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Drug Interactions with Therapeutic Proteins

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Resumo

Atualmente, as terapêuticas à base de proteínas apresentam uma alta taxa de sucesso na prática clínica, sendo reconhecidas unanimamente pelo seu potencial e eficácia. Mais de 100 proteínas terapêuticas modificadas originais e similares estão aprovadas para utilização clínica na União Europeia e nos EUA.

Inúmeras proteínas terapêuticas estão aprovadas ou em fase de avaliação clínica para o tratamento de doenças oncológicas e inflamatórias crónicas. O panorama atual de desenvolvimento experimental abrange as doenças respiratórias, metabólicas, do sistema nervoso central, bem como as doenças infeciosas.

Uma consequência do número crescente de indicações de biológicos é a administração concomitante destes agentes com farmacoterapias de pequenas moléculas estabelecidas, aumentando a possibilidade de interações entre estes dois grupos. Ao contrário das interações convencionais entre pequenas moléculas, os mecanismos dos biológicos são bastante complexos e ainda não estão bem descritos. Muitas destas interações são o resultado da conjugação de múltiplos fatores como a natureza e a gravidade da doença, o agressor e a vítima.

Os conhecimentos atuais indicam que os biológicos não provocam um efeito direto nas vias metabólicas/de depuração das pequenas moléculas. No entanto, as propriedades imunomoduladoras destes biológicos podem alterar indiretamente a depuração de certos fármacos através da atenuação de vias enzimáticas não-catabólicas. Existem outros mecanismos responsáveis por interações medicamentosas, tais como alterações no estado da doença, disposição do medicamento mediada pelo alvo, FcRn ou formação de anticorpos antifármacos.

É então necessária uma investigação mais extensa para melhor compreensão dos mecanismos subjacentes às interações medicamentosas que envolvam os biológicos do ponto de vista farmacocinético/dinâmico, toxicológico e de resposta clínica. A diversidade de alvos e de indicações de biológicos revela-nos um futuro promissor, tendo em contas as muitas e significativas necessidades médicas para as quais não existem atualmente soluções. Contudo, é igualmente premente a procura de uma melhor compreensão das interações medicamentosas com biológicos por parte do meio académico, da indústria e das agências reguladoras.

Palavras-chave: biológicos; fármacos de pequenas moléculas; interações medicamentosas; vítima; agressor

Abstract

Protein-based therapeutics are highly successful in clinic and currently enjoy unprecedented recognition of their potential. More than 100 genuine and similar modified therapeutic proteins are approved for clinical use in the European Union and the USA.

Presently, numerous therapeutic proteins are approved or are undergoing clinical evaluation for treatment of oncologic and chronic inflammatory diseases. The current experimental development landscape spans respiratory, metabolic, and central nervous system disorders as well as infectious disease.

A consequence of the expanding numbers of TPs indications is concomitant administration of these agents with established small molecule pharmacotherapies, which requires a comprehensive understanding of TPs–small molecule drug interactions. Unlike the conventional DDIs between small molecules, their mechanisms are quite complex and, at present, not well understood and elucidated. Many of those interactions are the result of interplay among the disease nature and severity, the victim, and perpetrator.

Current knowledge indicates that TPs do not elicit a direct effect on the metabolic/clearance pathways for small molecular therapeutics. However, the immunomodulatory properties of TPs can indirectly alter clearance of certain small molecule entities through the attenuation of non-catabolic enzymatic pathways. There are other significant mechanisms responsible for DDIs such as changes in disease state, target-mediated drug disposition, FcRn or antidrug antibodies formation.

Nevertheless, more extensive and inquisitive research is needed to help us better understand the underlying mechanisms of direct and indirect DDIs involving TPs from pharmacokinetic, pharmacodynamic, toxicological, and clinical response perspectives. The diversity of targets and disease indications for therapeutic TPs currently under evaluation in the clinic seems promising and offers hope for many significant unmet medical needs. However, it also imposes an imminent urgency to drug development scientists in academia, industry, and regulatory agencies to better understand the science of concomitant TP-TP and TP–small molecule drug interactions.

Keywords: Therapeutic proteins; Small molecule drugs; Drug Interactions; victim; perpetrator

List of Abbreviations

ADA Anti-Drug Antibody;

ADC Antibody-Drug Conjugate;

ADCC Antibody-Dependent Cellular Cytotoxicity;

ADME Absorption, Distribution, Metabolism, Excretion**;**

AIDS Acquired Immunodeficiency Syndrome;

AUC Area Under the Curve;

BDI Biologic-Drug Interaction;

BR Bendamustine and Rituximab;

BR-I Bendamustine and Rituximab plus Ibrutinib;

BTK Bruton's Tyrosine Kinase;

CAGR Compound Annual Growth Rate;

CAR-T Chimeric Antigen Receptor T;

CEA Anti-Carcinoembryonic Antigen;

Cmax Maximum Serum Concentration;

CRP C-reactive Protein;

CTLA Cytotoxic T-lymphocyte Associated Protein;

CYP Cytochrome;

DDI Drug-Drug Interaction;

DNA Deoxyribonucleic Acid;

EGFR Epidermal Growth Factor Receptor;

EMA European Medicines Agency;

Fc Fragment Crystallizable**;**

FcRn Neonatal Fc Receptor;

FDA Food and Drug Administration;

GLP Glucose-Dependent Insulinotropic Peptide;

HER2 Human Epidermal Growth Factor Receptor 2;

Ig Immunoglobulin;

INF Interferon;

IL Interleukin;

ITK Interleukin-2 Inducible Tyrosine Kinase;

mAb Monoclonal Antibody;

MHRA Medicines and Healthcare products Regulatory Agency;

MMAE Monomethyl Auristatin E;

mRNA Messenger Ribonucleic Acid;

MTX Methotrexate;

NF Nuclear Factor;

NMPA National Medical Products Administration;

NO Nitric Oxide;

NSAID Non-Steroidal Anti-Inflammatory Drug;

PCSK9 Proprotein Convertase Subtilisin/Kexin Type 9;

PD Pharmacodynamic;

PEG Polyethylene Glycol;

PIGF Placental Growth Factor;

PK Pharmacokinetic;

PXR Pregnane X Receptor;

PMDA Pharmaceuticals and Medical Devices Agency;

RA Rheumatoid Arthritis**;**

SMD Small-Molecule Drug;

TGA Therapeutics Goods Administration;

TNF Tumor Necrosis Factor;

TP Therapeutic Protein;

USA United States of America;

VEGF Anti-Vascular Endothelial Growth Factor;

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1. Introduction

In the 1970s, innovative technologies emerged making it possible to isolate, purify and analyze certain key regions of deoxyribonucleic acid (DNA). Human insulin was the first biological medicine to be developed in 1982, product of a bacterial culture (*Escherichia coli*) that had undergone genetic modifications. This was the first step that triggered a huge evolution in biological therapies, ensuring that the pharmaceutical industry could develop safer and more efficient molecules (1).

In recent times, we have seen an exponential growth in biological therapies, which are increasingly taking on a prominent role in healthcare worldwide leading to a great evolution in the clinical condition of various patients with chronic diseases, particularly cancer, rheumatoid arthritis (RA), diabetes, psoriasis, among others. In addition, they have shown themselves to be very important in the treatment of acute situations, such as myocardial infarction (2).

Nowadays, most of the active substances in biological medicines are synthesized from proteins, which can be as simple as insulin, growth hormones, or more complex, such as monoclonal antibodies (mAbs) and clotting factors (3).

Worldwide the use of biological medicines is increasing. For example, in Europe biological medicines represent 35% of all pharmaceutical expenditure, with a compound annual growth rate (CAGR) of 11,3%, from 2016 until 2022. On the other side of the globe, in the United States of America (USA), biologicals market represented 43% of the total pharmaceutical expenditure, corresponding to an amount of 211 billion dollars in 2019. Since 2014, 93% of the net spending on medicines worldwide has come from biologics. These figures are closely related to the increase in patient access to biological therapies and the importance these drugs are assuming in the healthcare panorama (4–6).

In this literature review, special emphasis is placed on drug interactions between biological and synthetic drugs, highlighting the main mechanisms of interaction between existing and emerging therapies, which is still a very controversial area that has been scarcely explored by the scientific community (7).

1.1 Concepts

1.1.1 Biologics

Biological medicines are different from other conventional therapies because they contain active substances of biological origin, such as animals, plant cells or other living organisms (humans and microorganisms such as bacteria or yeasts) (8).

Biopharmaceuticals are obtained using complex biotechnological methods such as recombinant DNA technology. Their purpose is to interfere in crucial stages of specific mechanisms that occur in certain diseases, offering greater selectivity and precision than ordinary medicines. Because of these properties, they end up being more difficult to analyze and characterize because of their larger and more complex structure. Due to the fact of being proteins, they are easily destroyed by the digestive system, making it impossible to administer them orally, resorting to intravenous or subcutaneous administration (9,10).

Given their high specificity for certain therapeutic targets, biologics have been a great asset in the treatment of patients suffering from RA, psoriasis, diabetes, cancer, hepatitis B and C, myocardial infarction, thromboembolism, among others, significantly improving their quality of life. However, there are several side effects associated with biological therapies, in particular the appearance of opportunistic infections due to the immunosuppression they induce. It is therefore essential for the medical team to closely monitor and follow up these patients (11).

After more than a decade of experimentation and studies carried out with biological drugs in numerous inflammatory rheumatic, skin and gastrointestinal pathologies, the risk-benefit ratio is generally considered favorable for most patients, making this class of drugs an increasingly popular choice compared to synthetic drugs (3,12).

1.1.2 Small Molecule Drugs

Synthetic drugs are produced by chemical means and are made up of molecules with a small, simple, and well-defined structure, which makes them the most widely used class of drugs in standard therapy. They are more easily analyzed and replicated, and all their components can be determined. In this way, they can be duplicated using less demanding and complex production methods compared to biologics. Industry producers can also adopt different manufacturing processes as long as the final product that has been analyzed is the same (13,14).

These drugs cover various therapeutic groups such as antibiotics, hormonal drugs, non-steroidal anti-inflammatory drugs (NSAIDs) and antidepressants, and are highly effective against a wide range of pathologies. They are also associated with low production costs and are easy to control in terms of safety and quality. However, numerous adverse effects such as kidney failure, death, antibiotic resistance, and endocrine disorders have been reported and studied in different animal species (14).

1.1.3 Drug-Drug Interactions

All effective medicines have the potential to produce both benefits and risks associated with desired and undesired effects. A patient's unique response to a drug is determined, in some way or another, by the concentration of that drug, and sometimes its metabolites, at the targets of action in the body. Therefore, it is appropriate to study the relationship between drug administration and response considering both the pharmacokinetic (PK) and the pharmacodynamic (PD) phases. By doing so, we can better understand why patients differ in how they respond to drugs, which involves genetics, age, disease, and the presence of other drugs (15).

Patients often receive several drugs at the same time. Some diseases, such as cancer and acquired immunodeficiency syndrome (AIDS), require combination therapies that work better than one of the drugs alone. In other cases, the patient has multiple conditions, each of which is being treated with one or more drugs. Given these situations and the many potential sites for interaction that exist in the body, it is not surprising that an interaction may occur between them (15,16).

In most cases, however, the interaction is not clinically significant because the response of most systems in the body is graded, with the intensity of the response varying continuously with the concentration of the compound causing it. It is only when the magnitude of the change in response is large enough that an interaction becomes clinically significant (17).

It is also important to bear in mind that some interactions are intended to be beneficial, as is often the case with combination therapy. It is the unintentional ones that are a cause for concern, resulting either in ineffective therapy due to antagonism, lower concentrations of the relevant drug, or, more worryingly, in excessive toxicity, sometimes severe enough to limit the use of the drug in question or, if it causes death, to lead to its withdrawal from the market (18).

1.1.4 Therapeutic Proteins vs Small Molecule Drugs

As mentioned before, combination therapies offer the potential for improved effectiveness. Therefore, in order to achieve greater therapeutic benefits, biologics are combined with conventional small-molecule drugs (SMDs) and/or with other biologics. By 2010, about 80 biologics had been approved, and very few biological license applications included information on biologic-drug interactions (BDIs) from clinical trials in the labelling (19).

Although numerous additional biologics were subsequently approved by the Food and Drug Administration (FDA) as therapeutics, the available information on BDIs remains limited. Unlike SMDs, there are only a few reported drug-drug interaction (DDI) studies for biologics. As shown in Table 1, since biologics do not undergo hepatic metabolism via cytochrome P450s (CYP450) enzymes or elimination by biliary excretion, it was previously assumed that biologics have a very low propensity for DDIs (20).

Table 1: Comparison of small-molecule medications and biologics (21)

Characteristic	Small-molecule drugs	Biologics
Production	Chemical synthesis	Through biotechnology and host cell lines
Size	Low molecular weight	High molecular weight
Physicochemical properties	Well defined	Complex
	Stable	Sensitive to heat, sheer stress (aggregation)
Manufacturing	Single entity, high chemical purity, standards well established	Heterogeneous mixture, broad specifications which may change during development, difficult to standardize
	Not affected by slight changes in production process and environmental conditions	Highly susceptible to changes in production process and environmental conditions
Analytic assays	Completely characterized by analytic methods	Difficult to characterize, assays not standardized
Decontamination	Easy to purify	Lengthy and complex purification process
Quality assurance and detection	Contamination can be avoided and easily detected and removable	High possibility of contamination, detection hard, and removable impossible
Pharmacokinetic properties	Administered through different routes	Parenteral route of administration most common
	Rapidly enters systemic circulation through capillaries	Larger molecules enter circulation through lymphatic system, subject to proteolysis and lymphatic transit
	Distributes to any organ and tissue	Distribution limited to plasma and extracellular fluid
Toxicity	Organ specific toxicity	Mostly receptor-mediated toxicity
Allergenicity	Often not antigenic	Usually antigenic

However, recent studies have shown that these combinations may lead to unexpected BDIs, with variations in the effectiveness and safety of both drugs. The complexity of biologics, in conjunction with their long half-lives, protein-based structure, and mechanism of action, presents a significant challenge to the assessment of BDIs (22).

In the context of PD characterization, a significant challenge has emerged due to the incomplete understanding of the downstream mechanisms of action of approved therapeutic proteins (TPs). Furthermore, the pleiotropic behavior of many TPs has not been fully elucidated. When a study is conducted in vitro or in vivo, it is challenging to obtain a comprehensive assessment of all mechanisms involved in TP activity. Nevertheless, it has been postulated that PD interactions represent the primary explanation for BDI (23).

1.1.5. Drug-Drug Interaction Risk Assessment for Therapeutic Proteins

While the best practices for DDI assessment of SMDs are well established, the regulatory perspective on DDI risk assessment of TPs has evolved in recent years. Development programs for TPs need to design the DDI part of the clinical pharmacology package on a case-by-case, risk-based approach, as factors such as disease state and target biology are often key mediators of TP-DDIs. Although the DDI section of the clinical pharmacology package for TPs may be leaner than that for small molecules, some clinical studies may be required, as it is important to address DDIs for these non-small molecule drugs (24).

In June 2023, the FDA issued a guidance on the risk assessment of potential interactions between TPs and other drugs. While the guidance applies to TPs, the general concepts can be similarly applied to other biological products such as cell and gene therapies (25,26).

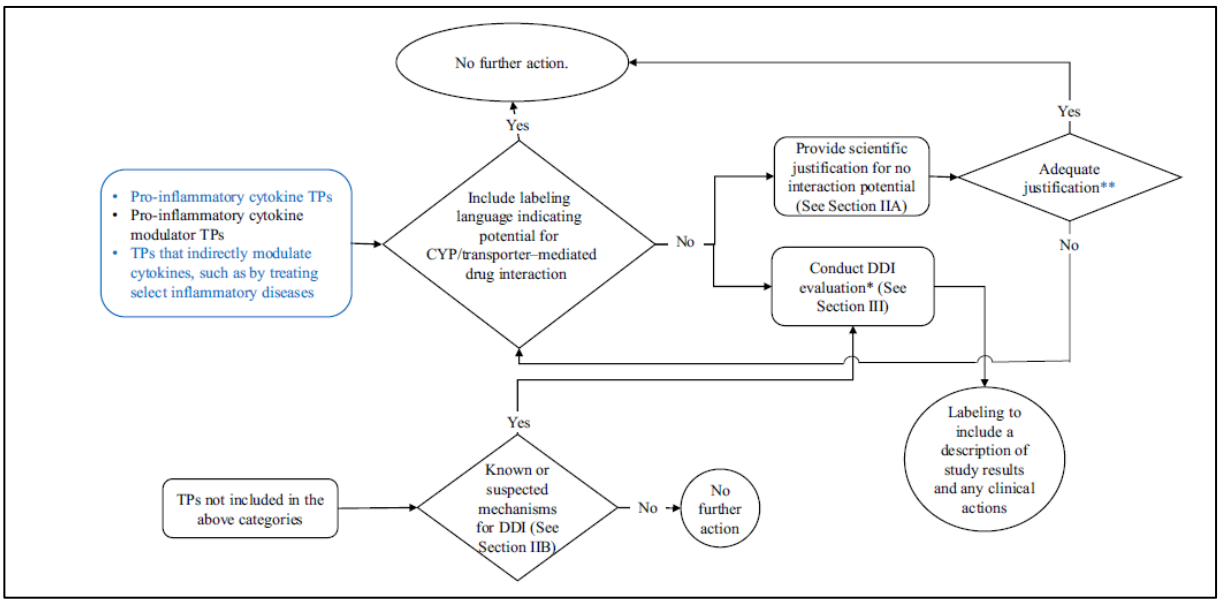
TPs exhibit a distinct interaction profile in comparison to small molecules. In light of the growing number of biologicals in development and their advancement to clinical trials, the recently released guidance from the FDA for TPs offers valuable insights on the necessity of DDI studies and their design, particularly in the context of TPs. This guidance also presents a decision tree that provides a practical approach to assess the necessity of DDI studies (26).

The document mentioned above offers a number of key insights, including a clarification of the expectations for DDI assessment for drugs that are proinflammatory cytokines or cytokine modulators, as well as for TPs with alternative DDI mechanisms and antibody-drug conjugates (ADCs) as victims and perpetrators of interactions. It also clarified that the translation of in vitro or animal data to humans for TP-DDIs is limited and provided general recommendations for clinical trial designs to assess TP-DDIs (24,26).

There are other enlightening articles on this subject, such as the 2007 “EU Therapeutic Proteins Guideline” which presents one of the first flow schemes for evaluation of DIs as shown

in Figure 1. China's National Medical Products Administration (NMPA) also published in 2021 the "Technical guideline for drug interaction studies (draft)" and the "Technical guideline for clinical pharmacokinetic studies of therapeutic proteins". All around the world, regulatory authorities like the European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency (PMDA), NMPA, Medicines and Healthcare products Regulatory Agency (MHRA) and Therapeutic Goods Administration (TGA) are carefully monitoring and updating scientific evidence about the potential interaction risk between these drugs (24,27).

Figure 1: Proposed flow scheme for evaluation of DIs (28)



2. Objective

Over the last years we have seen tremendous progress in the area of therapeutic biologics. As the use of TPs in polypharmacy settings continues to expand, and the potential toxicity risk of DDIs becomes more apparent, there is a clear need for a comprehensive review of potential DDIs involving therapeutic biologics during the drug development process. However, literature references on this topic have so far been scarce.

Thus, the main goal of this essay is to compile and present the current status of knowledge on concrete therapeutic DDIs. This work focuses on both theoretical and practical aspects of DDI assessments for therapeutic biologics in drug development, including topics like, PK-DDIs, PD-DDIs, utility of in vitro methods in DDI assessment and prediction, risk-based strategies for evaluating biologic DDIs and regulatory perspectives on biologic DDI assessments.

3. Materials and Methods

Several search engines were used to compile this monograph such as PubMed (https://pubmed.ncbi.nlm.nih.gov/), Google Scholar (https://scholar.google.pt/), Infomed (https://extranet.infarmed.pt/INFOMED-fo/), the official Infarmed's official website (https://www.infarmed.pt/), among others, which were used to search for relevant bibliographic documentation published between 1978 and 2023, in portuguese and english.

The research carried out was based on a set of concepts related to the subject of this essay, such as "biologics"; "therapeutic proteins"; "small molecule drugs"; "drug-drug interactions"; “mechanisms of drug interactions”; “interaction studies” among others.

4. Results and Discussion

4.1. Therapeutic Proteins: Main Mechanisms of TP-DDI

The key mechanisms behind clinically observed therapeutic TP and SMD's interactions include disease state changes in cytokines, target physiology, immunogenicity, and cytokines as therapeutic interventions. Pro-inflammatory cytokines such as interleukin (IL-6), IL-1β, tumor necrosis factor (TNF-α), interferon (IFN-γ), IFN-α, and IFN-β can be increased in autoimmune diseases, certain infection states, or as a consequence of therapeutic interventions. RA, psoriasis, Crohn's disease, and some viral infections such as those caused by the influenza virus are examples of disease states in which cytokines are elevated. In other instances, the goal of therapeutic intervention is to increase cytokine levels in the tumor environment, such as in immuno-oncology (7).

Elevated levels of pro-inflammatory cytokines are known to suppress CYP450 enzymes and therefore can potentially increase the exposure to SMD co-medications that are subtracts of CYP enzymes. Therapeutic interventions meant to correct these disease states may reduce levels of inflammatory cytokines, thereby increasing or normalizing the activity of CYP enzymes and/or drug transporters, resulting in normalization of the exposure to an SMD. It has been known for some time that infections can have an impact on the metabolism of SMDs: for example, influenza virus infection impairs the clearance of theophylline, a CYP1A2 substrate (29,30).

The phenomenon in question is attributed to the IFN molecules released following the virus infection, which cause a reduction in the activity of CYP450 enzymes. As a consequence of this reduction, there is a decrease in the clearance rate of the CYP1A2 substrate theophylline in patients undergoing allogeneic bone marrow transplantation. There was a significant correlation between pro-inflammatory cytokine production (i.e., IL-6) and a notable increase in cyclosporine systemic exposure. Consequently, pathological conditions such as inflammation or infection can influence the metabolic processes of SMDs through the release of cytokines (31,32).

In addition, therapeutic targets can be of significance in the context of TP-DDIs. The modulation of target levels by SMDs or TPs can influence the exposure of drugs that bind to the same target. Many mAbs display target-mediated drug disposition, whereby alterations in

the quantity of available targets can influence the observed systemic levels of mAbs (or targeting fusion proteins, TPs). Therefore, the presence of a second drug that modulates the available target of a mAb may result in a change in the PK profile of the mAb (33).

Another well-documented mechanism by which TP-DDI may occur is via immunogenicity. If a drug either stimulates or suppresses the immune system, it is possible that the immunogenicity toward the target protein could be affected relative to monotherapy. Stimulation of the immune system can result in enhanced production of anti-drug antibodies (ADA), which may lead to reduced exposure of the target protein or vice versa. For instance, the coadministration of mAb with an immunosuppressant such as methotrexate (MTX) may result in a higher exposure due to a reduced ADA response (34).

Therapeutic cytokines have been applied in the treatment of a multitude of human diseases. For example, IL-2 and IFNs are being used in the treatment of cancer and autoimmune diseases. The administration of exogenous cytokines can also influence the levels of CYP enzymes (35).

In general, SMDs as a perpetrator of TP-DDIs act through modulating immunogenicity or target biology to change the PK of TPs. TPs as perpetrators commonly typically change CYP enzymes and drug transporters through the modulation of cytokines levels. It is also possible for TPs to act as perpetrators by modifying the target levels of a second TP (7,22).

4.2. In Vitro Effects on CYP Enzymes and Transporters

Historically, the primary focus in the field of TP-DDIs has been on cytokines and cytokine modulators. In vitro studies in cultured human hepatocytes have demonstrated that pro-inflammatory cytokines generally result in a reduction in the expression of CYP450 enzymes and drug transporters in hepatocytes isolated from humans and preclinical species. However, the extent of these effects varies considerably for different enzymes and transporters, suggesting that multiple mechanisms may be involved (36,37).

A number of mechanisms has been proposed to explain the inflammation-mediated effects on drug-metabolizing enzymes and transporters. These mechanisms have been previously described in numerous reviews and are summarized briefly below:

I. CYP3A4 is responsible for the metabolism of over 50% of current prescription drugs and its expression is transcriptionally regulated by the pregnane X receptor (PXR)

which is a ligand-dependent transcription factor. It has been reported that nuclear factor (NF-κB) activation by lipopolysaccharides and TNFα plays a pivotal role in the suppression of CYP3A4 through interactions of NF-κB with the PXR·retinoid X receptor complex (38);

II. A modification in nitric oxide (NO)-dependent ubiquitination and subsequent proteasomal degradation has been implicated in cytokine-dependent degradation of CYP enzymes such as rat CYP2B1, although it is noteworthy that non-ubiquitin-dependent degradation has also been observed for CYP2C22. The impact of NO on CYP levels has been mostly investigated in rodents. However, recent studies have demonstrated that cellular NO, which is produced during infection and inflammation, can result in CYP2B6 enzyme degradation in human hepatocytes (39,40).

In vitro studies have been conducted to evaluate the impact of cytokines and cytokine modulators on the absorption, distribution, metabolism, and excretion (ADME) genes. These have been mainly conducted in primary cultured human hepatocytes. Despite the invaluable insights gained from current studies, which have identified the impact of these agents on CYP enzymes and transporters, it has not been possible to extrapolate the findings from in vitro to the clinic. There are multiple factors contributing to the difficulty to extrapolate data in hepatocytes to in vivo such as:

- The precise mechanisms responsible for the downregulation of ADME genes remain poorly understood;
- Use of isolated hepatocytes as a model for the disease state is not a representative approach and may be the reason why cytokine concentrations used in vitro are typically supraphysiological;
- There remains a substantial inter-lab variability, making comparisons of data between labs difficult;
- There is no experience in studying the interplay of multiple cytokines in vitro and finally the effect of cytokines can be indirect by the activation of immune cells resident in the liver such as Stellate and Kupffer cells (35,41,42).

Some progress has been made in this area by the establishment of a micropatterned hepatocyte-Kupffer cell coculture model supported by mouse fibroblasts. Overall, it was

concluded that hepatocyte Kupffer cell cocultures are a more robust in vitro system than hepatocytes alone thus representing a preliminary step toward the development of a more predictive in vitro model. However, they remain inadequate for accurately representing the complexity of the immune system and disease states (43).

4.3. Cytokine-Dependent Interactions

4.3.1. Cytokines and TPs targeting cytokines

The dosing of cytokines in clinical settings like IFNα, INFα2b, IL-2, IL-10, and IL-6, has been proved to reduce the clearance of SMDs with the observed effects ranging from 12% to 81%. As a concrete case, a study in healthy individuals showed that theophylline (a CYP1A2 substrate) clearance was reduced by 20% after administration of polyethylene glycol (PEG-IFN α2a), with no impact on substrates of other cytochromes. In a PK study of hepatitis C virus subjects concomitantly receiving methadone, treatment with PEG-IFN α2a was associated with 10% to 15% higher methadone levels than at baseline. Similarly, PEG-IFN α2b has been shown to increase the exposure of caffeine by up to 39% in patients with chronic hepatitis C and the exposure of dextromethorphan by up to 103% in healthy subjects (44,45).

Patients diagnosed with inflammatory diseases frequently display elevated levels of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which can lead to reduced CYP and transporter expression and activity. Following administration of a mAb that targets a proinflammatory cytokine, it is anticipated that the CYP expression will be normalized and return to levels observed in healthy subjects (19,20).

Experimentally, IFN-a at the optimal biological dose schedule, and in combination with gemcitabine has been shown to induce apoptosis in tumor-associated endothelial cells and to decrease the growth of human pancreatic cancer cells due to increased cell chemosensitivity. In a parallel study IFN-α was shown to modulate the susceptibility of Tenon fibroblasts to mitomycin C, resulting in increased cell death (46,47).

In RA, where inflammation is characterized by elevated serum C-reactive protein (CRP) levels, the area under the curve (AUC) of simvastatin decreased by 43% and 54.7%, respectively, following treatment with the anti-IL-6R mAbs tocilizumab and sarilumab. In another study, after three weeks of treatment with sirukumab (anti-IL-6 mAb) the probe substrates of midazolam (CYP3A4), omeprazole (CYP2C19), and S-warfarin (CYP2C9)

exhibited AUC reductions of 35%, 41%, and 18%, respectively. A correlation was found between the decreased exposure of SMDs and the reduced CRP levels observed following the treatment to decrease inflammation (48–50).

The potential effects of cytokine modulation to induce changes in CYP enzyme levels was a major concern in the context of other inflammatory diseases, in particular psoriasis. Nowadays, TP-DDI studies have been conducted between anti-cytokine mAbs (anti-IL-23: tildrakizumab, risankizumab, guselkumab) and anti-cytokine receptor mAbs (anti-IL4R: dupilumab; anti-IL-2R: daclizumab) in conjunction with SMD probe cocktails. CYP1A1, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 were monitored and the results reflected no reductions in SMD exposures. Furthermore, three programs examined the impact of midazolam. The administration of denosumab (anti-RANKL mAb) or secukinumab (anti-IL-17A mAb) had no effect on midazolam levels, however, for unknown reasons, these increased 24% when brodalumab (anti-IL-17R mAb) was administered (51–58).

The absence of an effect on SMDs observed in these studies suggests that it is crucial to ascertain whether treatment with a specific TP induces noteworthy alterations in cytokine levels and whether those changes exert an impact on tissues expressing CYPs. A study in ulcerative colitis patients examined the changes in intestinal CYP messenger ribonucleic acid (mRNA) expression following treatment with etrolizumab (α4β7 and αEβ7 integrin heterodimer mAb) and observed minimal change in expression (59).

The collective findings indicate that in psoriasis or ulcerative colitis, there may not be sufficient systemic inflammation in the disease state to reduce the expression of CYP enzymes. Therefore, when cytokine modulatory mAbs were used as treatment for local inflammation, few or no effects resulting of TP-DDI were observed on the coadministered substrates of CYP enzymes. A number of authors have proposed that these pro-inflammatory molecules, such as CRP or IL-6, may serve as potential biomarkers for those at risk of inflammation-related changes in CYP activity. Nevertheless, currently, no cutoff concentrations have been established, which would indicate a probable risk for TP-DDIs. Another factor that must be considered when evaluating the risk of a TP-DDI is whether the cells in which CYPs are expressed (e.g., hepatocytes) do not have receptors for the targeted cytokine as it happens with IL-23R (35,53,57,60).

4.3.2. Immunomodulatory Therapeutic Proteins

Besides cytokines which have been administered as therapeutic interventions and mAbs, which neutralize cytokines, there are other TPs which modulate the immune system by affecting the regulatory steps involved in the recognition of antigen-presenting cells by T cells. One illustrative case is that of blinatumomab, an antibody fragment lacking a fragment crystallizable (Fc) domain that simultaneously targets both CD19 on tumor cells and CD3 on T cells. Blinatumomab has been approved for second-line therapy in patients with Philadelphia chromosome-negative relapsed or refractory acute lymphoblastic leukemia. It results in transitory elevations of hepatic enzymes and elevated levels of inflammatory cytokines during the initial week of treatment. The administration of blinatumomab in a step-dosing regimen was found to be associated with a reduction in the levels of cytokine release and a lower mean body temperature. The concentrations of IL-6, IL-10, and INFγ were found to be at or above 1 ng/mL for three to four days which would be sufficient to suppress CYP3A4 activity completely in cultured human hepatocytes. A case study supported this by reporting a clinically significant drug interaction between intravenous busulfan and blinatumomab, observed through busulfan therapeutic drug monitoring. Busulfan clearance was reduced resulting in a higher AUC when it was administered 48 h after blinatumomab (41,61–63).

In human hepatocytes, blinatumomab demonstrated no effect on CYP activities. However, a cytokine cocktail was observed to suppress CYP3A4, CYP1A2, and CYP2C9 activities. While DDIs have not been directly investigated, the blinatumomab package insert does acknowledge the potential for DDIs with SMDs, warning that the treatment causes transient release of cytokines that may suppress CYP450 enzymes, mainly during the first 9 days of the first cycle and the first 2 days of the second cycle. Therefore, in patients receiving concomitant CYP450 substrates (e.g., warfarin, cyclosporine) it is advised to monitor and adjust the dose as needed (64,65).

Another example of a TP which modulates the immune system is belatacep, which was specifically designed to block T-cell activation. Belatacept is an immunosuppressive fusion protein comprising the extracellular domain of human cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and the constant-region fragment of immunoglobulin (Ig-G1). This TP has received approval as a treatment for organ rejection in individuals who have received a kidney transplant and are positive for the Epstein-Barr virus. The results of a probe cocktail TP-DDI study with belatacept showed no significant alterations in the levels of several cytokines

(TNFα, IFN-γ, IL-2, IL-6, IL-10, and IFNα) and no notable PK effects on the substrates of CYP450 enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (66).

4.4. Immunogenicity-Dependent Interactions

Immunogenicity frequently leads to reduced TP exposure, thereby indicating that one possible mechanism by which an SMD might affect TP exposure is by reducing immunogenicity. This type of DDI is exemplified in the treatment of RA by anti-TNFα TPs and MTX. MTX is a common treatment option for this disease and several anti-TNF antibodies, including infliximab, adalimumab, and golimumab, have shown higher exposure RA patients when MTX was present in their treatment plan compared to when it was absent. The increased exposure of anti-TNF TPs in the presence of MTX has been attributed to the immunosuppressive capacity of MTX, which results in a reduction of ADA activity towards the TPs. An alternative hypothesis has been proposed in which MTX lowers the expression of FcγR., potentially affecting PK of the mAbs in question (67–69).

A recent study suggests that the TP-DDI with MTX can mostly be attributed to reduced immunogenicity and immunogenicity-mediated clearance. Cynomolgus monkeys were dosed with concentrations of golimumab and MTX (1,1mg/kg) that exceeded those typically employed in the treatment of autoimmune diseases. The results of the MTX treatment indicated a delay in both the incidence and the time of onset of ADA to golimumab. No discernible changes were detected on the PK of golimumab prior to the onset of ADA and there was no observable effect on the expression of Fcγ1R. Furthermore, the GO-REVEAL trial data from patients with psoriatic arthritis indicated a correlation between MTX and the reduction in the incidence of ADA, and that subjects who did not receive MTX exhibited on average a 30% lower trough golimumab concentration. It is noteworthy that, in the ADA negative subjects, the mean trough concentrations were comparable with and without MTX treatment, which implies that the presence of ADA resulted in lower trough concentrations and that the observed TP-DDI is primarily modulated through a reduction in immunogenicity (70).

4.5. Target-Dependent Interactions

The PK of TPs can be affected by high concentrations of their target ligand, so drugs that can change the concentration of the target ligand can also cause TP DDIs. For example, statin treatment was associated with a 20% reduction in anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) mAb evolocumab maximum serum concentration (Cmax) and AUC as compared to without statins. Another anti-PCSK9 mAb, alirocumab, showed a similar reduction in exposure. The observation that this TP-DDI is target-related is supported by studies showing that statin treatment upregulates PCSK9 levels, which then leads to a reduction in anti-PCSK9 mAb exposure (71–74).

Another example of a target-mediated effect on PK was seen in a study with an anti-placental growth factor (PlGF) mAb (RO5323441) and an anti-vascular endothelial growth factor (VEGF) mAb bevacizumab in patients with glioblastoma. In early clinical studies, the exposure of RO5323441 was observed to be 50% higher when administered in combination with bevacizumab compared to monotherapy, while bevacizumab exposure was unaffected. The hypothesis for this TP-DD is that VEGF complexes with bevacizumab and, therefore, VEGFR-1 becomes available for binding with PlGF. In this situation, PlGF becomes "trapped" resulting in higher concentrations of unbound RO5323441(75).

For the treatment of lymphoma, the combination of bendamustine and rituximab (BR) is often indicated. In a clinical trial (HELIOS), the efficacy of BR plus ibrutinib, a Bruton's tyrosine kinase inhibitor (BR-I), was evaluated in subjects with previously treated relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. Reports displayed that systemic rituximab exposure was higher with BR-I vs BR. The effect of ibrutinib on the PK of rituximab was attributed to the rapid elimination of CD20-positive B cells, which resulted in a decreased clearance of rituximab (76).

Finally, the Fc domain of mAbs interacts with the neonatal Fc receptor (FcRn). The FcRn plays a critical role in the maintenance of IgG homeostasis and ensures a long half-life of IgG through FcRn-mediated recycling of IgG. It is expected that treatment with mAbs that block the Fc-FcRn interaction will result in increased clearance of both endogenous IgG and exogenously administered therapeutic antibodies. A study on rozanolixizumab, which is an anti-human FcRn mAb, showed up to 90% reduction of IgG on cynomolgus monkeys and no increase in the risk of infection was observed. It was also conducted a study of intravenous or subcutaneous rozanolixizumab in healthy subjects in order to evaluate safety and tolerability.

There were sustained dose-dependent reductions in serum IgG concentrations of the subjects, although adverse events occurred in the groups that received highest doses. Another study in healthy volunteers focused on M28 (anti FcRn antibody) reported mean IgG reductions of ≈85% from baseline, with no serious or severe adverse events and low incidence of infections. It is conceivable that therapeutic IgG antibodies coadministered with FcRn blocking agents could have greatly reduced half-life and exposure and therefore should be coadministered with caution (77–79).

4.6. Interactions based on physiology

A number of additional TP-DDI interactions have been observed that do not obey the previously discussed mechanisms. A pertinent example is the glucose-dependent insulinotropic peptide (GLP-1) receptor antagonists, including exenatide and dulaglutide. The administration of exenatide with acetaminophen resulted in a reduction of the latter. DDI studies were also conducted with albiglutide in combination with other SMDs. The AUC of simvastatin when coadministrated with this TP decreased by 40%, however, this interaction is unlikely to be of clinical relevance. It was hypothesized that the decrease of these drugs was the result of delayed gastric emptying, resulting in a slowed absorption rate (45,80).

An alternative means of interaction might be through the PD effects of angiogenesis inhibitors. Mouse studies have demonstrated that the angiogenesis inhibitors bevacizumab and sorafenib have the effect of reducing the distribution of an anti-carcinoembryonic antigen (CEA) mAb to the tumors of mice bearing CEA-expressing tumors. In the same studies, no changes in the plasma PK of the anti-CEA mAb were noted when co-dosed with the angiogenesis inhibitors. The observation of no alterations in PK has been corroborated by clinical studies of bevacizumab dosed in combination with other mAbs, including MEDI3617 (an anti-angiopoietin-2 mAb) and MINT1526A (an anti-α5β1 integrin mAb) (81,82).

It is also noteworthy to mention an interaction with MTX that falls in this category. Leucovorin is a folate analog used in the treatment of MTX toxicity and chemotherapy regimens. Once very elevated MTX concentrations are reached, enhanced elimination is essential, as leucovorin alone may be insufficient to overcome this toxicity. Glucarpidase (carboxypeptidase enzyme) is used to reduce toxic plasma MTX concentration through hydrolyzation in patients with delayed MTX clearance . A study showed that in patients with

cancer receiving high-dose MTX and leucovorin rescue, glucarpidase administered 2 hours before leucovorin reduced leucovorin AUC0-3h by 33% and Cmax by 52% (24).

4.7. Interactions Based on Binding to Proteoglycans

An example of an interaction based on the binding to proteoglycans is that of palifermin which is a recombinant human keratinocyte growth factor consisting of 140 amino acids. When palifermin was administered with heparin, the AUC of palifermin was fivefold higher with heparin than in its absence. Heparin protects growth factors from proteolysis, with complexed growth factors being cleared more slowly than unbound growth factors. Furthermore, heparin may compete with growth factors for binding to cell surface proteoglycans, resulting in increased cellular uptake and subsequent clearance (83,84).

4.8. Interactions of Antibody-Drug Conjugates

It is important to take caution when studying ADCs, as these are therapeutic modalities consisting of a mAb covalently bound to a SMD (usually a cytotoxic agent) through a chemical linker. ADCs are specifically designed to deliver a potent cytotoxic agent selectively to tumor cells via tumor-specific or overexpressed cell surface antigens. Following binding to the cell surface antigen, the ADC is internalized by tumor cells and undergoes lysosomal degradation, resulting in the release of the cytotoxic agent. Although mAb exposure is unlikely to be affected by coadministered SMDs, the ADC-released cytotoxic agents may be affected. It is anticipated that unconjugated cytotoxic agents formed via proteolytic degradation and/or deconjugation from ADC will exhibit similar behavior to SMDs, which can be metabolized and excreted by CYPs and transporters. It is possible that DDIs may still occur as a result of the modulation of important elimination pathways. In addition, the liver is the primary organ for the uptake of ADCs, which may result in interactions with phase 1 and 2 enzymes (85).

One example of an ADC program that investigated potential DDIs is brentuximab vedotin, an ADC in which the antibody targets CD30 and the conjugate is monomethyl auristatin E (MMAE). In this case, the ADC was not affected by either a CYP3A4 inhibitor or inducer. The PK profile of midazolam was also evaluated and it was not affected by brentuximab vedotin. However, when the potent CYP3A4 inhibitor ketoconazole was coadministered, the AUC for the MMAE component showed a 34% increase. Coadministration

of the ADC with rifampin (a potent CYP3A4 inducer) reduced exposure to MMAE by approximately 46%. In patients taking concurrent strong CYP3A4 inhibitors, close monitoring for adverse effects is strongly advised due to the increased exposure of MMAE (86).

In vitro and in vivo animal studies have occasionally been reported to evaluate the TP–drug interaction potential of other ADCs. The cytotoxic component of ado-trastuzumab emtansine is metabolized by CPY3A4 and CYP3A5, thus the potential for interactions with strong CYP3A4 inhibitors exist. Product labeling recommends avoiding concomitant administration of these medications with ado-trastuzumab emtansine to reduce the chance of increasing toxicities. Inotuzumab ozogamicin is a CD22-directed ADC that in clinically relevant concentrations, has a low potential to inhibit CYP450. Additionally it was observed an increase in the AUC and Cmax of onotuzumab ozogamicin when administrated with rituximab (45).

4.9. The Duality of Therapeutic Proteins-Drug Interactions

Over the past decade, the unprecedented increase in the clinical use of therapeutic biologics for a multitude of indications led to the appearance of therapeutic BDIs. However, this kind of DDIs is generally understudied or underreported due to a perception that DDIs involving therapeutic biologics are scarce and of limited relevance. Moreover, the underlying mechanisms of many of those DDIs are still poorly understood. In order to better assess the landscape of DDIs for therapeutic biologics, these interactions have been compiled on **Tabel 2 in Appendix A1** (involving therapeutic biologics either as victims or perpetrators based on current labeling information and scientific literature. This table also contains a brief description of the interaction mechanisms and pre-clinical/clinical benefits as well the references if available from which the DDI contents were obtained.

4.9.1. Biologics as the Perpetrators of Biologic-Drug Interactions

TPs and SMDs are distinct entities with different therapeutic targets and sites of action. Despite this, some TPs have been shown to influence the PK and PD of coadministered drugs, potentially affecting their efficacy and safety. The impact of TPs as perpetrators can occur directly through their effect on drug receptors or indirectly through their influence on the CYP metabolic pathway (22).

4.9.1.1. Effects of Therapeutic Proteins on Biologic Receptors

A significant number of drugs exert their effects by binding to a particular receptor. Any alteration in the membrane surface expression of receptors or in the environment around them may result in unpredictable responses. The intricate mechanism of action of some TPs the study makes of such interactions particularly challenging. The majority of the studies have not reported BDIs related to PK interactions in which TPs are the perpetrators. Therefore, the increase in efficacy of certain treatments may potentially be attributed to the interplay of PD interactions and the mechanisms lying underneath them such as genetic modulation, chemosensitization and enzymatic interference (87,88).

The anti-angiogenic mAbs aflibercept and bevacizumab are employed concomitantly in oncological treatment with several SMDs for the management of colon or rectal cancers, as well as for lung and breast cancers, respectively. Furthermore, both aflibercept and bevacizumab enhance the delivery of chemotherapy by increasing the diffusion function of tumor vessels. This is achieved through normalization of the stromal vasculature and the disruption of the tumor vasculature which in turn lead to higher chemotherapeutic concentrations in the tumor cells. The effects of certain drugs on angiogenesis can result in synergism as demonstrated in an interaction study where bevacizumab was coadministered with paclitaxel, docetaxel, or cyclophosphamide. Two additional studies corroborated the improved efficacy of bevacizumab in combination with topotecan or cisplatin and carboplatin or paclitaxel via intraperitoneal administration. The same results were achieved with a bevacizumab and paclitaxel combination in the treatment of ovarian cancers and with docetaxel (89–91).

Cetuximab, an anti-epidermal growth factor receptor (EGFR) chimeric mAb, also regulates tumor vasculature and displayed an increase in cell-killing efficacy when coadministered with chemotherapy in colon or rectal carcinomas. A study proposed that a treatment with oxaliplatin and cetuximab could be more effective on hypoxic gastric cancer cells than on normal cells, due to the decreased expression of VEGF that occurs in response to hypoxia. Furthermore, the administration of mAb before topotecan or irinotecan was found to reduce the growth inhibitory effect of the latter, indicating that treatment with anti-EGFR mAbs should follow chemotherapy. Additionally, several clinical trials showed benefits in the coadministration of cetuximab and DNA cross-linking agents like carboplatin, cisplatin, oxaliplatin and irinotecan due to downregulation of several essential genes involved in DNA repair (92–94).

Genetic modulation can also be involved in drug interactions, for instance, the combination of trastuzumab and chemotherapy, particularly with DNA-damaging agents, has been shown to have a synergistic effect in the treatment of both breast and gastric cancers. Trastuzumab inhibits the DNA damage repair mechanism, thus increasing the production of interstrand adducts and interstrand DNA crosslinks. Research indicates that this effect was more pronounced following multiple cycles of co-treatments with up to a 1000-fold therapeutic difference in cisplatin/antibody treatment and 200-fold in doxorubicin/antibody treatment. Moreover, there have been reports of additive interactions and even antagonism with other drugs as revealed by the antagonistic interaction between trastuzumab and 5-fluorouracil. These may be attributed to alterations in cell cycle distribution, intracellular pharmacological effects, or alterations in the enzymatic activity responsible for 5-fluorouracil conversion (95,96).

Another well-known mechanism is chemosensitization which is displayed in a study about the combination of ofatumumab and bendamustine for the treatment of chronic lymphocytic leukemia because of its synergistic nature. Since ofatumumab can induce caspase activation, it may be responsible for the observed chemosensitization. The results of the study indicate that the combination of ofatumumab with chemotherapy demonstrated superior tumor growth inhibition (96%) and tumor growth delay (42%), as compared with ofatumumab alone (16% and 14%, respectively) (97).

Regarding other mechanisms that lead to BDI, several studies have evidenced that the coadministration of infliximab with azathioprine for the treatment of inflammatory diseases, results in an increased concentration of the active metabolite 6-thioguanine nucleotides. Although infliximab does not alter the activity of the enzymes involved in the transformation of the pro drug azathioprine, this mAb is capable of elevating the blood levels of the active metabolite through an unidentified mechanism. In a distinct study, the combination of palivizumab and triamcinolone for respiratory conditions was able overcome the immunosuppressive effects of the glucocorticoids, leading to fewer adverse effects and a reduced rebound effect (98,99).

The majority of BDIs appears to improve the efficacy of chemotherapeutic agents. Nevertheless there is an increased incidence of new adverse events associated with these drugs, which may have implications for patient care and safety. For example, the administration of trastuzumab results in increased sensitivity of cardiac cells to cardiotoxic agents due to the downregulation of human epidermal growth factor receptor 2 (HER2). The etiology of this

toxicity may be attributed to alterations in myocardial gene expression, particularly those genes that are essential for heart development. Doxorubicin metabolites are elevated in the presence of trastuzumab, although the measured concentrations are challenging to interpret in a clinical context. In comparison, concurrent administration of other antineoplastic agents, including carboplatin, capecitabin, or docetaxel, does not seem to elevate the risk of cardiotoxic adverse effects (100,101).

4.9.1.2. Impact on CYP Metabolism

The modulation of CYP450 isoenzyme expression is a process that is not exclusively attributed to chemical drugs. This phenomenon has been well-documented in the context of disease-DDIs, including those involving inflammation, infection, and cancer. It is likely that this effect results from the release of proinflammatory cytokines. This means that a TP capable of altering the concentration of these cytokines may impact directly or indirectly the metabolism of SMDs (102).

Basiliximab is among the most studied mAb, with a number of studies reporting its particular PK/PD properties as well its interactions with SMDs. Basiliximab is a chimeric anti-CD25 mAb with affinity for the IL-2 receptor similar to that of IL-2. It competes effectively with IL-2 and inhibits IL-2–driven proliferative responses to antigens, reducing in this way acute organ rejections. IL-2 is known to reduce the expression of several CYP450 isoenzymes in vitro, including CYP1A2, CYP-2C, CYP-2E1, and CYP-3A4, and therefore, coadministration of basiliximab with substrates that are metabolized by these enzymes may potentially result in significant BDIs. The observed increase in the concentrations of cyclosporine and tacrolimus in patients treated with basiliximab by 12% and 62%, respectively, may potentially be explained by this mechanism. Another example is muromonab (CD3 receptor antibody) that co-administered with cyclosporine also increases its serum concentrations (20,103,104).

An investigation on the safety of imatinib combined with increasing doses of aldesleukin (recombinant analog of interleukin-2) in patients affected by refractory advanced solid tumors showed that the co-administration of IL-2 increases the systemic exposure of patients to imatinib and its main metabolite, CGP74588. The Cmax and AUC of imatinib and CGP74588 were significantly increased by 49 and 61%. In addition to IL-2's ability to limit the enzymatic activity of CYP450, this IL is also able to affect plasma membrane transporters,

hence leading to increased efflux of some drugs. These PK modifications may partly be explained by decreased P-glycoprotein expression (105).

Tocilizumab shows a similar mechanism, only this time involving the proinflammatory cytokine IL-6 responsible for the suppression of CYP450 isoenzyme expression. The coadministration of tocilizumab normalizes the expression of CYP1A2, CYP-2C9, CYP-2D6, CYP-2E1, and CYP-3A, overcoming the effects of serum IL-6. Another mAb with similar indications and outcomes is adalimumab. A study shows that adalimumab can decrease the levels of TNF-α in patients with inflammatory diseases thus removing the inhibitory effect of TNF-α on the expression of CYP450 isoenzymes, increasing the clearance of drugs metabolized through this pathway, like duloxetine and pregabalin (106).

4.9.2. Biologics as Victims of Biologic-Drug Interactions

SMDs lack the capacity to alter complex biological processes, such as fluid-phase endocytosis, phagocytosis, and catabolism. However, in regard to the current understanding of the clearance of TPs, which encompasses proteolytic catabolism, salvage by the FcRn, and receptor-mediated clearance, some drugs may cause BDDs through alterations in receptor expression and even interference with immune regulation (17).

4.9.2.1. Examples of Immunogenicity

mAbs are a crucial asset for human health and modern medicine, however, the repeated administration of mAbs can be highly immunogenic. It is well established that drug immunogenicity manifests itself in the generation of ADAs and that some mAbs show immunogenicity in up to 70% of patients. The alteration of a drug's PK and PD properties by ADAs can result in a reduction in drug efficacy and, in more severe cases, ADAs may neutralize the drug's therapeutic effects or cause severe adverse events to the patient. While there are clear indications that more humanized mAbs are less immunogenic, the issue persists as all currently available mAbs demonstrate some level of immunogenicity (107).

Adalimumab was the first fully humanized recombinant mAb. Nevertheless, it has been observed that ADAs may develop in 20-38% of patients undergoing monotherapy with this mAb. The concomitant administration of MTX has been found to reduce the incidence of ADAs in patients to a rate of between 7% and 12% and the clearance of ADAs has been proved to

decrease significantly following multiple dosages. These results are in alignment with a reduction in the immunogenic response. In contrast to adalimumab, infliximab is a mouse-human chimeric mAb, with an ADA rate of 24% to 75% in monotherapy. When co-administered with MTX, ADA development is reduced to 43-46%. Another study reported similar results and attributed the significant decrease in infliximab clearance to the immunosuppressive effect of MTX, as it can reduce both the ADA concentration and the generation of ADA to infliximab. It was also shown that azathioprine and 5-mercaptopurine have the same properties of MTX. Despite the immunosuppressive effects of these agents, the ability to reduce the immunogenic response to infliximab is not a class-specific property. For instance, cyclosporine and sulfasalazine do not produce any pharmacological benefit when used with infliximab (108–110).

Two additional TPs, certolizumab pegol and golimumab exhibited disparate PK profiles when administered concomitantly with specific mAbs. The addition of PEG to certolizumab pegol results in an increase in the half-life as well a reduction in the ADA to 7% whereas the rate of ADAs decreased by 75% with MTX. Nevertheless, the utilization of PEGylated proteins increases the probability of developing anti-PEG antibodies. In the case of golimumab, the development of ADAs was observed in 8% of cases with monotherapy, as opposed to 3% with MTX therapy, accompanied by a 36% reduction in clearance (111,112).

Recombinant human erythropoietin (epoetin) is used in the therapy of anemia of patients undergoing hemodialysis. There are rare cases of patients undergoing this treatment which develop pure red cell aplasia caused by antibody to erythropoietin. It was reported that administration of cyclosporine, along with hemodialysis lead to a graduate decrease in the antibody level, representing therefore a DDI of potential clinical importance in cases where ADAS are formed (113).

4.9.2.2. Effect on FcR Expression

In general, IgG-based TPs have half-lives of approximately 21 days. As mentioned before, a critical factor contributing to the observed poor clearance and long half-life is the protection offered by FcRn. The binding of a mAb to the above receptor prevents its degradation by impeding its trafficking into the lysosome, thereby promoting the recirculation of the mAb. Any modification to the FcRn pathway may have a profound impact on the PK of mAbs (77).

The most likely mechanism for the reduction of ADA against adalimumab is the impact of MTX on the immunogenicity of adalimumab. An alternative hypothesis is that MTX may suppress CD64 (e.g., FcγRI) expression on monocytes but not FcRn, like other immunosuppressive drugs. A study indicates a correlation between the decreased expression of CD64 and the markedly reduced clearance of adalimumab when MTX was administered weekly. The same outcome was obtained with the administration of azathioprine and 5-mercaptopurine. Fusion proteins, such as etanercept and abatacept, exhibit a similar affinity to FcγR as antibodies, yet no interaction has been reported between these and immunosuppressive drugs. Due to their reduced FcRn affinity, these TPs have shorter half-lives which may impair the efficacy of MTX on FcγR, thus reducing the impact on clearance (114,115).

While dedicated DI studies focused on FcRn are not known to date, the label of the recently approved FcRn blocker efgartigimod recommends close monitoring of the effectiveness of concomitantly administrated antibodies or antibody derivatives and the discontinuation of efgartigimod in case the long-term use of such medications is essential for patient care (28).

4.9.2.3. Effect on Biologic Receptor Expression

mAbs can exert their pharmacological effects through a variety of mechanisms such as: antigen neutralization; antigen modulation; toxin delivery and receptor activation. When mAbs target soluble antigens, they typically exhibit linear PK over a broad dose range, displaying a clearance that is independent of the administered dose. On the other hand, when they bind to membrane receptors, non-linear PK is typically observed. Accordingly, only when the non-linear component of clearance reaches saturation that clearance becomes dose independent. Therefore, any alteration of the target proteins imposed by SMDs can potentially modify the clearance of mAbs and, subsequently, their efficacy in disease modulation (116,117).

The anti-CD20 mAb rituximab is capable of inducing complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC). Concerning the first, the expression of both CD55 and CD59 represents a determining factor in susceptibility to lysis. By reducing the expression of CD55, fludarabine is capable of influencing complement-dependent cytotoxicity by incorporating into mRNA, inducing premature chain termination, thus impairing the expression of proteins. It is proposed that this interaction is crucial for overcoming rituximab resistance associated with CD55 and CD59 overexpression. A recently discovered drug, ibrutinib, an irreversible Bruton's tyrosine kinase (BTK) inhibitor, has been

found to inhibit ADCC, thereby antagonizing the effect of rituximab. In order for the ADCC mechanism of rituximab to be effective, stimulation of FcR is required. Despite this, given the homology between BTK and interleukin-2 inducible tyrosine kinase (ITK), ibrutinib binds in a non-specific manner to ITK, decreasing the ADCC of rituximab. Consequently, an optimized schedule or selective BTK inhibitors are essential to maintain its activity (116,118).

Modification of a target receptor represents another method of interference with mAbs. A study reported that the administration of acetylsalicylic acid prior to the administration of abciximab results in the acetylation of the glycoprotein IIb/IIIa receptor, which is the target of abciximab. In these circumstances, the bleeding time exhibited a 40% increase, thereby demonstrating a synergistic effect between the two drugs. Another paper demonstrated a synergistic effect between abciximab and clopidogrel, an antiplatelet agent. Similarly, ticlopidine has shown interactions of the same nature with this mAb. Considering the treatment alone, this SMD led to a 31% reduction in the total amount of platelets deposited, thereby prolonging the inhibitory effect on mural thrombosis formation (119,120).

A key event in overcoming the immunosuppressive microenvironment of some cancers is the activation of the immune system. Catumaxomab, a trifunctional bispecific mAb, represents a novel class of immunotherapy. When administered in conjunction with chemotherapeutic agents, such as cisplatin or oxaliplatin, immune activation is more pronounced, potentially leading to an increased susceptibility of tumor cells to chemotherapy. The synergistic effects result in a combination of direct cell-mediated killing and the release of cytokines. Despite this, in vivo and in vitro studies have indicated that some drugs may suppress cytokine release. For example, glucocorticoids exert an antiproliferative effect by inhibiting cytokine expression and stimulating the production of the NF-κB inhibitor IκB. A study indicated that the administration of lipopolysaccharides and dexamethasone resulted in a significant suppression of cytokine expression. Notably, even in the presence of a high concentration of catumaxomab, there was a dose-dependent reduction in cytokine levels. Alternatively, non-glucocorticoid steroids do not influence cytokine synthesis (121,122).

An additional immunosuppressive interaction may be observed with nivolumab and pembrolizumab, both of which are immune stimulatory monoclonal antibodies. Given their capacity to prevent T cell inhibition, induce cytokine release and promote cell-mediated killing, it is possible that similar interaction pathways may occur with corticosteroids. Accordingly, it

is advised that clinicians refrain from administering corticosteroids to patients prior to immunotherapy (123).

4.9.2.4. Impact on CYP Metabolism

As previously discussed, there is substantial scientific literature indicating that mAbs may indirectly influence hepatic clearance as a consequence of their pharmacological properties. In reality, it is unlikely that the PK modulation of the hepatic metabolism of a TP by SMDs will occur. Nevertheless, a single case report regarding the use of brentuximab vedotin has been described. Brentuximab vedotin consists of a human chimeric immunoglobulin G1 antibody directed against CD30 that is covalently linked to the potent microtubule-disrupting agent MMAE by a protease-cleavable linker. The binding of brentuximab vedotin to CD30 on the tumor cell membrane triggers a cascade of events that ultimately results in apoptotic death of the CD30-expressing tumor cell. This drug has been shown to have efficacy in the treatment of CD30+ Hodgkin's lymphoma. Despite the antibody portion being metabolized as a protein, it was demonstrated in vivo that the cytotoxic conjugate was metabolized via the CYP3A4 or CYP2D6 pathways. Accordingly, MMAE behaves as an SMD and is susceptible to metabolism based DDIs. A study showed that MMAE exposure was found to be 46% lower in the presence of rifampicin, a CYP450 inducer, and 36% higher in the presence of ketoconazole, a CYP450 inhibitor (124,125).

5.Conclusion

Over the last decades, therapeutic proteins, in particular, antibody-based biotherapeutics, have played an increasingly important role in pharmacotherapy. In addition to this, in some therapeutic areas, such as immune-mediated inflammatory diseases and oncology, therapeutic proteins have fundamentally changed the therapeutic paradigm.

As a result of an expected increase in the coadministration of biotherapeutic agents with established pharmacotherapy regimens, there is an increasing likelihood for the occurrence of clinically relevant drug interactions. TPs, however, have long been perceived to have a very low propensity for DDIs because they are eliminated via catabolic routes, either nonspecific pathways or target-mediated pathways, that are independent from the elimination pathways of small molecules, which are usually eliminated by non-catabolic pathways such as hepatic metabolism via CYP, renal excretion, and biliary excretion.

Despite that, a greater comprehension of the potential DDIs between biologics and SMDs and the mechanisms underlying them has been achieved due to the increase in clinical studies regarding these type of drug interactions. A review of the available data indicates that SMD as a victim is most commonly explained by modulation of CYP enzymes, either by disease states such as infection and inflammation or by drug treatment of the disease state. On the other hand, it is probable that TP-DDIs with mAbs as victims are caused by increased immunogenicity or mAb target modulation through an SMD or another TP.

Although the understanding of the mechanisms behind DDIs with biologics has increased, prospective quantitative predictions still need experimental investigation and verification. In contrast to SMDs, the lack of predictive in vitro assay systems representative of the disease state, a limited understanding of disease biology or the mechanistic action of the TP largely contribute to this discrepancy. The latter makes the generation and application of PD and PK models challenging. As the number of emerging therapeutic modalities used in clinical practice, particularly those that can cause significant release of inflammatory cytokines such as immune-stimulating protein and chimeric antigen receptor T (CAR-T) cell therapy, increases, it is possible that some may have an impact on the metabolism of SMD and other modalities. Further research is required to determine the extent to which DDIs will have a clinical impact.

Following this, the scientific methodologies employed in the assessment of BDIs are undergoing significant evolution at both the regulatory and industry levels. A number of guidelines have been recently published with the aim of guiding researchers in their studies thus

facilitating the production of more comparable studies and the delivery of precise and useful information. In the present review, a large amount of information was presented regarding therapeutic proteins DDIs, including specific examples extracted from a variety of clinical studies. However, information on the outcomes of the treatment with SMDs and biologics in patients is scarce, calling for more comprehensive investigation of this topic.

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Appendix

A1. Therapeutic proteins and small molecule drugs

Table 2. List of BDIs between TPs and SMDs. The respective mechanism and pre-clinical/clinical benefits are presented when known

Therapeutic Protein	Interacting Drug (ID)	Effect of TP on ID	Effect of ID on TP	Pre-clinical/clinical benefit	Evidence	Ref.
Abciximab	Acetylsalicylic acid	NA	GPIIb/IIIa acetylation	↑Bleeding time by 40%	3	(120)
	Clopidogrel	NA	↑Antiaggregatory effects of A	↔	2	(120)
	Ticlopidine	NA	Prolonged reduction in mural thrombus formation	↓Platelets deposit by 31%	1	(120)
Adalimumab	Azathioprine or 6-mercaptopurine	NA	↓ADAs formation	↓Clearance	2	(108)
	Cyclosporine or Sulfasalazine	NA	↔	↔	1	(108)
	Duloxetine	CYP450 induction	NA	↓Concentration	1	(106)
	Methotrexate	↔	↓ADAs formation	↓Clearance by 29% (SD) or 44% (MD)	1	(115)
	Pregabalin	CYP450 induction	NA	↓Concentration	1	(106)
Aflibercept	5-FU + irinotecan	Improve chemotherapy delivery	↔	↓Concentration	3	(91)
	Docetaxel ₸	Antiangiogenic synergism	NA	↑PFS by 32%, ORR by 44% and OS by 11%	2	(91)
	Paclitaxel ₸	Antiangiogenic synergism	NA	↑PFS by 21% and ORR by 62%	0	(91)
Albiglutide	Digoxin	↔	↔	↔	3	(45)
	Simvastatin	Slowed gastric emptying	NA	↓AUC by 40%	3	(45)
	Warfarin	↔	↔	↔	3	(45)

Aldesleukin	Imatinib	↓ Intestinal P-gp	NA	↑AUC by 61% and Cmax by 49%	3	(105)
Alirocumab	Statins	NA	Upregulation of PCSK9 concentrations	↓Concentration	2	(73)
Basiliximab	Azathioprine	NA	Affect the expression of A receptors	↓Clearance by 22%	3	(103)
	Cyclosporine	CYP450 inhibition	NA	↑Concentration	3	(103)
	Mycophenolate mofetil	NA	Affect the expression of A receptors	↓Clearance by 51%	3	(103)
	Tacrolimus	CYP450 inhibition	NA	Trough TAC blood levels by 63%	3	(104)
Belatacept	Mycophenolate mofetil	↔	NA	↑AUC0-12 by 40%	0	(45)
Bevacizumab	Carboplatin	Improve chemotherapy delivery	NA	↑OS by 44%	0	(90)
	Cisplatin	Enhance sensibility	↔	Tumor growth inhibition	0	(90)
	Cyclophosphamide	Enhance sensibility	NA	Tumor growth inhibition by 32%	0	(89)
	RO5323441	↔	NA	↓Clearance by 53%	0	(75)
	Topotecan	Improve chemotherapy delivery	NA	↑Concentration by 6.5-fold	0	(90)
Blinatumomab	Busulfan	CYP450 inhibition	NA	↓Clearance	1	(63)
Brentuximab vedotin	Ketoconazole	NA	CYP450 inhibition	↑MMAE exposure by 34	3	(86)
	Midazolam	↔	NA	Careful monitorization	3	(86)
	Rifampicin	NA	CYP450 inhibition	↓MMAE exposure by 46%	3	(86)
Brodalumab	Midazolam	↔	NA	↑Exposure by 61%	2	(58)
Catumaxomab	Cisplatin	NA	Immunesensitization	↓EC50 by 52%	3	(121)
	Glucocorticoids	NA	Inhibit synthesis of cytokines	↓Carcinoma cell killing	3	(121)
Certolizumab pegol	Azathioprine or 6-mercaptopurine	NA	↓ADAs formation	↓Clearance	–	(111)
	Cyclosporine or Sulfasalazine	NA	↔	↔	–	(111)
Cetuximab	5-Fluorouracil	DNA repair inhibition	↔	Combination index below 1 (synergistic)	0	(92)

	Carboplatin	DNA repair inhibition	↔	Combination index below 1 (synergistic)	0	(92)
	Cisplatin	DNA repair inhibition	↔	↑The extent of apoptotic cell death up to 11.6 fold	0	(94)
	Docetaxel	DNA repair inhibition	↔	Combination index below 1 (synergistic)	0	(92)
	Irinotecan	DNA repair inhibition	↔	↑ORR by 53%, PFS by 67% and OR by 20%	2	(93)
	Oxaliplatin	DNA repair inhibition	↔	↓IC_{50} by 41%	0	(92)
Dulaglutide	Sitagliptin	NA	DPP-4 enzyme metabolizes the target GLP-1	↑AUC by 38%	1	(45)
Epoetin	Cyclosporine	NA	↓ADAs formation	Concentration management	1	(113)
Etanercept	DMARDs	NA	↔	↔	–	(114)
	Methotrexate	NA	↔	↔	3	(114)
	NSAIDs	NA	↔	↔	3	(114)
Evolocumab	Statins	NA	Upregulation of PCSK9 concentrations	↓Concentration by 20%	2	(71)
Exenatide	Acetaminophen	Slowed gastric emptying	NA	↓Concentration by 11%-24%	3	(80)
Glucarpidase	Leucovorin	Hydrolysis	NA	↓Concentration by 33%	3	(24)
	Methotrexate	Hydrolysis	NA	↓Concentration	3	(24)
Golimumab	Corticosteroids	NA	↔	↔	3	(68)
	Methotrexate	NA	↓ADAs formation	↓Clearance by 36%	3	(68)
IFN- α2	Theophylline	CYP1A2 inhibition	NA	↓Clearance 20%	3	(20)
	Gemcitabine	↑ Cell sensitivity	NA	Tumor growth inhibition	0	(47)
	Mytomicine-C	↑ Cell sensitivity	NA	↑Cell death	0	(46)
Infliximab	6-mercaptopurine	NA	↓ADAs formation	↓Clearance	3	(98)
	Azathioprine	Thiopurine methyltransferase inhibition	↓ADAs formation	↑6-tg concentration by 38% || ↓Clearance	3 || 3	(98)
	Cyclosporine or Sulfasalazine	NA	↔	↔	2	(98,109)

	Methotrexate	NA	↓ADAs formation	↓IMM by 73%	3	(109)
Inotuzumab ozogamicin	Rituximab	NA	Depletion of B cells	↓Clearance by 16%	2	(24)
Muromonab	Cyclosporine	CYP450 inhibition	NA	↑Concentration	3	(20)
Necitumumab	Gemcitabine	Antiangiogenic synergism	NA	↑Concentration	3	(20)
Nivolumab	Corticosteroids	NA	↓Immune response	Suppress the recruitment of T cells	0	(123)
	Immunosuppressants	NA	↓Immune response	Suppress the recruitment of T cells	0	(123)
Ofatumumab	Bendamustine	Chemosensitization	↔	↑TGI by 91% and ↑TGD by 67%	0	(97)
Palifermin	Heparin	NA	Binding to proteoglycans	↓Clearance by 70%–80%	3	(83)
Palivizumab	Corticosteroids	Overcome the immunosuppressive effect	NA	↑Peribronchiolitis score by 83%	0	(99)
Panitumumab	5-Fluorouracil + Irinotecan	DNA repair inhibition	↔	↑PFS by 19% and ORR by 32%	2	(96)
	5-Fluorouracil + Oxaliplatin	DNA repair inhibition	↔	↑PFS by 17%	2	(96)
PEG-IFN α2a	Theophylline	CYP1A2 inhibition	NA	↓Clearance by 20%	3	(20)
	Methadone	CYP3A4 inhibition	NA	↑Concentration by 10-15%	3	(20)
PEG- IFN α2b	Caffeine	CYP1A2 inhibition	NA	↑AUC by 18–39%	3	(45)
	Desipramine	CYP2D6 inhibition	NA	↑Concentration by 30%	3	(45)
	Dextromethorphan	CYP2D6 inhibition	NA	↑Concentration by 103%	3	(45)
Pembrolizumab	Corticosteroids	NA	↓Immune response	Suppress the recruitment of T cells	0	(123)
	Immunosuppressants	NA	↓Immune response	Suppress the recruitment of T cells	0	(123)
Rituximab	Cyclophosphamide	↔	↔	↔	3	(116)
	Dasatinib	NA	Downstream the B-cell receptor	↔	3	(116)
	Fludarabine + Cyclophosphamide	NA	Downregulation of CD55 complement inhibited protein	↑PFS by 33%	3	(116)
	Ibrutinib ¥	NA	Downstream the B-cell receptor	↔	3	(118)

Sarilumab	Simvastatin	CYP3A4 induction	NA	↓Concentration by 55%	3	(48)
Sirukumab	Midazolam	CYP3A4 induction	NA	↓Concentration by 35%	3	(49)
	Omeprazole	CYP2C19 induction	NA	↓Concentration by 41%	3	(49)
	S-warfarin	CYP2C9 induction	NA	↓Concentration by 19%	3	(49)
	Caffeine	↔	NA	↑Concentration	3	(49)
Tocilizumab	Cyclosporine	CYP450 induction	↔	↓Concentration	2	(50)
	Simvastatin	CYP3A4 induction	NA	↓Concentration by 43%	3	(50)
	Omeprazole	CYP2C19 induction	NA	↓Concentration by 28%	3	(45)
Trastuzumab	5-Fluorouracil	Antagonistic effect	↔	No tumor size reduction	0	(95)
	Capecitabine	↔ || Antagonistic effect	NA	↔ || no tumor size reduction	3	(101)
	Carboplatin	DNA repair inhibition	NA	↓Colony count by 75%	0	(95)
	Cisplatin	↔	↔	↔	3	(95)
	Cyclophosphamide	↔ || DNA repair inhibition	NA	↔ || ↓ tumor volume by 300%	3||0	(95)
	Docetaxel	DNA repair inhibition	↔	↑OS by 27% and ORR by 51%	3	(101)
	Doxorubicin	↔	↔	↔	3	(100)
	Epirubicin	↔	NA	↔	3	(95)
	Gemcitabine	Synergistic Effect	↔	Combination index <1	3	(95)
	Paclitaxel	↔	↔	↔	3	(88)
	Vinorelbine	Synergistic effect	NA	Combination index <1	0	(95)

Controversial data: ↔; Animal or in vitro studies with limited predictive value for the human in vivo situation: 0; Incomplete, published reports: 1; Well documented, published reports: 2; Controlled, published interaction studies in humans: 3; Tioguanine: 6-tg; ADA: Antibody-drug Antibody; ASA: Acetyl Salicylic Acid; CR: Clinical Response; Cyc: Cyclosporine; CYP: Cytochrome; DMARD: Disease-modifying

Antirheumatic Drug; MD: Multiple Dose; MMAE: Monomethyl Auristatin E; NA: Not Applicable; NSAID; Non-steroidal Anti-inflammatory Drug; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-free Survival; P-gp: P-Glycoprotein; SD: Single Dose; TAC: Tacrolimus