relevant and non-relevant interactions based on data from interaction studies. Furthermore, in case of lack of study data, a third category of interactions which might occur due to pharmacological mechanisms was introduced [12]. This approach is based on the chemical structure of drugs and their corresponding mechanisms found in interaction programs and literature. Therefore, the RBS can also be used as a theoretical framework flagging DDIs especially for newly registered pharmaceuticals in case there are no head-to-head data available. In Table 1 the classification criteria of both systems are summarised.

Results

NSAIDs, PPIs, analgesics and glucocorticoids

NSAIDs are a commonly prescribed medication for treating inflammatory arthritis patients. NSAIDs such as diclofenac, ibuprofen, naproxen, and piroxicam are mainly metabolised via CYP2C9 [13]. Co-prescribing of PPIs (pantoprazole, omeprazole, esomeprazole, and lansoprazole) with non-selective NSAIDs is strongly recommended. In vitro studies showed that almost all PPIs are metabolised via CYP2C19 and CYP3A4 into inactive metabolites. Pantoprazole additionally showed inhibitory effects on CYP2C9 [14]. DDIs between NSAIDs and PPIs, especially pantoprazole, might be possible. However, all three interaction programs and the

Table 1 Classification of interactions according to the system of evidence-based medicine (EBM) and relevance-based system (RBS)

EBM	
Grade of evidence	Evidence
Ia	> 1 Well-designed randomized controlled trial
Ib	≥ 1 Well-designed controlled trial without randomization
IIa	≥ 1 Controlled non-randomized study
IIb	≥ 1 Experimental study
III	Evidence obtained from case–control-studies
IV	Reports and opinions of respected authorities and expert committees
RBS	
Relevance	Criteria of relevance
√	Interaction that can occur theoretically. No data available regarding the concomitant use of two drugs or an interaction between them
√√	In vitro interaction and/or interaction observed in animal experiments, ≤ 1 case report, probably no clinical relevance
√√√	Clinical relevant interaction, clinical trials and/or ≥ 1 case report are available

literature research did not show any clinically relevant interactions between NSAIDs and PPIs.

A pharmacodynamic interaction is given between NSAIDs and glucocorticoids. Their concomitant use increases the risk for gastrointestinal bleeding [9–11] and even short term NSAIDs intake can cause ulcers. Normally, body tissue regenerates by producing prostaglandin E. Concomitantly administered steroids inhibit the production of cytokines as well as the secretion of gastric mucosa and protective growth factors. As a result, the autoregulatory mechanisms of ulcer repair are inhibited [15]. With regards to severity the interaction is graded as major risk/monitoring recommended.

COX-2 inhibitors and opioids (tramadol, oxycodone and buprenorphine) are alternatives for mitigating pain. These two classes of drugs are metabolised by CYP2D6, resulting in a pharmacokinetic interaction [9, 10]. Tramadol is changed into its active form o-desmethyltramadol by CYP2D6. Its analgesic efficacy can be reduced by inhibition of its enzymatic activation [16]. When coxibes and

oxycodone or buprenorphine are administered together, the plasma concentration of the two opioids may rise, leading to an increased risk for side effects [17]. However, no clinical studies documenting a direct interaction between coxibes and opioids could be found. A summary of the above mentioned interactions is shown in Table 2.

Therapy with conventional disease-modifying antirheumatic drugs (cDMARDs)

cDMARDs combined with NSAIDs

Between MTX and NSAIDs a pharmacokinetic interaction was found [9–11]. Approximately 80% of MTX is excreted unchanged through glomerular filtration. Furthermore, it is eliminated by active transporters such as organic anionic transporters (OAT) 1 and 3 and multidrug-resistance-proteins (MRP) 2 and 4 in the kidney [18]. NSAIDs inhibit glomerular filtration through impairment of renal blood flow following inhibition of prostaglandin synthesis.

Table 2 Interactions with NSAIDs, analgesics and glucocorticoids

Comedication	Grades from EBM	Clinical relevance	Type of interaction	Mechanism of interaction	Resulting effect
NSAIDs + glucocorticoids [15]	Ia	√√√	PD	Suppression of ulcer-protective cytokines	Delayed regeneration of NSAID-induced ulcer
Opioids (tramadol) + COX-2 inhibitors [16, 17]	IV	√	PK	Inhibition of CYP 2D6 by COX-2 inhibitors	Potentially increased plasma concentration of affected opioids, decreased bioactivation of tramadol and therefore reduced analgesic effect

Subsequently MTX is filtrated more slowly [19]. NSAIDs are also inhibitors of the active transporters mentioned above in vitro [19, 20]. In terms of severity the interaction is graded as major risk. However, the interaction between MTX and NSAIDs seems to have little relevance in low-dose-MTX therapy, equivalent to a dose of up to 30 mg once weekly.

With regards to leflunomide (LEF) and NSAIDs there is a possible pharmacokinetic interaction [9–11]. NSAIDs are metabolized by CYP2C9 in the liver. The active metabolite of LEF, teriflunomide, inhibits CYP2C9. It was shown that LEF inhibits NSAID metabolism via CYP2C9 in vitro. There seems to be no relevant interaction in vivo [21].

The interaction between sulfasalazine (SSZ) and NSAIDs is a pharmacodynamic one. The interaction programs state an interaction between NSAIDs and salicylates because SSZ is partly a salicylate. This can potentially lead to an increased risk for gastrointestinal bleeding. The concomitant use of NSAIDs and aspirin causes increased gastrototoxicity, but it is not supported by any data if the same interaction also applies to SSZ [11, 22, 23]. Furthermore, there is an increased risk for hepatotoxicity when SSZ and diclofenac are administered together [10].

The pharmacodynamic interaction between hydroxychloroquine (HCQ) and diclofenac leads to hepatotoxicity, as both substances can cause elevated liver enzymes. Diclofenac is the NSAID with the greatest potential for hepatotoxicity [10], whereas HCQ normally has a small risk for hepatotoxic effects. No studies could be found where these two drugs were administered and investigated together. DDIs between cDMARDs and NSAIDs are summarised in Table 3.

cDMARDs combined with other analgesics

The pharmacodynamic interaction between MTX and the analgesic drug metamizole can trigger haematological side effects [10, 11]. However, only one case report describing bone marrow suppression due to the concomitant use of MTX and metamizole could be found [24]. In terms of severity the interaction is rated as major risk.

Based on a pharmacodynamic interaction, combining SSZ and metamizole increases the risk of haematological side effects, especially agranulocytosis, although no studies regarding the concomitant use could be identified [10, 25, 26].

Between the antimalarials (CQ, HCQ) and paracetamol a theoretical pharmacokinetic interaction is described as paracetamol is changed partly by CYP2D6 into one of its toxic metabolites, *N*-acetyl-*p*-benzoquinone-imine (NAPQI) [10, 27]. Chloroquine (CQ) and HCQ both have the ability to inhibit CYP2D6, so the toxification of paracetamol might be inhibited [28]. However, the toxicity of already formed NAPQI can be enhanced by CQ and HCQ inhibiting

lysosomal digestion of injured organelles. This results in cell death and subsequent liver necrosis [29].

The antimalarials may also interact with opioids through pharmacokinetic mechanisms [10]. As mentioned before, some opioids are metabolised by CYP2D6 [16]. The ability of CQ and HCQ to inhibit CYP2D6 [28] might reduce the analgesic efficacy of tramadol and lead to higher plasma concentrations of oxycodone and buprenorphine. No studies regarding the concomitant use of these two classes of drugs could be identified, so the clinical relevance remains unclear. Possible interactions of cDMARDs and analgesics are shown in Table 3.

cDMARDs combined with glucocorticoids

The interaction between MTX and glucocorticoids can be characterized as a pharmacokinetic one. Referring to mediQ, glucocorticoids inhibit cellular uptake of MTX and therefore the efficacy of MTX might be decreased [10]. Literature research in PubMed showed that hepatotoxicity is increased when combining MTX and long-term glucocorticoids. This is probably due to the steroids influencing various active transporters involved in the excretion of MTX, particularly multidrug-resistance protein (MRP) and breast cancer resistance protein (BCRP) [30].

Between LEF and glucocorticoids a pharmacodynamic interaction is given. Both drugs can cause hypertension and hyperlipidaemia [10]. Hypertension is a common side effect of both drugs so the combination is likely to increase the risk of high blood pressure [31]. Regarding hyperlipidaemia, it remains unclear if their combination increases the risk [32].

SSZ and glucocorticoids can trigger hematotoxicity due to a pharmacodynamic interaction [10]. However, few studies regarding the concomitant use of the two drugs could be found [33, 34].

The interaction between the antimalarials and glucocorticoids is a pharmacodynamic one. As both drugs carry a risk for myopathy and cardiomyopathy [10], the combination of two myotoxic agents might increase the risk of developing such severe side effects [35, 36]. An overview on these DDIs is given in Table 3.

cDMARDs combined with PPIs

The interaction between MTX and PPIs is a pharmacokinetic interaction [9–11]. PPIs are able to inhibit the excretion of MTX through various transport systems like OAT3 [37] and BCRP [38]. The interaction seems to be less relevant in low-dose-MTX therapy [7, 39], nevertheless it might be important to pay attention in individual cases.

The interaction of PPIs with the antimalarials is a pharmacokinetic one [10]. PPIs increase the lysosomal pH-value.

Table 3 Interactions with cDMARDs

Comedication	Grades from EBM	Clinical relevance	Type of interaction	Mechanism of interaction	Resulting effect
Methotrexate					
NSAIDs [9–11, 18–20]	Ia	√√	PK	Inhibition of OAT1, OAT3, MRP2 and MRP4 by NSAIDs	Increased plasma concentration of MTX, less relevant in low-dose-therapy
Metamizole [24]	IV	√	PD	Additive toxicity (blood count)	Increased risk for haematologic side effects
Glucocorticoids [10, 30]	IIb	√√√	PK	Increased AUC (MTX), decreased CL (MTX)	Increased hepatotoxicity
PPIs [7, 9–11, 37–39]	Ia	√√	PK	Inhibition of OAT3 and BCRP by PPIs	Increased plasma concentration of MTX, less relevant in low-dose-therapy
Folic acid [10, 11, 41]	Ia	√√√	PD	Inversion of MTX-induced folic acid deficiency	Reduction of MTX-induced toxicity without meaningful loss of efficacy
Leflunomide					
NSAIDs [21]	IV	√	PK	Inhibition of CYP 2C9 by LEF	Probably increased plasma concentration of NSAID, according to literature unproblematic
Glucocorticoids [10, 31, 32]	IV	√	PD	Amplification of side effects	Potentially increased risk for hypertonia and hyperlipidaemia
Sulfasalazine					
NSAIDs [11, 22, 23]	IV	√	PD	Synergistic effects	Increased risk for gastrointestinal bleeding
Metamizole [25, 26]	IV	√	PD	Additive haematotoxicity	Potentially increased risk for developing agranulocytosis
Glucocorticoids [10, 33, 34]	IV	√	PD	Additive haematotoxicity	Potentially increased risk for haematologic side effects
Chloroquine and hydroxychloroquine					
Diclofenac [10]	IV	√	PD	Additive hepatotoxic effects	Potentially increased risk for elevated liver enzymes
Paracetamol [27–29]	IIb	√√	PK	1) Weak inhibition of CYP 2D6 and 2) inhibition of autophagy by CQ and HCQ	1) Increased plasma concentration of unchanged paracetamol; 2) increased toxicity induced by toxic paracetamol-metabolites
Opioids (tramadol, oxycodone) [10, 16, 28]	IV	√	PK	Weak inhibition of CYP 2D6 by CQ and HCQ	Potentially increased plasma concentration of affected opioids, decreased bioactivation of tramadol and therefore reduced analgesic effect
Glucocorticoids [10, 35, 36]	IV	√	PD	Amplification of side effects	Potentially increased risk for developing myopathy or cardiomyopathy
PPIs [10, 40]	IV	√	PK	Decreased resorption of CQ/HCQ by PPIs	Probably reduced efficacy of CQ and HCQ

Theoretically, the lysosomal resorption and therefore efficacy of CQ and HCQ might be decreased subsequently [40]. However, it remains unclear if this mechanism is relevant in clinical practice (Table 3).

No interactions were found for the combination of PPIs, LEF, and SSZ.

Methotrexate combined with folic acid

In clinical practice, it is mandatory to add folic acid to a therapy with MTX to reduce the side effects caused by folate deficiency. It was suggested by the interaction programs that folic acid might reduce the efficacy of MTX therapy [10, 11]. It could be figured out that supplementation with folic

acid significantly reduces side effects without a noteworthy reduction of its efficacy [41] (Table 3).

Therapy with biological DMARDs (bDMARDs)

bDMARDs often used in rheumatology are TNF α -inhibitors (adalimumab, etanercept, certolizumab pegol, golimumab, infliximab), various IL-antagonists (tocilizumab, sarilumab, secukinumab, ustekinumab, ixekizumab) and antibodies against B-cells and T-cell activation (rituximab, abatacept). As they are not metabolised by CYP-isoenzymes or excreted by active transporters, there are no pharmacokinetic interactions with other drugs involving liver enzymes and transport proteins [42]. However, some of them influence the expression of CYP-enzymes [10].

There may be a pharmacodynamic interaction when MTX and TNF α -inhibitors are administered together. Elevation of liver enzymes is a frequent side effect of MTX, but this can also occur during therapy with TNF α -inhibitors. Due to the fact that there are only few case reports available, it could not be fully elucidated if the combination results in an increased risk for hepatotoxicity [43]. Between MTX and TNF α -inhibitors there is a potential for pharmacokinetic interaction, too. The occurrence of anti-drug-antibodies seems to be reduced when MTX is applied concomitantly. Other DMARDs don't seem to have such "protective" effects on the immunogenicity of biologicals [42, 44, 45].

The combination of the TNF α -inhibitors with LEF leads to a potentially increased risk for hepatotoxicity, because both agents have hepatotoxic effects. However, no studies could be found investigating the combination of both [45].

Tocilizumab, an inhibitor of the IL-6 receptor causes pharmacokinetic interactions with various CYP-substrates. IL-6, which is formed during inflammatory processes, suppresses the expression of CYP and therefore the metabolism

of the respective substrates is impaired [10, 11]. By inhibiting the IL-6-mediated signalling pathway the activity of CYP normalises and the metabolism of CYP-substrates is increased subsequently. This makes dose adjustments necessary [46]. The same type of interaction was suggested for the IL-17A-antagonist secukinumab and IL-17-antagonist ixekizumab [47] in the interaction program mediQ, but no studies could be identified [10]. Other cytokines inhibiting IL-12/IL-23 have no effect on microsomal CYP-enzymes in vitro [48]. Due to lack of data no information regarding severity is available.

A summary of possible interactions is given in Table 4.

Therapy with targeted synthetic DMARDs (tsDMARDs)

Novel drugs used in the therapy of inflammatory arthritis are the two Janus kinase inhibitors (JAKinibs) tofacitinib and baricitinib and the PDE-inhibitor apremilast.

Tofacitinib is metabolised through various CYP-enzymes, especially CYP3A4, but CYP1A2, 2C9, 2C19 as well as 2D6 seem to be involved to a smaller extent. Therefore interactions with CYP3A4-inhibitors are mostly relevant [49] (Tables 5, 6). Among PPIs, lansoprazole seems to have the greatest potential for inhibiting CYP2C19, whereas pantoprazole has the lowest potential for causing interactions [50]. Tofacitinib is often combined with MTX in patients with inflammatory joint diseases. No change in the pharmacokinetics of MTX and tofacitinib was found [51]. In another study, the incidence of side effects was similar in the monotherapy and the combination therapy [51, 52] (Table 5).

Baricitinib is metabolised mainly via CYP3A4, but only to the extent of approximately 10%. As the drug is a substrate for OAT3, there could be interactions with NSAIDs and PPIs, which are inhibitors of OAT3 [53], however, no

Table 4 Interactions with bDMARDs

Comedication	Grades from EBM	Clinical relevance	Type of interaction	Mechanism of interaction	Resulting effect
TNFα-inhibitors					
Methotrexate [42–45]	(1) IV (2) Ia	(1) $\sqrt{\quad}$ (2) $\sqrt{\sqrt{\sqrt{\quad}}}$	(1) PD (2) PK	(1) Additive hepatotoxicity and 2) decreased CL of TNF α -inhibitors by MTX	(1) Potentially increased risk for elevated liver enzymes; (2) increased bioavailability of the TNF α -inhibitor and therefore increased efficacy
Leflunomide [45]	IV	$\sqrt{\sqrt{\quad}}$	PD	Additive hepatotoxicity	Increased risk for elevated liver enzymes
IL-antagonists					
CYP-substrates [10, 11, 46]	IIa	$\sqrt{\sqrt{\quad}}$	PK	Normalization of expression and activity of CYP-isoenzymes	Increased metabolism of CYP-substrates and reduced bioavailability of concerning drugs

Table 5 Interactions with tsDMARDs

Comedication	Grades from EBM	Clinical relevance	Type of interaction	Mechanism of interaction	Resulting effect
tsDMARD + methotrexate [49–54]	Ia	√√√	PD	Increased efficacy on disease activity	Increased efficacy of the combination compared to monotherapy
Tofacitinib + CYP-inhibitors [49–54]	IV	√	PK	Inhibition of CYP-isoenzymes	Potential risk for inhibition of enzymatic catabolism of tofacitinib

study was found. Baricitinib is also an inhibitor of OAT3 in vitro which could lead to possible interactions with MTX [53], but again no study was found.

Apremilast is metabolised mainly via CYP3A4, with participation of CYP1A2 and 2A6. Interactions with CYP-inhibitors do not seem to be critical, but the drug should not be combined with potent CYP-inducers. The combination with MTX did not show any changes in pharmacokinetics for these two drugs [54] (Table 6).

Due to lack of data no information regarding severity is available.

Discussion

A systematic database supported analysis of DDIs in the therapy of inflammatory joint diseases was carried out. Drug-related problems in RA patients like drug-choice, dosing, drug use and drug interaction problems were generally discussed by Ma et al. [3]. A further study was found focusing on the quantification of polypharmacy in RA patients and investigating the interaction risk of these patients [4]. The majority of previous reviews, however, is focused on the risk of potential interactions of single drug combinations with methotrexate (MTX) [5–8], but so far there is no detailed review on the whole range of drugs used for managing inflammatory joint diseases.

Interactions between drugs used for the pharmacotherapy of inflammatory arthritis were assessed using a software detection approach based on three different computerised interaction programs and classified according to their clinical relevance by applying EBM and the specifically developed RBS. Drug combinations were selected according to the EULAR treat-to-target recommendations for treating rheumatoid arthritis and psoriatic arthritis patients [1, 2]. Nowadays a considerable amount of computer programs based on pharmacological studies is available for checking drug interactions. We selected three programs offering clinically useful information about DDIs: Apotronik was decided upon as this is a frequently applied program in

retail pharmacies in Austria. MediQ is a highly approved Swiss program and Micromedex is a leading international program widely used in hospital pharmacies. This selection allows the concise evaluation of DDIs from a national as well as international point of view. The theoretical background of relevant effects is described in greater detail in the Micromedex program and is additionally supported by an included description of the underlying DDI mechanisms and references [55].

Generally, and for the most part DDIs are attributed to metabolising enzymes including phase I and phase II reactions as well as CYP genes. Depending on the molecular structure and based on comparable functional chemical moieties, CYP3A4 is the key enzyme for metabolising drugs used in the therapy of inflammatory joint diseases. Therefore, it has to be kept in mind that all inhibitors of CYP3A4 can lead to increased plasma levels of the drug and consequently to an increased risk of side effects. We obtained similar results with regards to type and severity of interactions, mentioning that no contraindication was found. Based on the results of these programs, the screened combinations seem to generally be quite safe. Noteworthy is the fact that clinically relevant drug interactions within the group of bDMARDs seem to be limited to IL-6 receptor blockers, IL-17A- and IL-17-antagonists, substances normalising down-regulated CYP activity caused by uncontrolled inflammation. A subsequent increase of the metabolism of CYP-substrates makes dose adjustments necessary.

Knowledge of CYP enzyme metabolism and transport systems is crucial especially in case of polypharmacy in elderly patients suffering from treatable comorbidities (e.g., hypertension, heart failure, renal failure, depression and osteoporosis). The risk for interactions increases with the number of drugs taken. According to Rottenkolber et al. medication side effects account for 3.25% of all non-elective admissions to internal medical departments [56]. Whereas this is already an unexpectedly high number, drug-related hospitalisation rises up to 11% in the group of elderly patients [57]. Hence, alertness with regards to potential interactions saves patients wellbeing. Closer

Table 6 Summary of in vitro studies with CYP-enzymes and transport systems of mainly administered drugs in inflammatory rheumatic diseases

CYP-enzymes										Transport-systems					
1A1	1A2	2A6	2A13	2C8/2C9	2C19	2D6	2E1	3A4	PGP	BRCP	OAT1	OAT3	MRP2	MRP4	
Initial Therapy															
		S**		S							<i>i</i>	<i>s/i</i>	<i>i</i>	<i>i</i>	
	S					S	S	S	S ⁺		<i>i</i>				
								S ⁺							
				<i>i</i>	<i>s/i</i>	<i>i</i>		<i>s/i</i>		<i>i</i>		<i>i</i>			
DMARDs															
										S	S	S	S	S	
	S			<i>i</i> **	S			S		<i>s/i</i> **	<i>i</i>	<i>i</i>			
										<i>i</i>					
tsDMARDs															
	S			S	S	S		S							
								S	S		<i>i</i>	<i>s/i</i>			
	S	S						S	<i>s/i</i>						
substrate, <i>i</i> inhibitor, <i>i</i> ⁺ inducer, <i>s</i> ** naproxen, <i>i</i> ** teriflunomide															

s substrate, i inducer, s⁺ inducer, s** naproxen, i** teriflunomide

interdisciplinary cooperation between drug prescribing physicians and pharmacists is recommended as a very important safety enhancing tool.

As all possible DDIs evaluated in this paper refer to standard dosage schemes, thus the interaction(s) may be significantly more distinct or only present in higher therapeutic drug concentrations. For the anchor drug MTX the interaction potential may well be overestimated due to a reduced dosage in rheumatology as opposed to high dose administration in oncology. Interactions with active transporters for drugs new to the market such as tofacitinib and baricitinib are possible and therefore more studies investigating pharmacokinetic interactions with JAK inhibitors are required. Furthermore, every additional single drug as well as ethanol and dietary supplements can influence drugs' kinetics. Hence these factors as well as comorbidity, aspects related to patients, and medication administration including dosages, time, and sequences, were not reviewed and therefore are the limitations in this paper and warrant further investigation.

Summarising these investigations, it can be emphasised that pharmacotherapy in the treatment of inflammatory arthritis is quite safe and well evidence-based. Interactions between drugs used for this treatment were screened by comparing three different computerised interaction programs supported with extensive literature research, especially for drugs new to the market. The applied screening software in this paper is limited to a 1:1 analysis so you only get one tessera of the mosaic for inflammatory joint disease patients. To obtain a more comprehensive picture, the results were combined in clearly structured tables which allows a quick overview on potential interactions. They can be used on an individual basis to identify patients at risk, e.g., patients with (multiple) comorbidities and therefore under polypharmacy. Furthermore, it allows simple adjustment to new drugs and thus maybe contributes to a reshaping of future treatment algorithm.

Acknowledgements Open access funding provided by University of Graz. All authors would like to thank Dr. Schäffer and Mag. Knoll for their helpful technical assistance.

Author contributions All authors take full responsibility for the integrity of the manuscript. SP and AO conceived, designed and coordinated the search. KB and ML extracted the data. RP and WG revised the data and provided critical feedback. All authors approved the revised version manuscript and agreed to be accountable for all aspects of the current review.

Funding No funding was received.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

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