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Risk-based strategy for the assessment of pharmacokinetic drug–drug interactions for therapeutic monoclonal antibodies

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Biological agents are used to treat a variety of diseases in many therapeutic areas, including oncology, rheumatology, gastroenterology, dermatology, respiratory disease, hormone deficiency and infection. While biologics constitute many of the recently approved new therapies, clinical research of drug–drug interactions with biologics has been scant. This review presents a risk-based assessment strategy for evaluating drug–drug interactions with monoclonal antibodies, a predominant class of therapeutic biologics. The key parameters of this strategy are described here, as well as suggested studies that should be considered as part of the overall drug development process for therapeutic biologics.

Introduction

Currently, biological therapies play a crucial role in the pharmacotherapy of a variety of therapeutic disease areas, including those in rheumatology, gastroenterology, dermatology, oncology, hormone deficiency and infection. Chemically, therapeutic biologics are mainly represented by (glyco)proteins composed of L-amino acids and various sugar molecules. A survey conducted by the Pharmaceutical Research and Manufacturers of America (PhRMA) in 2004 estimated that more than 300 biologics were in development for almost 150 diseases [1].

In 1982, human insulin became the first recombinant DNA drug approved by the Food and Drug Administration (FDA). Since then, many therapeutic biologics have gained regulatory approval, and the biotechnology sector has become a mature industry and now is rivaling traditional pharmaceutical industry in several ways [2]. Therapeutic biologics encompass several categories including monoclonal antibodies (mAbs); recombinant protein therapeutics (e.g. therapeutic cytokines); hybrid and modified molecules (e.g. pegylated, glycoengineered, and fusion proteins); endogenous proteins/peptides (e.g. insulin); and others (e.g. gene transfer products and antisense oligonucleotides) [3]. Of these categories, mAbs represent a predominant class of therapeutic proteins with a relatively stable molecular construct. More than 150 mAbs are in different stages of clinical development [4] and, to date, 21 therapeutic mAbs have been approved for use by FDA (Table 1). Few formal drug–drug interaction studies have been performed for these therapeutic mAbs. Two recent review papers [5,6] give excellent overviews of drug–drug interactions for therapeutic biologics including therapeutic mAbs. Generally speaking, drug–drug interactions (DDIs) for mAbs have either been underexplored or underreported.

It has long been a prevailing opinion that therapeutic mAbs are generally safe and well tolerated and their target-related toxicities are usually predictable from preclinical studies [7]. Nevertheless, unexpected adverse events can occur following administration of therapeutic mAbs. The withdrawal and subsequent relaunch of Tysabri [8] and the tragic events surrounding the first-in-human study of TGN1412 [9,10] are just two examples of situations that have elevated concerns about the safety of therapeutic mAbs. Recently, the FDA has mandated stronger warnings about the risk of developing opportunistic fungal infections following treatment with anti-tumor necrosis factor alpha (TNFα) [11]. Because therapeutic mAbs are used primarily to treat moderate to severe and chronic diseases, they are often used with more than one concomitant medication, especially among geriatric patients. Therefore, potential DDIs may arise owing to the multiple medications and polypharmacy situations.

There is currently no universal regulatory guidance available for DDIs tailored for mAbs. This article is intended to propose a risk-based framework for assessing potential DDI of mAbs with other biologics and/or small molecule drugs.

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TABLE 1

Therapeutic monoclonal antibodies approved for use in United States

Generic name	Antibody target	Concomitant therapy[a]	Potential drug–drug interaction (DDI)[a]
Muromonab-CD3	CD3	Single therapy	Not applicable
Abciximab	GP IIb/IIIa	Heparin, aspirin, warfarin, β-adrenergic receptor blockers, calcium channel antagonists, ACE inhibitors, nitrates, ticlopidine	No PK DDI results reported
Rituximab	CD20	Methotrexate, cyclophosphamide, vincristine, prednisone doxorubicin, ibritumomab tiuxetan	No PK DDI results reported
Daclizumab	IL-2Rα	Cyclosporine, mycophenolate mofetil, ganciclovir, acyclovir, azathioprine, corticosteroids	No PK DDI results reported
Basiliximab	IL-2Rα	Cyclosporine, corticosteroids, azathioprine, mycophenolate mofetil	PK DDI results reported: azathioprine and mycophenolate mofetil reduced clearance of basiliximab by 22% and 51%, respectively
Palivizumab	RSV	Bronchodilators, corsticosteroids	No PK DDI results reported
Infliximab	TNFα	Methotrexate, 5-minosalicylates, corticosteroids, antibiotics, 6-Mercaptopurine, azathioprine	No PK DDI results reported
Trastuzumab	HER2	Doxorubicin, cyclophosphamide, paclitaxel	PK DDI results reported: paclitaxel resulted in a 1.5-fold increase in trastuzumab serum levels
Gemtuzumab ozogamicin	CD3-conjugate	Single therapy	Not applicable
Alemtuzumab	CD52	Single therapy	Not applicable
Ibritumomab tiuxetan	CD20-conjugate	Rituximab	No PK DDI results reported
Adalimumab	TNFα	Methotrexate, DMARDs, glucoroticoids, salicylates, NSAIDs, aminosalicylates, corticosteroids, 6-Mercaptopurine, azathioprine	PK DDI results reported: methotrexate reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44%, respectively
Omalizumab	IgE	Inhaled corticosteroids. oral corticosteroids, β-agonists	No PK DDI results reported
Tositumomab; I131	CD20	Thyroid protective agents	No PK DDI results reported
Efalizumab	CD11a	Topical steroids	No PK DDI results reported
Cetuximab	EGFR	Camptosar, irinotecan, pemetrexed, erlotinib, docetaxel	No PK DDI was observed between cetuximab and irinotecan
Bevacizumab	VEGF	Interferon, itrinotecan, carboplatin, paclitaxel, pemetrexed	PK DDI results reported: Approximately 33% higher SN38 (the active metabolite of irinotecan) with bevacizumab co-administration; 3/8 of subjects experienced lower paclitaxel exposure with bevacizumab co-administration.
Natalizumab	α4-intergrin	None	No PK DDI results reported
Ranibizumab	VEGF-A	Verteporfin photodynamic therapy	No PK DDI results reported
Panitumumab	EGFR	Bevacizumab, oxaliplatin-based 5-fluorouracil regimen, irinotecan-based 5-fluorouracil-containing regimen	No PK DDI results reported
Eculizumab	Complement C5	Anticoagulants, systemic corticosteroids	No PK DDI results reported

[a] On the basis of United States Food and Drug Administration-approved product labeling. PK: pharmacokinetic; GP: platelet glycoprotein; IL: interleukin; RSV: respiratory syncytial virus; TNFα: tumor necrosis factor alpha; HER2: human epidermal growth factor receptor-2; VEGF: vascular endothelial growth factor; EGFR: epidermal growth factor receptor; IgE: immunoglobulin E; DMARDs: disease-modifying anti-rheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; ACE: angiotensin converting enzyme; PK: pharmacokinetic.

Consequence of drug–drug interactions

Many of the DDIs observed for small molecule drugs give rise to serious clinical events. One study indicated that approximately 7.4% of patients taking two or more drugs concurrently might have had serious clinical consequences [12]. An interaction is considered clinically relevant when changes in therapeutic activity and/or toxicity require a dosing regimen adjustment for the medication. Many of these documented, clinically relevant DDIs have been summarized in several excellent review papers [13–18], and books [19–22]. One well-known example of a clinically

relevant DDI is the pharmacokinetic interaction of terfenadine and ketoconazole via cytochrome CYP3A4 that resulted in severe and even life-threatening ventricular arrhythmia (*torsades de pointes*) in some people [23,24]. The majority of DDIs, however, are generally of minor clinical consequence. In some situations, interactions can actually be used in a positive approach to achieve desirable therapeutic goals. For example, reducing the dose of an expensive drug such as cyclosporine by combining it with a much less expensive drug such as ketoconazole, can result in lower costs [25]. Another example is the combination therapy of ritonavir and saquinavir in the treatment of human immunodeficiency disease. The systemic exposure of saquinavir can be elevated by more than 50-fold with the addition of ritonavir [26], resulting in much greater efficacy.

Unlike small molecules, few DDIs for therapeutic proteins have been documented to date [5,6]. One prominent example is the effect of cytokines (i.e. interferons) on CYP450 [27–33]. For instance, one study found that administration of interferon-α before administration of cyclophosphamide caused a decrease in cyclophosphamide clearance by 63% ($p = 0.004$), a 137% higher peak plasma concentration ($p = 0.006$), and a 137% longer half-life ($p = 0.004$) compared with the control group [32]. If severe myelosuppression is observed during combination use, dose adjustment of cyclophosphamide may be warranted. Another example of a drug–biologic interaction is the effect of methotrexate on adalimumab. While the co-administration of adalimumab with methotrexate does not affect the pharmacokinetics of methotrexate in patients with rheumatoid arthritis [34], the concomitant administration of weekly methotrexate significantly decreases the clearance of adalimumab [35]. It was hypothesized that methotrexate may affect the disposition of adalimumab through decreased CD64 expression on monocytes [36].

One of the reasons that fewer incidences of clinically relevant DDIs have been observed for mAbs than for small molecules could be attributable to the fundamental differences in the clearance mechanisms of mAbs and small molecules [37,38].

Most DDIs between small molecules are based on their interactions with drug-metabolizing enzymes [39]. The most important class of drug-metabolizing enzymes is cytochrome (CYP) P450. The following major CYP enzymes are usually assessed for alteration in activity during drug development: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A, CYP2C8, and CYP2B6 [38]. Most recently, CYP4F2 [40] has also been implicated in the increase of fingolimod blood levels via ketoconazole inhibition. Other major known drug-metabolizing enzymes besides CYPs include flavin-containing monooxygenases (FMOs), monoamine oxidases (MAOs), UDP–glucuronosyltransferases (UGTs), sulfotransferases (ST), molybdenum-containing oxidases (Mo-CO), methyltransferases, acetyltransferases, and glutathione-*S*-transferases (GSTs). The major enzymes that are involved in oxidative metabolism of small molecule drugs include CYPs, FMOs, MAOs, and so on. In addition to oxidative metabolism, hydrolytic metabolism and conjugative metabolism are two other major metabolic pathways for small molecules [39].

Unlike small molecules, those drug-metabolizing enzymes are not involved in the metabolism of mAbs. Monoclonal antibodies (mAbs) can be cleared primarily through two clearance pathways: non-specific (non-antigen-mediated clearance) and specific (antigen-mediated clearance). The non-specific pathway operates through the reticuloendothelial system, which is usually a linear process. The specific pathway is mediated by the binding of the mAb to its antigen with subsequent internalization and degradation of the antibody–antigen complex. This pathway usually occurs for membrane-associated antigens and is non-linear at low drug concentration and saturable. FcRn, a neonatal Fc receptor, regulates IgG homeostasis and functions as a salvage receptor, regulating IgG catabolism [41–43]. FcRn-bound antibody is protected from degradation by a recycling pathway to the cell surface where the neutral pH facilitates dissociation and release of IgG into the circulation. Unbound IgG, on the contrary, undergoes a degradation pathway resulting in proteolysis in acidic lysosomes [44].

Currently there is no universal regulatory guidance for DDI assessment for mAbs. Nor are there consistent approaches used among pharmaceutical companies and research institutes. A risk-based strategy is proposed here for the evaluation of potential DDIs of mAbs.

Risk-based strategy for drug–drug interaction assessment of mabs

A risk-based strategy has been built as a theoretical framework to assess potential DDI of mAbs in clinical development. Several key parameters have been identified as important assessment variables in this framework.

Therapeutic target (soluble or cellular)

Monoclonal antibodies (mAbs) now represent one of the most important classes of approved therapeutic biological agents. The rise of mAbs as therapeutic proteins is a function of the improvement in technologies used to improve the characteristics of the molecules and the methods used to produce them. An increase in the number of specific targets has also led to the increase of mAbs as therapeutics. In a broad sense, these therapeutic targets (antigens) can be classified as either 'soluble' or 'cellular'. Those mAbs that target cellular antigens (e.g. alemtuzumab, a humanized IgG1 mAb that targets the CD52 antigen) may have complex, non-linear pharmacokinetics [37]. By contrast, those mAbs that target soluble antigens (e.g. ustekinumab, a human IgG1 mAb that targets interleukin-12/23 p40) usually have linear pharmacokinetics over a wide dose range [45]. The clearance of mAbs that bind soluble targets is mostly dose-independent, while the clearance of mAbs that bind cellular targets usually decreases with increasing dose in a low dose range, and after the target-mediated, non-linear pathway is saturated, the clearance becomes stabilized. If a DDI study is designed for a mAb with a cellular target, then the selection of an appropriate dose is very important in order to avoid uninterpretable, ambiguous results. To our knowledge, so far no data have suggested if a mAb with a cellular target has higher propensity for DDI than a mAb with a soluble target.

Therapeutic window (wide or narrow)

Another important factor that needs to be considered is the width of the therapeutic window. Similar to small molecule drugs, the wider the therapeutic window, the less safety concern there is about a biologic of interest even if a significant DDI occurs. Though quite empirical, a biologic with a safety margin of 10 or

greater can usually be considered to have a wide therapeutic window.

Plausible mechanisms for interactions

*Drug–drug interaction potential from **in vitro** and **in vivo** studies*

Many of the biologics in clinical development have novel mechanisms of action and potential DDIs that may not be readily revealed until late development. Although *in vitro* screening for potential DDIs of biologics has limitations, evidence from *in vitro* testing may sometimes provides important guidance for a more sensible DDI program in clinical development [29]. Some signals detected in early phase I studies may also reveal some important leads for further exploration or confirmation. As expected, pharmacokinetic and pharmacodynamic data obtained in target patient populations are usually more informative than those obtained from *in vitro* studies because these patients usually also received several concomitant medications.

Known drug–drug interaction mechanisms

If a biologic under clinical development belongs to a class that is known to affect a DDI pathway (e.g. suppression of certain CYP450 isoenzyme activities by IL-6) [46], the potential for DDI may be greater than for those agents without known mechanisms or liability. For this kind of biologic therapy, it may be advisable to consider dedicated pharmacokinetic DDI studies. Similarly, a 'cocktail' approach may be also useful if an appropriately validated cocktail of relevant CYP substrates is available [47,48]. This method is described further below.

With a large number of mAbs commercially available or in development there is a reasonable chance that they will be used in combination in clinical practice. This may result in DDI(s), mostly at a pharmacodynamic level; however, the possibility of a DDI at a pharmacokinetic level cannot be precluded.

Available drug–drug interaction assessment approaches for mAbs

***In vitro** screening*

Unlike small molecules, *in vitro* experiments of DDIs are seldom performed for mAbs. There has been reasonable success in using *in vitro* studies to predict DDIs via CYP450 for some biologics such as interferons [49]. An extensive literature search did not reveal publication of *in vitro* screening to assess potential DDIs for a mAb. On the basis of personal communications, however, an *in vitro* study was performed with a cytokine added to a hepatocyte culture to determine the effect of that cytokine on CYP expression, and in the same experiment, a mAb specifically targeting the cytokine was added to determine whether the effect of the cytokine could be reversed by the mAb. The utility of *in vitro* experiments for therapeutic mAbs is, however, still in question and more research is needed before a definitive recommendation can be put forward.

Dedicated drug–drug interaction study

It is quite common to conduct dedicated pharmacokinetic DDI studies during clinical development of small molecule drugs. Several designs, including crossover, sequential, or parallel designs, have been used with the crossover design being recommended. A crossover design has the unique advantages of robustness in assessing and interpreting study results and usually requires a smaller number of subjects than the other designs since only intra-subject pharmacokinetic variability instead of inter-subject pharmacokinetic variability is used for the sample size calculation. For many biologics with a half-life of about two to three weeks, such as humanized and human mAbs, and a moderate to high occurrence of immunogenicity, a crossover design is not feasible. While for biologics with a half-life of days or shorter, a typical crossover design may still be useful [50]. A recent example of dedicated DDI studies for tocilizumab provided useful therapeutic monitoring recommendations for combination with warfarin or cyclosporine [51].

'Cocktail' drug–drug interaction study

The cocktail approach has been proposed as an *in vivo* screening tool for potential DDIs involving CYP450 isoenzymes. Simultaneous administration of several *in vivo* CYP450 probes of drug-metabolizing enzymes offers several unique advantages over the individual administration of specific CYP450 probes in multiple studies [46,47]. This approach was used to assess the interaction of peg–interferon-α2a on drugs metabolized by CYP450 [52].

Population pharmacokinetic modeling-based assessment

Population pharmacokinetic modeling has gained popularity in all phases of drug development, from discovery to post-marketing surveillance. Likewise, population pharmacokinetic modeling-based assessments of DDIs have become more common. Unlike traditional methods, population-based studies provide clinically relevant results that can be applied directly to a target patient

TABLE 2

Recommended pharmacokinetic drug–drug interaction assessment approaches on the basis of drug–drug interaction potential of a biologic

Anticipated DDI potential	Recommended methods	Examples
High	• *In vitro* DDI screening (microsomes or hepatacytes) • Dedicated DDI studies (or 'Cocktail' study) plus • Population PK modeling-based assessments	• IFNs on CYPs (IFN-α 2a/2b) • MTX on anti-TNFα mAbs (e.g. adalimumab) • Antagonistic mAbs targeting certain receptors with known effect on CYPs (e.g. tocilizumab)
Low	• Population PK modeling-based assessments • If significant signals are observed after population PK modeling-based assessments, a 'cocktail' study or dedicated DDI studies can be considered	• Antagonistic mAbs targeting receptors with no or unknown effect on CYPs (e.g. ustekinumab)

DDI: drug–drug interaction; PK: pharmacokinetic; IFN: interferon; MTX: methotrexate; TNFα: tumor necrosis factor alpha; mAbs: monoclonal antibodies; CYP: cytochrome P450.

TABLE 3

Risk-based assessment for the drug–drug interaction of ustekinumab

Risk factor	Assessment	Reason
Therapeutic target		
• **Soluble or cellular**	• Soluble	IL-12 and IL-23
Therapeutic window (index)		
• **Narrow or wide**	• Wide	Therapeutic dose (human): 45 mg or 90 mg; NOAEL monkey): 50 mg/kg
Plausible mechanism for DDIs		
• ***In vitro* evidences**	• Not performed	Neither *in vitro* evidences for DDIs, nor *in vivo* evidences from early clinical studies
• ***In vivo* signals**	• Not observed	No evidences have suggested that IL-12 and IL-23 have any impact of CYP activities
• **Impact on cytokines**	• Yes	
• **Cytokines on CYPs**	• Not expected	
Assessment approaches		
• ***In vitro* experiments**	• Not necessary	Low risk potential for DDI
• ***Dedicated DDI studies***	• Not necessary	Only a population PK modeling-based approach is recommended
• **'Cocktail' study**	• Not necessary	
• **Population PK modeling-based**	• Recommended	

mAb: Monoclonal antibody; DDI: drug–drug interaction; IL: interleukin; PK, pharmacokinetic; NOAEL: no observable adverse effect level.

population. Moreover, population-based studies do not demand the traditional requirements of intensive pharmacokinetic sampling, rigorous inpatient stays, or stringent blood sample assessment schedules. These types of studies can effectively confirm anticipated DDIs; moreover, they can also reveal DDIs that might otherwise have gone undetected with traditional methods [53,54]. In most cases, the population pharmacokinetic modeling-based approach usually assesses a one-way interaction, that is, the impact of concomitant medications (mostly small molecules) on the disposition of the investigational agent (e.g. therapeutic biologic), but seldom the affect of the investigational agent on the concomitant drug.

Depending on the potential of a mAb to cause a DDI, appropriate DDI assessment approaches can be recommended, as illustrated in Table 2.

A case study—ustekinumab drug–drug interaction assessment

A risk-based assessment strategy (Table 3) was used to identify potential ustekinumab DDIs with 28 commonly co-administered

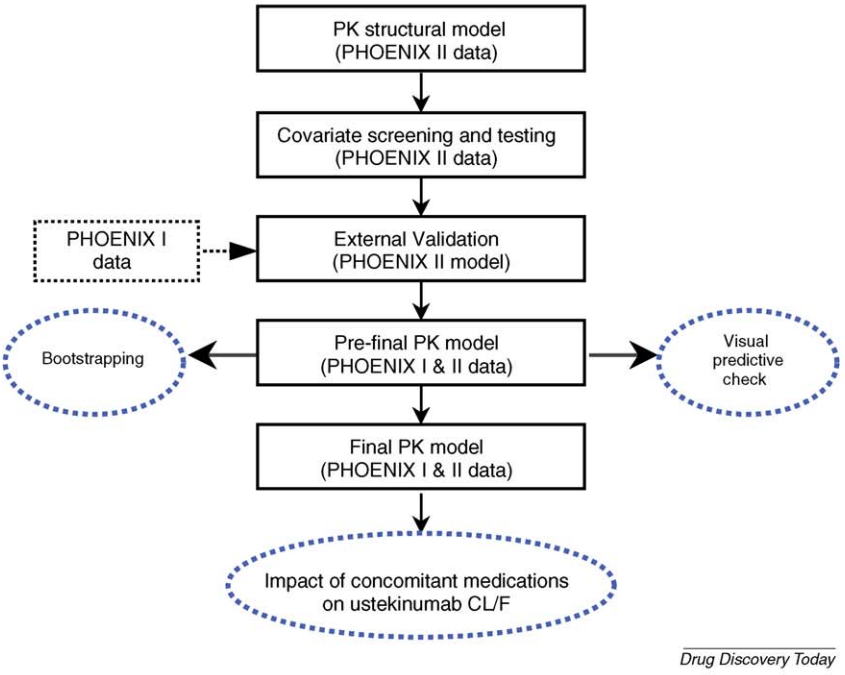

FIGURE 1

Ustekinumab Population PK model development scheme.

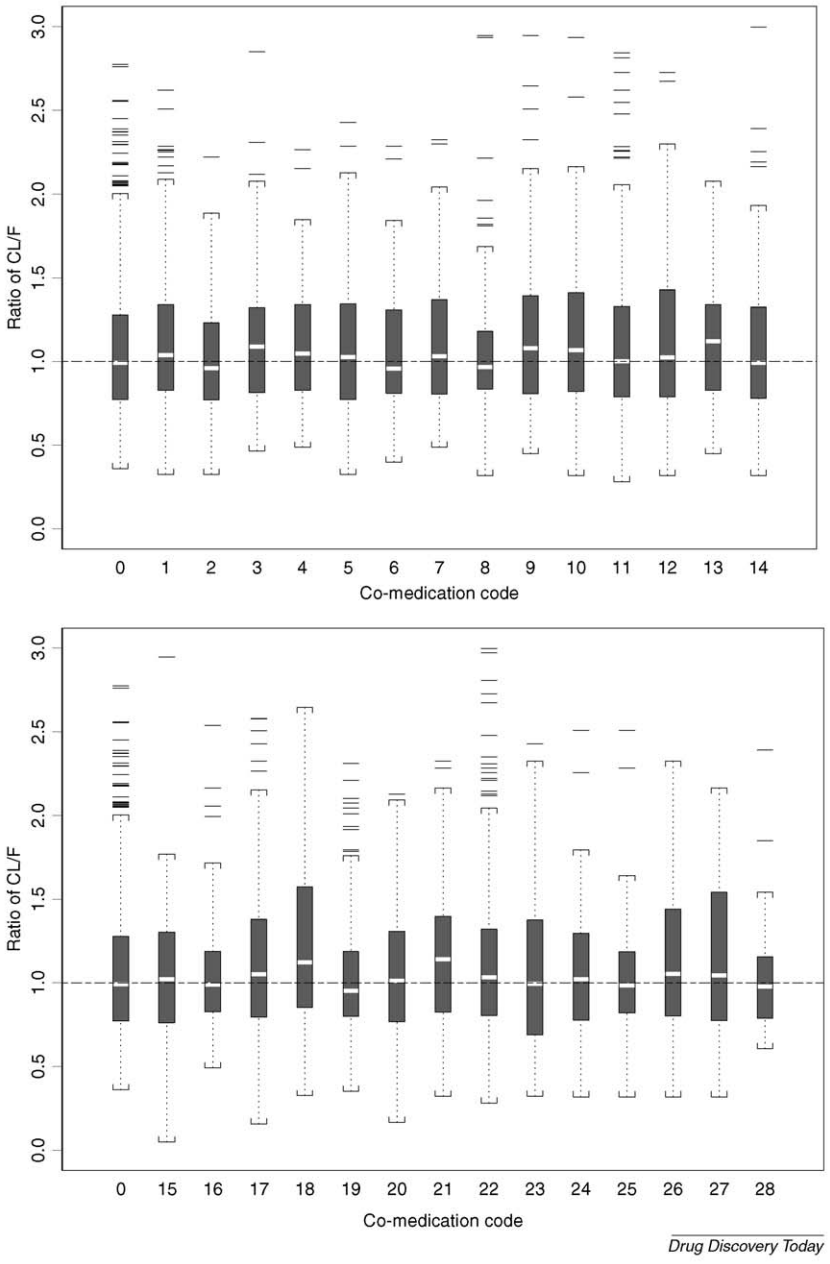

FIGURE 2

Assessment of impact of concomitant medications on pharmacokinetics of ustekinumab by a population pharmacokinetic modeling-based method. The ratio is calculated as the CL/F in patients with concomitant medication divided by the population mean CL/F of 0.465 L d^{-1}. The median ratio of each subgroup is depicted as a white band inside the box. Concomitant medication codes: (0) none; (1) acetylsalicylic acid; (2) amlodipine; (3) amoxicillin; (4) atenolol; (5) atorvastatin; (6) celecoxib; (7) citalopram; (8) diphenhydramine; (9) hydroclorothiazide; (10) hydroxyzine; (11) ibuprofen; (12) influenza vaccine; (13) isoniazid; (14) levothyroxine; (15) lisinopril; (16) medinite; (17) metformin; (18) metoprolol; (19) naproxen; (20) omeprazole; (21) panadeine CO; (22) paracetamol; (23) ramipril; (24) salbutamol; (25) azithromycin CO; (26) cefalexin; (27) hydrocortisone; and (28) vicodin.

small molecule drugs. Ustekinumab, a human mAb that targets IL-12/23 p40, has been approved for treatment of moderate to severe plaque psoriasis and is under clinical development for additional indications.

After the risk-based assessment, ustekinumab was considered to have a low risk potential for DDIs. As a result, only a population pharmacokinetic modeling-based method was used to evaluate if the pharmacokinetic properties of ustekinumab could be affected by the most commonly used concomitant medications in two pivotal phase III studies. The impact of ustekinumab on the pharmacokinetics of these concomitant medications was not evaluated because blood samples for measuring the concentration of those small molecule drugs were not collected.

A total of 9938 post-administration serum concentrations of ustekinumab from 1937 patients with psoriasis in two phase III studies (PHOENIX I and PHOENIX II) were included in the population pharmacokinetic modeling [45]. Figure 1 illustrates a flow diagram of population pharmacokinetic model development.

A population pharmacokinetic model was developed and adequately validated for ustekinumab following subcutaneous administration of 45 mg or 90 mg at weeks 0, 4 and every 12 weeks afterwards. Several variables, including demographics, baseline disease characteristics, prior use of systemic therapies for psoriasis, immune response status, and comorbidities, were evaluated during the covariate selection and identification process. Three covariates—body weight, diabetic comorbidity, and positive immune response status were found to affect the apparent clearance (CL/F) of ustekinumab by at least 20%. Only body weight was found to be clinically relevant [45].

The potential effect on the pharmacokinetics of ustekinumab was assessed for the 28 concomitant medications that were most frequently used by patients in the trials. Among these medications, non-steroidal anti-inflammatory drugs (acetaminophen, ibuprofen, acetylsalicylic acid, and naproxen), oral hypoglycemics (metformin), dyslipidemics (atorvastatin), diuretics (hydrochlorothiazide), thyroid hormone (levothyroxine) and influenza vaccine were used by at least 5% of the study population. The effect of each concomitant medication on CL/F was assessed by the maximum likelihood null hypothesis testing against the final covariate model as the reference and none of the concomitant medications had a significant effect on the CL/F of ustekinumab, as shown in Figure 2. This was not unanticipated as CYP450 enzymes or transporters that are usually associated with the elimination of many small molecule drugs are unlikely to be involved in the disposition of immunoglobulin G-based mAbs. Although no prospective DDI studies had been performed for ustekinumab, the results from the current population PK modeling-based method failed to detect a DDI, which was consistent with the original hypothesis of a lack of DDI with ustekinumab.

Future perspectives

Unlike small molecule drugs [55], there is currently no universal DDI strategy available for therapeutic biologics including mAbs. A sensible DDI assessment strategy for a mAb should be integrated into the overall drug development program. The risk-based strategy, in our opinion, may fill in a strategy gap for the evaluation of DDIs for mAbs that is always underappreciated and sometimes ignored. Since mAbs will continue to enter the drug development pipeline in the coming years, an integrated risk-based DDI strategy can assist in rational drug development for them.

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