The impact of non-genetic factors on drug metabolism: towards better phenotype predictions

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Chapter 5

A systematic review on disease-drug-drug interactions with immunomodulating drugs: A critical appraisal of risk assessment and drug labelling

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British Journal of Clinical Pharmacology, 2022 Jun 16. doi: 10.1111/bcp.15372

Abstract

Aim: Use of immunomodulating therapeutics for immune-mediated inflammatory dis-eases may cause disease-drug-drug interactions (DDDIs) by reversing inflammation-driven alterations in the metabolic capacity of cytochrome P450 enzymes. European Medicine Agency (EMA) and US Food and Drug Administration (FDA) guidelines from2007 recommend that the DDDI potential of therapeutic proteins should be assessed. This systematic analysis aimed to characterize the available DDDI trials with immunomodulatory drugs, experimental evidence for a DDDI risk and reported DDDI risk information in FDA/EMA approved drug labelling.

Method: For this systematic review, the EMA list of European Public Assessment Reports of human medicine was used to select immunomodulating monoclonal anti-bodies (mAbs) and tyrosine kinase inhibitors (TKIs) marketed after 2007 at risk for a DDDI. Selected drugs were included in PubMed and Embase searches to extract reported interaction studies. The Summary of Product Characteristics (SPCs) and the United States Prescribing Information (USPIs) were subsequently used for analysis of DDDI risk descriptions.

Results: Clinical interaction studies to evaluate DDDI risks were performed for 12 of the 24 mAbs (50%) and for none of the TKIs. Four studies identified a DDDI risk, of which three were studies with interleukin-6 (IL-6) neutralizing mAbs. Based on (non)clinical data, a DDDI risk was reported in 32% of the SPCs and in 60% of the USPIs. The EMA/FDA documentation aligned with the DDDI risk potential in 35% of the20 cases.

Conclusion: This systematic review reinforces that the risk for DDDI by immunomodulating drugs is target- and disease-specific. Drug labelling information designates the greatest DDDI risk to mAbs that neutralize the effects of IL-6, Tumor Necrosis Factor alfa (TNF-α) and interleukin-1 bèta (IL-1β) in diseases with systemic inflammation.

What is already known about this subject

- Inflammation can change the drug metabolizing capacity of individuals and may hence affect drug exposure.
- Immunomodulating therapeutics may, through resolution of inflammation, trigger disease-drug-drug interactions (DDDI), for which the EMA and FDA have instructed guidelines for risk assessment.

What this study adds

- This is the first study that systematically compared available clinical and non-clinical evidence for the risk assessment of DDDIs to the drug labelling of immunomodulating therapeutics.
- This study reinforces that the risk for DDDI by immunomodulating drugs occurs to be target and disease specific.
- We highlight that the available evidence to determine a DDDI risk is not always reflected in the drug labelling that is approved by the EMA and FDA, and risk assessment differs between regulatory authorities.

Introduction

Inflammation can contribute to inter-individual variability in drug response, potentially resulting in under- or overexposure of the drug and thereby ineffective treatment or toxicity (1–3). Indeed, in patients with an acute or chronically increased inflammatory status, drug clearance is altered, resulting in phenoconversion (4–7). These changes in drug clearance are attributed to inflammation-associated cytokines that can impair or induce expression of the cytochrome P450 (CYP) enzymes involved in drug metabolism of small molecules (8–10). For example acute COVID-19 infection leads to an isoform specific modulation of CYP activity and studies in rheumatoid arthritis patients have shown increased plasma concentrations of prescribed drugs (11–13).

In the last decades, immunomodulating monoclonal antibodies (mAbs) that target specific cytokines or their receptors have increasingly been deployed in the treatment of immune-mediated inflammatory diseases (IMIDs). These immunomodulating mAbs are not metabolized via CYP enzymes and are therefore also unable to directly induce or inhibit the activities of these metabolic enzymes. For this reason, the risk that mAbs change the pharmacokinetics of concomitant medication and trigger traditional direct drug-drug interactions (DDIs) is generally considered to be low. However, mAbs that resolve inflammation may, through the reversal of cytokine-mediated effects on the expression of drug metabolizing enzymes, restore CYP mediated clearance (14). Immunomodulating mAbs may hence indirectly change the pharmacokinetics of concomitant medication and induce disease-drug-drug interactions (DDDIs).

Immunomodulation may not be restricted to mAbs, but also occur following the administration of small molecules that target downstream signalling pathways of inflammatory mediators. The effects of inflammation on CYPs are presumed to occur via activation of cytokine signalling pathways (10). As such, inhibitors of these pathways might also indirectly reverse the impact of inflammation. In theory, tyrosine kinase inhibitors (TKIs) that interfere with the signalling pathways of cytokines may also be prone to induce DDDIs in patients suffering from an inflammatory disease.

The potential of therapeutic proteins, including mAbs, to trigger DDDIs is acknowledged by both the European Medicine Agency (EMA) and the U.S. Food and Drug Administration (FDA). In 2007, the EMA updated their DDI guidelines

by recommending to assess the potential risk for DDDIs with therapeutic proteins that are either pro-inflammatory cytokines themselves or have the potential to modulate pro-inflammatory cytokines (15). The current FDA guidelines (2020) state that labelling of this type of therapeutic proteins should include a risk analysis in which the potential for DDDIs is defined (16). Input for this risk analysis can be retrieved from in vitro or animal studies, population PK modelling or physiologically based pharmacokinetic (PBPK) modelling, or a dedicated clinical DDDI study (16).

A CYP phenotyping cocktail approach is considered the gold standard for assessing a therapeutic protein's potential for inducing DDDIs. These studies compare the pharmacokinetics of probe substrates for critical CYP enzymes in drug metabolism (e.g. CYP3A4, CYP2D6, CYP2C19, CYP2C9 and CYP1A2) prior and after the start of an immunomodulating mAbs in the intended target population. An advantage of this is that every patient serves as its own control – excluding inter-individual variability in drug metabolism as a confounding factor. Changes in the exposure parameters C_{max} and $AUC_{0\text{-}inf}$ of the individual probe substrates that exceed the limits for bioequivalence (80–125%) are an indication that drug metabolism is affected by the investigated drug. Through this approach, the potential of a therapeutic protein to indirectly change drug metabolism of small molecules via immunomodulation can be defined and accordingly inform on the risk of DDDI.

Results from DDDI studies with cytokine-targeting mAbs have been summarized before (2,17,18), but interpretation of these results is limited and not connected to DDDI risk assessment approved by regulatory authorities. To address this gap, this review aimed to provide a systematic overview of all available evidence for DDDIs with immunomodulating drugs and the associated risks stated in the drug labelling information approved by the FDA and EMA between 2007 and 2021. To this end, in this review the results from clinical studies for mAbs and TKIs examining the potential shift in drug exposure following intervention with immunomodulatory therapies are summarized. Secondly, the DDDI risks of therapeutic proteins that are cytokine modulators as described in the EMA's summary of product characteristics (SPC) and the FDA's United States prescribing information (USPI) were analysed and compared to the identified evidence from clinical and non-clinical studies. Finally, the outcome of this analysis was

used to provide recommendations for future assessment of DDDI risks with immunomodulating therapeutics.

Methods

For this systematic review on DDDI studies and labelling information, identification and selection of pharmaceuticals and related studies was performed. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to prepare the report (19). The EMA list with European Public Assessment Reports (EPARs) of human medicine was used to identify all authorized pharmaceutical products between January 2007 and November 2021 (20). Only original trade names of drugs were included, thereby excluding biosimilars from the analysis. To identify immunomodulatory drugs, the following pharmaceutical groups were selected: (selective) immunosuppressant, antineoplastic agents, protein kinase inhibitor, interleukin (IL)-inhibitors, monoclonal antibodies, drugs for obstructive airway diseases, and agents for dermatitis. Drugs targeting any cytokine (receptor) were included together with drugs that selectively inhibit the JAK/STAT, MAPK/MEK/ERK, NF-κB or PI3K/AKT signalling pathways downstream of cytokine receptors, as these pathways have been linked to effects of inflammation on drug metabolism (10). Immunosuppressants without a specific immune-related target were excluded from this analysis. The IUPHAR/BPS Guide to PHARMACOLOGY was used to standardize the nomenclature of all drugs and targets (21).

Pubmed, Cochrane and Embase were with the support of a librarian used to identify all published clinical interaction studies with eligible immunomodulating drugs. Search terms consisted of the drug name together with terms describing interaction studies. Only English language papers with original data were included. Subsequently, ongoing interaction studies wherefore results are available were identified via clinicaltrials.gov (10). Evidence from non-clinical studies on potential DDDI risks was collected and summarized based on the recently reviewed in vitro impact of the targeted cytokines on CYP activity. Only studies utilizing primary human hepatocytes (PHHs) were included for this assessment, since they are considered the golden standard for in vitro studies. Next, the EPAR documents published by the EMA (Annex I, SPC) and the USPI documents published by the FDA of all selected drugs were examined to retrieve information on described

potential risks for DDDIs. The potential risk of each individual drug to induce DDDIs was determined and categorized as 'yes', 'caution', 'no' or 'unknown', based on the provided information. When the SPC or USPI stated: 'perform therapeutic monitoring (TM) of effect or drug concentration' (of victim drug) or 'TM is recommended', the DDDI risk was classified as 'yes'. When the SPC or USPI stated: 'consider performing therapeutic monitoring of effect or drug concentration' the DDDI risk was classified as 'caution'. When SPC or USPI stated: 'clinical significance is unknown' or there was no mention of any DDDI related information, the DDDI risk was classified as 'unknown'. Additionally, the type of studies that were available in literature for assessing DDDI risks – independent from evidence used by regulatory authorities – were determined and classified into the following groups: Class 0: no data, class 1: experimental (in vitro) data; available experimental evidence examining the potential effect of the targeted cytokine to modulate CYP activity in primary human hepatocytes (PHH), class 2: PBPK modelling, class 3: clinical data with a substrate for one CYP enzyme, or class 4: clinical data based on investigations with a probe cocktail for multiple CYP enzymes.

Lastly, the agreement on risk information of mAbs was compared between the SPC and USPI. This analysis was limited to mAbs, since TKI drug labels did not address DDDIs.

Results

In this systematic review a total of 1573 drugs with an EPAR classified as human medicine between January 2007 and November 2021 were identified. After screening, 37 pharmaceutical products were identified that, based on their mechanism of action, would make them eligible for a DDDI study (Figure 1). Following a review of their EPARs and a literature search in Pubmed and Embase databases in April 2022, conducted clinical CYP interaction study were identified for 12 of the 24 mAbs (50%) and for none of the TKIs (0%) (Table 1). Of these, seven studies exploited a CYP cocktail approach (58%) whereas the other five studies (42%) determined the potential of DDDI using a CYP3A4 substrate (Table 1). There are drugs for which no clinical interaction study was performed, but in the product label a DDDI risk was stated based on non-clinical data (Table 2 & Supplementary Table S1).

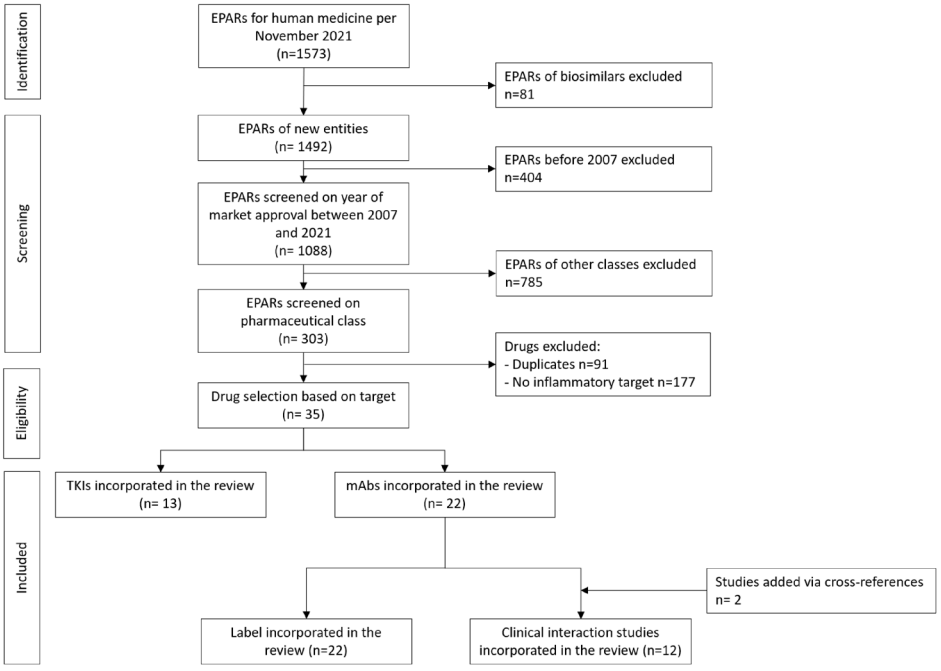

Figure 1 Study flow diagram of the retrieval and review process. Drugs targeting any cytokine (receptor) and drugs that selectively inhibit the JAK/STAT, MAPK/MEK/ERK, NF-κB or PI3K/AKT signalling pathways downstream of cytokine receptors were included in the analysis.

The included immunomodulating mAbs where subdivided based on their target, categorized as acute signalling cytokines, IL-17/IL-23 cytokines, Th2-type cytokines, or Th1-type cytokines (Figure 2). Since TKIs do not target a specific receptor, but rather inhibit the cellular signalling pathways that are initiated after cytokine binding to the receptor, they span multiple categories.

Table 1 Results of performed clinical disease-drug-drug interaction studies. Studies are ordered based on target and study population. Impact of mAb treatment initiation on CYP activity of major CYP enzymes is indicated with colour patterns.

Target	Drug	Study population	N[c]	Moment of PK evaluation (day 0 = mAb initiation)[d]	CYP3A4[e]	CYP2C19[e]	CYP1A2[e]	CYP2D6[e]	CYP2C9[e]	Reference
IL-6	Sirukumab[a]	Rheumatoid arthritis	12	Day 7 & 21 & 42	Midazolam	Omeprazole	Caffeine		Warfarin[g]	(22)
	Tocilizumab	Rheumatoid arthritis	12	Day 7 & 35	Simvastatin					(23)
IL-6Ra	Sarilumab	Rheumatoid arthritis	19	Day 7	Simvastatin					(24)
IL-6	Clazakizumab[b]	Kidney transplant	10	Day 84 & Day 364	Pantoprazole[f]	Pantoprazole				(25)
IL-17RA	Brodalumab	Psoriasis	20	Day 9	Midazolam					NCT01937260
IL-17A	Ixekizumab	Psoriasis	26	Day 8 & 85	Midazolam	Omeprazole	Caffeine	Dextromethorphan	Warfarin[g]	NCT02993471
	Secukinumab	Psoriasis	24	Day 8 & 36	Midazolam					(26)
IL-23	Risankizumab	Psoriasis	21	Day 90	Midazolam	Omeprazole	Caffeine	Metoprolol	Warfarin[g]	(27)
	Tildrakizumab	Psoriasis	17	Day 57	Midazolam	Omeprazole	Caffeine	Dextromethorphan	Warfarin[g]	(28)
	Guselkumab	Psoriasis	12	Day 7 & 28	Midazolam	Omeprazole	Caffeine	Dextromethorphan	S-warfarin[g]	(29)
IL-4Ra	Dupilumab	Atopic dermatitis	13	Day 28	Midazolam	Omeprazole	Caffeine	Metoprolol	S-warfarin[g]	(30)
IL-2	Daclizumab[a]	Multiple sclerosis	20	Day 84	Midazolam	Omeprazole	Caffeine	Dextromethorphan	Warfarin[g]	(31)

[a] application retracted, [b] applied for market approval, [c] that completed the study, [d] baseline is not included, [e] No effect is when geometric mean ratio (90% CI) of $AUC_{0\text{-}inf}$ (probe alone vs probe + mAb) is within 80–125% equivalence limits, [f] Involvement of CYP3A4 in pantoprazole metabolism is limited, [g] Warfarin is also metabolized by CYP1A2, CYPC19 and CYP3A4. Colour indicate effect on probe drug exposure: vertical lines green = no change, horizontal lines red = decreased exposure, gridlines orange = increased exposure, clear white = not determined.

Table 2 Summary of experimental and clinical evidence for DDDI risks and according labelling information of mAbs documented by the EMA and FDA

								Type(s) of evidence available for DDDI risk assessment[c]			
	Target	**Drug**	**Indication**	**Non-clinical evidence from PHHs (9,56,64–67)**	**Clinical evidence[b]**	**DDDI risk in SPC**	**DDDI risk in USPI**	**Experimental data**	**PBPK modelling**	**Clinical data with one substrate**	**Clinical data with multiple probe substrates**
Acute signalling cytokines	IL-6	Tocilizumab	RA / COVID-19 / (systemic) JIA / CRS	Yes - CYP1A2 - CYP2C9 - CYP2C19 - CYP2D6 -CYP3A4	Yes - CYP3A4 (probe)	Yes	Yes				
	IL-6R	Sarilumab	RA		Yes - CYP3A4 (probe)	Yes	Yes				
	IL-6	Siltuximab	GLNH/ MCD		Not conducted	Yes	Yes				
	IL-6/ IL-6R	Satralizumab	NMO		Not conducted	Caution	Unknown				
	TNF-α	Golimumab	JIA	Yes - CYP1A2 - CYP2C9 - CYP2C19 - CYP2D6 -CYP3A4	Not conducted	Unknown	Yes				
		Certolizumab pegol	RA / axSpA / PsA / plaque psoriasis		Not conducted	Unknown	Unknown				

Table 2 continues on next page.

Table 2 *Continued*

	Target	Drug	Indication	Non-clinical evidence from PHHs (9,56,64–67)	Clinical evidence[b]	DDDI risk in SPC	DDDI risk in USPI	Type(s) of evidence available for DDDI risk assessment[c]			
								Experimental data	PBPK modelling	Clinical data with one substrate	Clinical data with multiple probe substrates
	IL-1β	Canakinumab	Gouty arthritis / CAPS / TRAPS / HIDS / MKD / FMF / Still's disease	Yes - CYP3A4	Not conducted	Yes	Yes				
		Rilonacept[a]	CAPS		Not conducted	Yes	Yes				
IL-17/IL-23 axis	IL-17RA	Brodalumab	Plaque psoriasis	Not determined	Yes - CYP3A4 (probe)	No	Caution				
	IL-17A	Bimekizumab	Plaque psoriasis		Not conducted	Caution	No drug label				
		Ixekizumab	Plaque psoriasis / PsA / axSpA		No effect (cocktail)	No	Caution				
		Secukinumab	Plaque psoriasis		No effect (cocktail)	No	Caution				

Table 2 *Continued*

	Target	Drug	Indication	Non-clinical evidence from PHHs (9,56,64–67)	Clinical evidence[b]	DDDI risk in SPC	DDDI risk in USPI	Type(s) of evidence available for DDDI risk assessment[c]			
								Experimental data	PBPK modelling	Clinical data with one substrate	Clinical data with multiple probe substrates
	IL-23	Risankizumab	Plaque psoriasis	No	No effect (cocktail)	No	No				
		Tildrakizumab	Plaque psoriasis		No effect (cocktail)	No	No				
		Guselkumab	Plaque psoriasis / PsA		No effect (cocktail)	No	Caution				
	IL-23/ IL-12	Ustekinumab	Plaque psoriasis / Crohn's Disease / UC		Ongoing	No	Caution				
Th2-type cytokines	IL-4Rα	Dupilumab	AD / asthma / CRSwNP	Not determined	No effect (cocktail)	No	Caution				
	IL-13	Tralokinumab	AD	Not determined	Ongoing	Unknown	No drug label				

Table 2 continues on next page.

Table 2 *Continued*

	Target	Drug	Indication	Non-clinical evidence from PHHs (9,56,64–67)	Clinical evidence[b]	DDDI risk in SPC	DDDI risk in USPI	Type(s) of evidence available for DDDI risk assessment[c]			
								Experi-mental data	PBPK modelling	Clinical data with one substrate	Clinical data with multiple probe substrates
	IL-5	Mepolizumab	Severe EA / CRSwNP / EGPA / HES	Not determined	Not conducted	No	Unknown				
		Reslizumab	EA		Not conducted	No	Unknown				
	IL-5Rα	Benralizumab	EA		Not conducted	No	Unknown				
Th1-type cytokine	IL-2	Daclizumab[a]	MS / allogenic renal transplantation	Yes - CYP2C19 - CYP2D6	No effect (cocktail)	Unknown	No				

[a] application retracted, [b] altered CYP activity is defined as: when GMR (90% CI) of $AUC_{0\text{-}inf}$ is beyond equivalence limits 80–125%, [c] Type of DDDI evidence is based on available data in literature on potential modulating effect of cytokine/mAbs on CYP metabolic capacity. DDDI risk categories are classified as: Yes (TM should be performed), Caution (consider monitoring for drug/effect), No, or Unknown (clinical significance is unknown or not mentioned). Type of DDDI evidence available, independent of risks stated in regulation labelling: 0 = no data available. RA = Rheumatoid arthritis, COVID-19 = coronavirus disease 2019, JIA = juvenile idiopathic arthritis, CRS = T cell-induced severe or life-threatening cytokine release syndrome, GLNH = Giant lymph node hyperplasia, MCD = multicentric Castleman's disease, NMO = Neuromyelitis Optica, axSpA = axial spondylarthritis, PsA = psoriatic arthritis, CAPS = cryopyrin-associated periodic syndromes, TRAPS = tumour necrosis factor receptor associated periodic syndrome, HIDS =hyperimmunoglobulin D syndrome, MKD = mevalonate kinase deficiency, FMF = familial Mediterranean fever, UC = ulcerative colitis, AD = Atopic dermatitis, CRSwNP = chronic rhinosinusitis with nasal polyposis, EA = eosinophilic asthma, CRSwNP =chronic rhinosinusitis with nasal polyps, EGPA = eosinophilic granulomatosis with polyangiitis, HES = hyper eosinophilic syndrome, MS = multiple sclerosis.

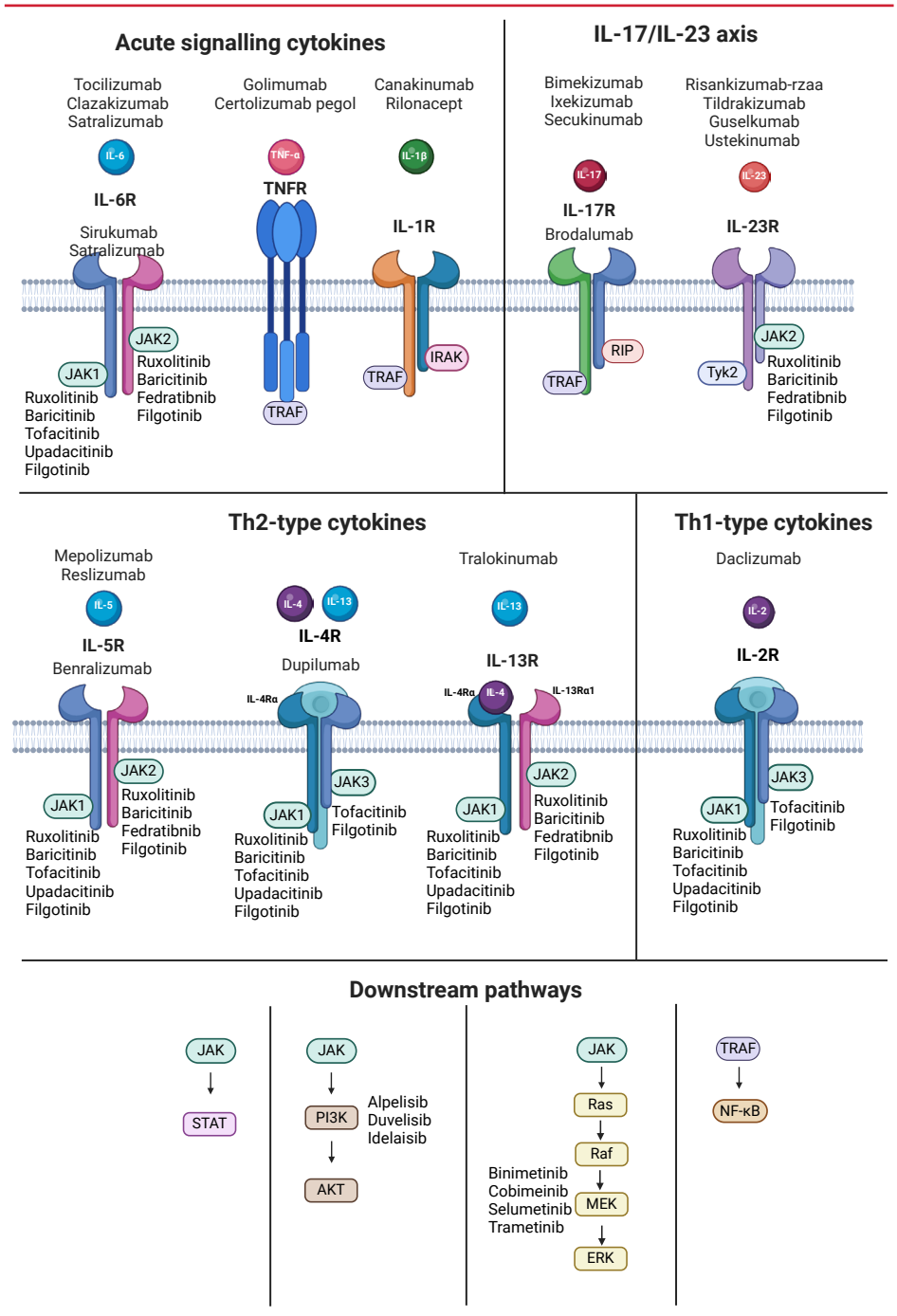

Figure 2 Schematic interpretation of the cytokine pathways targeting monoclonal antibodies and tyrosine kinase inhibitors (68–70).

Acute signalling cytokines: IL-6, TNF-α and IL-1β

IL-6, TNF-α and IL-1β are the main cytokines involved in inducing the acute phase response during inflammation (40). Of these, IL-6 is the most studied member, and a vast body of evidence exists showing that IL-6 can impact multiple CYP isoforms (4,8,9,41–43). As such, for mAbs targeting IL-6, it seems important to study the disease-mediated effects of the mAb on the pharmacokinetics of CYP substrates. In patients suffering from active rheumatoid arthritis (RA), IL-6 levels are often elevated in both the systemic circulation and the synovial fluid (44), making this a relevant population to study potential DDDIs elicited by IL-6 targeting mAbs.

Interaction studies

Four separate clinical trials investigated the effect of IL-6 neutralization on CYP-mediated drug metabolism of probe substrates (Table 1). In RA patients, sirukumab treatment led to a decrease in exposure (based on AUC_{inf}) for midazolam (CYP3A4), omeprazole (CYP2C19) and warfarin (CYP2C9) with geometric mean ratios ranging from 65–70%, 55–63% and 81–82% respectively over a period of 1 to 6 weeks (22). In contrast, sirukumab treatment led to an increase in exposure (based on AUC_{inf}) for caffeine (CYP1A2) with geometric mean ratios ranging from 120–134% over a period of 1 to 6 weeks. In the case of sarilumab and tocilizumab, single dose mAb treatment in RA patients resulted in a decrease in exposure (based on AUC_{inf}) for simvastatin (CYP3A4 substrate) with a geometric mean ratio of 55% (based on AUC_{inf}) after 1 week (sarilumab) (24) and geometric mean ratios of 43% to 61% (based on AUC_{last}) after 1 and 6 weeks respectively (tocilizumab) (23).

The use of anti-IL-6 mAbs is not restricted to RA. Clazakizumab is an anti-IL-6 mAb currently under investigation for potential benefit in counteracting late antibody-mediated rejection (ABMR), a main reason for renal transplant failure. A sub-study of the phase 2 trial investigated the impact of clazakizumab treatment on the PK of pantoprazole, a CYP2C19 substrate with minor involvement of CYP3A4 in kidney transplant recipients, but found no effect on pantoprazole PK throughout the study period (52 weeks) (Table 1) (25). However, it is important to note that both C-reactive protein (CRP) and IL-6 levels were not elevated in this patient population, and CYP iso-enzyme expression may therefore not have been impacted by elevated IL-6 levels at the start.

Altogether these results imply that IL-6 targeting antibodies have the potential to restore CYP metabolic capacity of CYP3A4, and potentially CYP2C19 and

CYP2C9 in RA patients. Because of this DDDI risk, the plasma levels of concomitant medication might be lower in this treated patient population. In disease populations were baseline IL-6 levels are not elevated, such as renal transplant patients, mAb treatment seem not to interfere with CYP activity.

For the other acute signalling cytokines TNF-α and IL-1β, no drug interaction studies have been performed to the best of our knowledge.

DDDI risks

The labelling information discussing the potential of a DDDI for acute signalling cytokine targeting mAbs is summarized in Table 2. Experimental evidence in PHH models strongly suggest that IL-6 modulates metabolic capacity of multiple CYP isoforms. Three independent clinical trials indicated a DDDI risk with IL-6 neutralizing antibodies. However, clinical evidence for the reversal of IL-6 mediated effects on metabolic capacity of CYP isoforms other than CYP3A4 is limited, given that only one clinical trial exploited a CYP cocktail approach. Still, the USPIs and the SPCs indicate a clear risk for DDDIs with IL-6 mAbs in the labelling, stating therapeutic monitoring of effect or concentration is warranted, up to weeks after discontinuation of the IL-6 mAb therapy. An exception is satralizumab, where the SPC suggests TDM and the USPI states that the DDDI risk is unknown.

No clinical studies have been performed for mAbs targeting TNF-α or IL-1β to evaluate their potential risk for inducing DDDIs. Risk assessments are thus solely based on experimental findings in PHH models where TNF-α and IL-1β strongly downregulate CYP expression and CYP activity. Consequently, both SPC and USPI of IL-1β targeting antibodies contain a general statement that an increase in cytokine levels during inflammation can alter the activity of CYP enzymes (Table 2). As such, monitoring the effect or active substance concentration is highly recommended for concurrent medicated CYP substrates with a narrow therapeutic window. The USPI label of golimumab, a mAb that neutralizes TNF-α, contains an even more general warning, stating that an effect of golimumab initiation on PK of CYP substrates can be expected. In contrast, the SPCs of golimumab and certolizumab do not mention a potential risk for a DDDI.

IL-17/IL-23 axis

The pro-inflammatory IL-17/IL-23 axis has been linked to the pathophysiology of many autoimmune diseases, most notably psoriasis (45). Several mAbs that oppose

the actions of IL-17 or IL-23 have shown to be successful in reducing inflammation and relieving symptoms in psoriasis patients. Because of these anti-inflammatory effects it is considered important to assess the potential for DDDIs of these drugs.

Interaction studies

Three clinical trials investigated whether IL-17 neutralization by mAb treatment would impact the PK of CYP substrates (Table 1). A cocktail approach showed that twelve-week ixekizumab treatment did not impact the PK of CYP probe substrates midazolam, omeprazole, caffeine, dextromethorphan, and warfarin in patients with psoriasis (NCT02993471). Secukinumab initiation did not impact CYP3A4 metabolic capacity (26). In contrast, a single subcutaneous dose of brodalumab in patients with moderate to severe plaque psoriasis increased the exposure of midazolam (CYP3A4) with a geometric mean ratio of 124%. (NCT01937260).

Regarding IL-23 neutralization, risankizumab, tildrakizumab and guselkumab treatment in patients did not result in altered CYP metabolic capacity, as all changes were within the bioequivalence limits (28,29). A clinical study evaluating the impact of ustekinumab in patient with Crohn's disease or ulcerative colitis is ongoing (NCT03358706). As such, despite the clinically relevant suppression of IL-17/IL-23 in psoriasis patients, this did not result in altered metabolic capacity of CYPs except for the CYP3A4 alteration by brodalumab.

DDDI risks

DDDI risks for the IL-17/IL-23 axis targeting therapeutics are summarized in Table 2. No experimental studies were conducted to assess the effect of IL-17 on CYP activity in PHHs (10). Based on data of three clinical trials, the potential for interactions between IL-17 targeting mAbs and co-administrated drugs that rely on CYP-biotransformation in psoriasis patients is very low (Table 1). Based upon these results, the SPC product labels of brodalumab, ixekuzumab and secukinumab indicate no risk for a DDDI, considering that the magnitude of change in midazolam exposure after brodalumab treatment does not require dose adjustments. The SPC of bimekizumab states that therapeutic monitoring of concurrent medication should be considered since no clinical interaction study is performed to inform on the DDDI risk. The USPIs of brodalumab, ixekuzumab and secukinumab contain a general suggestion to monitor the effect when concomitant drugs with a narrow therapeutic window are added on top of IL-17 targeting antibodies, based upon the

general assumption that CYP450 enzyme expression is modulated by inflammatory cytokines. Bimekizumab is not approved by the FDA yet.

Both experimental and clinical data indicate no effect of IL-23 on CYP metabolic capacity (Table 2). The SPC risk labelling for IL-23 targeting antibodies indicates no risk for an altered exposure of concomitant medication after initiation or discontinuation of an IL-23 targeting mAb. For ustekinumab, this conclusion was based on in vitro data since the clinical trial is ongoing. For the other mAbs, the absence of a risk was based on the results of clinical trials. The FDA documentation differs in the risk assessment included in the drug labelling. For ustekinumab, a risk is identified based on the general assumption that cytokines downregulate CYPs. For guselkumab, although the results of the cocktail trial indicate no risk for interactions, the reliability of the results is considered low because of the low number of subjects. Therefore, the USPI still indicates that monitoring the effect or concentration of concurrent mediated small molecule drugs with a narrow therapeutic window should be considered. For risankizumab and tildrakizumab, no DDDI risk is identified based on the results of the cocktail study.

Th2-type cytokines

The cytokines IL-4, IL-5 and IL-13 are essential in type 2 immunity and play a central role in the pathogenesis of allergic diseases, through their effects on the synthesis of IgE, eosinophils and epithelial or epidermal cells (46). For the treatment of asthma and atopic dermatitis (AD), mAbs have been developed against either IL-5 signalling (mepolizumab, reslizumab, benralizumab) or the IL-4Ra (dupilumab), that is responsible for the actions of IL-4 and IL-13 (tralokinumab).

Interaction studies

One clinical DDDI trial explored the potential shift in CYP-mediated metabolism upon dupilumab treatment, but none of the investigated CYPs were impacted, suggesting a low potential for DDDI with dupilumab (30). For mepolizumab, reslizumab and benralizumab, no DDDI trials were executed. For tralokinumab, a CYP interaction trial is ongoing in patients with moderate to severe atopic dermatitis (NCT03556592).

DDDI risks

No experimental studies have assessed the effects of IL-4, IL-5 or IL-13 on the activity of CYP enzymes, though most of the receptors for these cytokines are considered low or absent in the liver (46). Hence the results of the clinical trial investigating the potential modulating effect of dupilumab on CYP metabolic capacity are in line with this (Table 1). Accordingly, in the SPC risk documentation, dupilumab does not exhibit a DDDI risk. Despite the negative results from the cocktail study, the USPI of dupilumab contains a potential risk for a DDDI, based on the general idea of downregulation of CYP activity by cytokines.

For IL-5 neutralizing antibodies, the SPCs state no DDDI risk – where the risk assessment is mainly based on in vitro data. In contrast, the USPIs marks an unknown risk for DDDI for the IL-5(R) targeting antibodies, since no formal drug interaction studies have been performed.

Tralokinumab is not yet authorized for marketing by the FDA and therefore lacks an USPI. The tralokinumab SPC states an unknown risk since the results of the DDDI trial with tralokinumab are not yet publicly available.

Th1-type cytokines

IL-2 is a cytokine released from activated T lymphocytes, which effects the proliferation and differentiation of T cells, making it an important member of the Th1 type cytokine response.

Interaction studies

Daclizumab is a high-affinity IL-2 receptor blocker that was approved in 2016 for the treatment of relapsing forms of multiple sclerosis but was withdrawn in 2018 after several cases of severe inflammatory brain disease (47–49). The clinical trial evaluating the impact of daclizumab on CYP enzyme activity showed that exposure of substrates of CYP3A4, 1A2, 2C9, 2C19 and 2D6 remained unaltered (31).

DDDI risks

Both experimental and clinical data of the withdrawn product daclizumab show that IL-2 does not impact CYP activities (Table 2). The SPC does not provide any information on daclizumabs DDDI risk, whereas the USPI indicates no risk based on the interaction trial.

Tyrosine kinase inhibitors

Reversion of the effects of inflammation can also occur by inhibiting the signalling pathways downstream of the receptors that are responsible for the cytokine actions. TKIs that interfere with these cytokine signalling pathways could therefore in theory also induce a DDDI interaction (Figure 2). Through our search, we identified thirteen immunomodulating TKIs that inhibit the JAK/STAT, MAPK/MEK/ERK, Nf-kB or PI3K/Akt pathway(s), whose involvement has been linked to the cytokine-mediated downregulation of CYP enzymes.

Interaction studies and DDDI risks

There are no clinical DDDI interaction studies performed for TKIs, and experimental evaluations of a DDDI risk is very limited (Supplementary Table S1). For 7 of the 13 TKIs, a CYP phenotyping cocktail, probe or PBPK study was conducted to determine traditional DDI risks. However, these studies were all conducted in healthy volunteers and not in patients with inflammatory disease, which substantially limits their informative power on the DDDI risk (50–56). Moreover, the SPCs and USPIs only evaluate the traditional DDIs and do not state any inflammation-related interaction risks for these products. The only label that discusses a potential DDDI is the label of tofacitinib, which states that treatment with tofacitinib does not normalize CYP enzyme activity in RA patients and will likely not result in relevant increases in the metabolism of CYP substrates in this population (57). As such, the DDDI risk is expected to be low.

EMA vs FDA documented DDDI risks

It is worth noticing that there is discrepancy in DDDI risk assessment for immunomodulatory antibodies between the EMA SPCs and the FDA USPIs (Figure 3). The EMA documentation described a DDDI risk for 32% of the included mAbs, and an absence of a risk in 50% of the cases. The defined risks in the SPC always followed the results of executed cocktail trials. The FDA USPI describes a DDDI risk for 28% of the drugs, and advice to take caution when initiating treatment for 29% of the mAbs – sometimes in contradiction with a negative result from a cocktail trial. No risk for a DDDI is only attributed to 14% of the drugs. Given that the FDA is more conservative in its risk assessment, there is agreement on the DDDI risk in 38% of the cases.

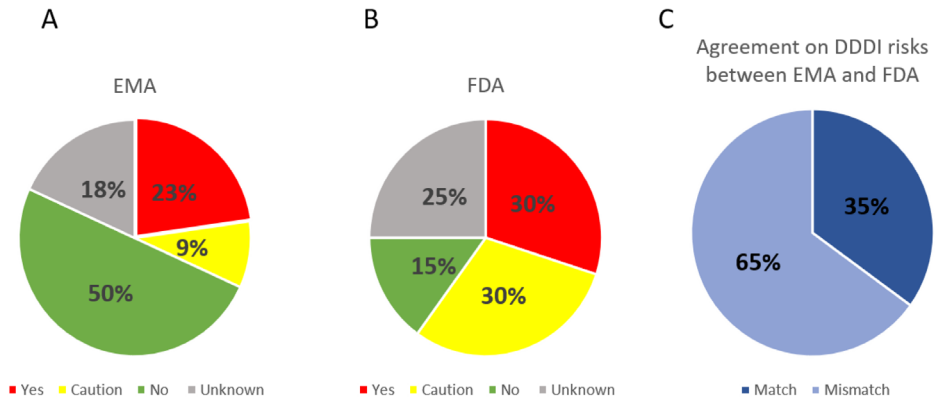

Figure 3 Summary of the DDDI risks for immunomodulatory mAbs assessed by extracting information from the SPC **(A)** or USPI **(B)** and the agreement between them **(C)**.

Discussion

This systematic review was set out to explore the available evidence for DDDIs with immunomodulating therapeutic antibodies marketed after 2007 and the associated DDDI risk descriptions indicated in the European and American product labels. Additionally, we investigated whether DDDI studies were executed for other type of immunomodulating therapeutics, such as TKIs that inhibit the signalling pathways downstream of inflammatory mediators. This is the first systematic review that links the outcomes of the executed DDDI trials to the risk evaluations stated in the SPCs and USPIs. In short, dedicated DDDI studies were performed for twelve mAbs, where modulating effects on CYP probe substrates were reported for sirukumab (IL-6), tocilizumab (IL-6), sarilumab (IL-6RA) and brodalumab (IL-17RA). The indicated DDDI risk assessment in labels for the mAbs was not always in line with the available experimental and clinical data and showed discrepancies in labelling statements between the SPCs and USPI. Drug labelling indicated the greatest DDDI risk for mAbs that neutralize the effects of IL-6, TNF-α and IL-1β in diseases with systemic inflammation. For TKIs, no DDDI interaction studies were performed, and no DDDI risks were reported in the labelling.

Factors that determine DDDI risk

The summarized DDDI studies suggest that the risk for a DDDI is both dictated by the target and the indicated disease population. With respect to drug target, antibodies that impair the actions of IL-6 have consistently shown to alter CYP-dependent metabolism of probe substrates. Both tocilizumab, sirukumab and sarilumab altered CYP metabolic capacity in RA patients, showing that the impaired drug metabolizing capacity during inflammation is (partly) restored after administration of IL-6 targeting mAbs. Importantly, the changes in CYP3A4 metabolic capacity induced by different mAbs were of similar magnitude (~2-fold), indicating a class-effect. The sirukumab trial provided evidence that antagonism of IL-6 in RA patients reversed the IL-6 induced downregulation of not only CYP3A4 but also of CYP2C9 and CYP2C19. In contrast, clinical trials executed with mAbs targeting IL-17, IL-23, IL-4R or IL-2 showed no clinically relevant changes in CYP-mediated metabolism. As such, mAbs that target the acute signalling cytokines appear to have the greatest DDDI risk.

The diseased population is another critical indicator, as the type and degree of systemic inflammation observed in the studied population may determine the potential for DDDIs. No clinically meaningful alterations in CYP metabolizing capacity were observed following the use of immunomodulating antibodies in psoriasis and AD patients. This may be attributed to the type of inflammation in AD and psoriasis patients, as this is characterized by either elevation of type 2 inflammatory cytokines (e.g. IL-4, IL-5 and IL-13) or the IL-17/IL-23 axis cytokines, which are shown not to impact metabolic liver function. Secondly, markers of systemic inflammation, such as C-reactive protein or IL-6, are only elevated in a small proportion of AD or psoriasis patients, and profoundly lower than in patients with RA (58–61). As such, in diseases with only moderate systemic inflammation, the increases in cytokine levels will be insufficient to change CYP expression, simultaneously indicating that the likelihood for a DDDIs within these populations is low.

The importance of conducting a DDDI study in the relevant patient group is emphasized by the discrepancy between the results of mAb treatment in kidney transplant recipients versus RA patients (22–25). In disease populations such as renal transplant recipients, where baseline IL-6 levels are not elevated, the CYP metabolic capacity was unchanged upon IL-6 targeting mAb treatment whereas

significant impact on CYP metabolic capacity was noted for sirukumab, tocilizumab and sarilumab in RA patients. In line with this, the FDA recommends studying the potential DDDI in the population group with the highest inflammatory burden, in order to extrapolate and generalize results to other patient groups (16).

DDDI risk for TKIs

Immunomodulation is not restricted to therapeutic proteins targeting cytokine (receptors) but may also apply to TKIs that inhibit the signalling pathways of inflammatory mediators. For example, the JAK inhibitors tofacitinib and ruxolitinib reduce the plasma levels of IL-6 levels and other pro-inflammatory cytokines, and counteracted the suppressive effects of IL-6 on CYP enzymes in PHHs (47,48,62). Importantly, ruxolinitib was able to fully counteract the downregulatory effects of IL-6 on CYP enzymes, even at supraphysiological concentrations of IL-6 stimulation (47). Considering the increasing use of JAK inhibitors for the treatment of autoimmune disease and other inflammatory diseases, there is a need to determine the risk for DDDI for immunomodulating TKIs, e.g., in COVID-19 patients (49).

The SPCs and USPIs of TKIs did, with exception of tofacitinib, not discuss a potential DDDI risk. TKIs are small molecules, dependent on CYP-mediated biotransformation, and therefore also capable of directly inducing or inhibiting CYP enzymes. In contrast to therapeutic proteins, it is therefore difficult to distinguish traditional DDIs from DDDIs for TKIs. This forms a major hurdle for defining the DDDI risk. Traditional DDIs are evaluated in healthy volunteers, whereas the occurrence of DDDIs may, as earlier discussed, only show in diseased patients. Even though there may be financial constraints, it would be worthwhile to compare the effect of TKIs on a CYP phenotyping cocktail between healthy volunteers and patients with systemic inflammation to reveal the true DDDI potential of immunomodulating TKIs.

DDDI risks in drug labels

Since 2007, the SPC and USPI should include labelling language evaluating the risk for a DDDI with therapeutic proteins that are either cytokines themselves or target cytokines (15,16). We classified the reported DDDI risks in drug labels and identified the available data for every mAb and TKI to determine the potential DDDI risk.

Both EMA and FDA documentation identified a DDDI risks for most of the acute signalling cytokine targeting mAbs. In line with experimental data, the various IL-6 mAb trials identified a clear DDDI risk, although clinical evidence for a modulating effect on multiple CYP isoforms is still limited. Interestingly, even though novel mAbs against TNF-α and IL-1β were brought to market after instalment of the renewed DDDI guidelines, no dedicated clinical study has yet investigated the effects of these mAbs on a CYP substrate or CYP cocktail. Importantly, in experimental models, both TNF-α and IL-1β can alter the expression of multiple CYP isoforms (10). Based on this, the SPC and USPIs of canakinumab and rilonacept (both IL-1β) contain a general warning message to monitor the effect or drug concentration upon initiation or discontinuation of the mAb in patients treated with medication metabolized by CYP enzymes with a narrow therapeutic window. For mAbs that target beyond the acute signalling cytokines, drug labelling does not report a clear DDDI risk. However, sometimes therapeutic monitoring of drug or effect is advised based on the general assumption that cytokines downregulate drug metabolizing enzymes or the lack of available evidence to base the advice on. Of note, the implementation of the advised therapeutic monitoring of drugs that are at risk for causing a DDDI still needs further investigation, since drug or effect monitoring in clinical practice is currently only available for a select group of drugs.

It is also interesting to note that there is often discrepancy between the stated risks in the EMA and FDA documentation (mismatch in 62% of the labels) and that the authorities do not always base their risk assessment on the same available non-clinical and clinical evidence. The EMA guidelines on DDIs with therapeutic proteins are general in its recommendations and highlight the need for a dedicated in vitro or in vivo interaction studies to assess the potential for a DDDI on a case-by-case basis (15). Subsequently, the EMA documentation always uses the outcomes of clinical DDDI trials as a leading point for their risk analysis. In contrast, the FDA documentation on DDDI risks is more conservative. The USPI often suggests monitoring of therapeutic drug levels or effect, even when the cocktail trial did not identify a risk for a DDDI, thereby often referring to experimental data that showed the impact of cytokines on CYP activity to justify their precaution. This contrasts the statement in the FDA draft guideline for therapeutic proteins where they describe that justification of not including DDDI risk labelling can be based on negative results of a clinical DDDI study (16).

Recommendations for assessing future DDDI risks

In vitro studies have been instrumental in dissecting the impact of individual cytokines on CYP enzymes involved in drug metabolism. The utility of in vitro models for predicting clinical DDDI has however been debated during the FDA/IQ consortium workshop in 2012 (63). One particular concern was the limitations of in vitro models for predicting DDDI risk for cytokine targets for which the effect on drug metabolizing capacity may not take place in hepatocytes, but instead develop via immunomodulating effects on other cell types in the liver. Thus, although in vitro PHH models adequately predicted tocilizumab DDDI potential to reverse the IL-6 induced impairment of metabolic CYP capacity (64), the use of such models would not be informative for all cytokine targets. However, liver co-culture platforms have shown to increase our predictive power of in vitro systems. For example, the lack of DDDI risk for IL-23 in experimental co-culture models was confirmed by multiple IL-23 clinical interaction trials (32). One could therefore argue that in vitro system(s), accompanied with physiology-based PK models, could have utility for predicting when clinical DDDI studies with immunomodulatory mAbs are truly needed.

In accordance with the FDAs guidelines which state that justification for a low DDDI risk can be based on results from mAbs with similar targets, considerations on conducted DDDI trials in the same patient population are valuable for assessing the need for a novel DDDI trial (16,64). In the case of IL-23 mAbs, three individual cocktail studies have been performed in psoriasis patients, which all concluded that IL-23 neutralization did not affect CYP metabolic capacity. Considering that DDDI clinical trial patients are scarce (65), novel trials with IL-23 targeting mAbs or biosimilars seem unnecessary.

The potential risks of mAbs for DDDI in clinical trials has been assessed using CYP cocktails or CYP3A4 substrates. The latter approach may have important limitations, as both experimental and clinical studies have indicated that the effects of inflammation on drug metabolism may differ among CYP isoforms (1). CYP3A4 and CYP2C19 mediated metabolism generally declines in the presence of inflammation, whereas CYP2D6 and CYP2C9 mediated metabolism respectively do not change, or even increase during inflammation (10–12). These studies illustrate the distinct sensitivities and opposite effects of inflammation on the different CYP isoforms. Thus, although studies using CYP3A4 probes may

adequately inform on the likelihood of a DDDI, the outcomes of such studies cannot be directly extrapolated to other CYP isoforms and therefore limitedly inform on the DDDI risk for concomitant medication. For future DDDI trials, the cocktail approach would therefore be preferred.

Real-world impact in the clinic

Beyond the defined risks for DDDIs documented by the EMA and FDA, it is also important to understand the consequences of DDDIs with immunomodulating therapeutics for clinical practice. The impact of a DDDI is dictated by 1) the magnitude of the inflammation-driven changes in drug exposure and 2) the therapeutic window of the victim drug. Maximum exposure ($AUC_{0\text{-}inf}$) alterations due to immunomodulatory antibodies are reported to be 2-fold. Compared to conventional DDIs that rely on CYP induction or inhibition, this magnitude of change is limited. Still, for concurrent drugs with a narrow therapeutic window, the initiation of mAb therapy can still lead to under- or overexposure of the victim drug and potential toxicity or lack of efficacy. To date, only incidental case reports have linked the start of mAb treatment against IL-6 or TNF-α to increased clearance of anti-coagulants and immunosuppressants, and hence reported on the real-world impact of DDDI (66,67). In addition, recent studies have shown that the start of direct-acting antivirals against hepatitis C virus infections or antimalarial agents were associated with reversal of inhibited CYP2C19 activity (68,69). This indicates that these type of DDDIs are not restricted to immunomodulating mAbs, but also involve small molecules. Still, data on the clinical consequences of DDDIs remains scarce and more real-world evidence is needed to better define the true impact of DDDIs for patients in the clinic.

Study limitations

It should be acknowledged that our systematic literature search has some limitations. First of all, the completeness of the analysis cannot be assured since we were limited to published (clinical trial) studies and some trials are still ongoing. Secondly, the set period of 2007 until now limits our analysis on the DDDI risk information in drug labels to a particular set of immunomodulatory mAbs. Thirdly, we choose to include immunomodulatory drugs that target either a cytokine (receptor) or specific downstream signalling pathway. As such, broader immunosuppressive

drugs were not included in our analysis but might still impact CYP metabolic capacity and thus be at risk for a DDDI.

Conclusion

In conclusion, the risk for DDDIs appears to be specific to the targeted cytokine and the intended disease population. SPC and USPI drug information designates the greatest DDDI risk to mAbs that neutralize the effects of IL-6, TNF-α and IL-1β in diseases with systemic inflammation, although for the latter two clinical evidence is lacking. Since in vitro data and already executed DDDI trials with the same target shows predictive value for the outcome of a DDDI risk, these factors should be considered in evaluating the need for a novel DDDI trial for drug labelling. Especially since eligible patient populations for clinical studies are scarce (70). If clinical assessment of a DDDI risk is warranted, this should preferably be conducted through a cocktail approach, since evidence is growing that the impact of inflammation is different for the multiple CYP isoforms. Lastly, efforts are needed to translate the described DDDI risks in drug labelling into guidelines for clinical practice which can ultimately benefit the patient.

Acknowledgements

We are particularly grateful for the assistance on search terms given by Jan Schoones of the Walaeus library (LUMC). For creation of the graphical abstract and Figure 2, BioRender.com was used.

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Supplemental information

Supplementary Table 1 Summary of experimental and clinical evidence for DDDI risks with TKIs, according to labelling information documented by the EMA and FDA

Target	Drug	Indication	Non-clinical evidence from PHHs (51, 71, 72)	Clinical evidence[a]	DDDI risk in SPC	DDDI risk in USPI	Type(s) of evidence available for DDDI risk assessment[b]			
							Experimental data	PBPK modelling	Clinical data with one substrate	Clinical data with multiple probe substrates
JAK1	Upadacitinib	RA / PsA / AS / UC / JIA	Not determined	Not conducted	Not mentioned	Not mentioned				
JAK2	Fedratinib	Myelofibrosis	Not determined	Not conducted	Not mentioned	Not mentioned				
JAK1/ JAK2	Ruxolitinib	Myelofibrosis / PV	Yes - CYP1A2 - CYP2B6 - CYP3A4	Not conducted	Not mentioned	Not mentioned				
	Baricitinib	RA / AD / AS / PsA / COVID-19		Not conducted	Not mentioned	Not mentioned				
JAK1/ JAK3	Tofacitinib	RA / PsA / AS/ UC / JIA / AD	Yes - CYP1A2 - CYP2B6 - CYP3A4	Not conducted	No	No				
JAK1/ JAK2/ JAK3	Filgotinib	RA / UC	Not determined	No Not conducted	Not mentioned	Not mentioned				

Supplementary Table 1 continues on next page.

Supplementary Table 1 *Continued*

Target	Drug	Indication	Non-clinical evidence from PHHs (51, 71, 72)	Clinical evidence[a]	DDDI risk in SPC	DDDI risk in USPI	Type(s) of evidence available for DDDI risk assessment[b]			
							Experimental data	PBPK modelling	Clinical data with one substrate	Clinical data with multiple probe substrates
MEK1/ MEK2	Trametinib	Melanoma / NSLC	Not determined	Not conducted	Not mentioned	Not mentioned				
	Cobimetinib	Melanoma		Not conducted	Not mentioned	Not mentioned				
	Binimetinib	Melanoma		Not conducted	Not mentioned	Not mentioned				
	Selumetinib	PN		Not conducted	Not mentioned	Not mentioned				
PI3K	Idelalisib	Leukaemia / FL	Not determined	Not conducted	Not mentioned	Not mentioned				
	Alpelisib	Breast Neoplasms		Not conducted	Not mentioned	Not mentioned				
	Duvelisib	Leukaemia /FL		Not conducted	Not mentioned	Not mentioned				

[a] altered CYP activity is defined as: when GMR (90% CI) of $AUC_{0\text{-}inf}$ is beyond equivalence limits 80–125%, [b] Type of DDDI evidence is based on available data in literature on potential modulating effect of cytokine/mAbs on CYP metabolic capacity. DDDI risk categories are classified as: Yes (TM should be performed), Caution (consider monitoring for drug/effect), No, or Unknown (clinical significance is unknown or not mentioned). Type of DDDI evidence available, independent of risks stated in regulation labelling: 0 = no data available. RA = rheumatoid arthritis, PsA = psoriatic arthritis, UC = ulcerative colitis, JIA = Juvenile idiopathic arthritis, AS = ankylosing spondylitis, PV = polycythaemia vera, AD = atopic dermatitis, COVID-19 = coronavirus disease 2019, NSLC = non-small lung cancer, PN = plexiform neurofibromas, FL = follicular lymphoma.

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