DRUG–DRUG INTERACTIONS FOR THERAPEUTIC BIOLOGICS
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PREFACE

In the past two decades we have seen tremendous progress in the area of therapeutic biologics. With more and more therapeutic proteins being used in poly-pharmacy settings and the potential toxicity risk of drug-drug interactions, there is during drug development a need for a thorough review of potential drug-drug interactions involving therapeutic biologics. However, literature references on this topic have so far been scarce. Thus, we feel the scientific community would benefit from a systemic presentation of the current status of knowledge on this topic. The proposed book project is intended to fill this void.

The book is expected to greatly benefit scientists and researchers in the pharmaceutical and biotech industry as well as academia who are involved in drug development for both therapeutic biologics and traditional small molecule drugs. The expected audience will be pharmaceutical and biotech scientists, clinical pharmacologists, medicinal chemists, and toxicologists. Scientists and clinicians in pharmaceutical and biotech industry can utilize the book as a resource to strategize, plan and implement drug-drug interaction assessments involving therapeutic biologics. Academic pharmacokinetics, pharmacology, and biochemistry scientists working on mechanisms for biologic drug-drug interactions will also find this book very useful as a compilation of the current state-of-the-art.

The current book focuses on both theoretical and practical aspects of drug-drug interaction assessments for therapeutic biologics in drug development. We are fortunate that many of the experts and opinion leaders from various areas of therapeutic biologics drug development and drug-drug interactions have participated in the writing of this book, and we are indebted to them for their time and dedication to participate in this project. The content includes topics such as drug-drug interaction risks (both theoretical and observed) in combination with small molecules and with
other biologics, pharmacokinetic drug-drug interactions, pharmacodynamic drug-
drug interactions, utility of *in vitro* methods in drug-drug interaction assessment
and prediction, modeling-independent and modeling-based methods to assess
potential drug-drug interactions, risk-based strategies for evaluating biologic drug-
drug interactions, strategies to minimize drug-drug interaction risk and mitigate
toxic interactions, and regulatory perspectives on biologic drug-drug interaction
assessments.

Though there are several books covering drug-drug interactions for conventional
small molecules, a book that is comprehensive with all the above topics for biother-
apeutics is not currently available. Thus, we are convinced that that textbook
addresses a currently unmet need in drug development sciences and we are confi-
dent that the scientific community will benefit from the experience and expertise of
the contributors to this book project.

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1.1 INTRODUCTION

Over the last three decades, therapeutic proteins, in particular, antibody-based biotherapeutics, have played an increasingly important role in pharmacotherapy, and in some therapeutic areas, such as immune-mediated inflammatory diseases (IMIDs) and oncology, therapeutic proteins have fundamentally changed the therapeutic paradigm. Therapeutic proteins have also presented enormous commercial potential. For example, the top 10 antibody-based biotherapeutics accounted for around $50 billion of worldwide sales in 2011.\textsuperscript{1} The majority of these are either in IMID (adalimumab, etanercept, infliximab, rituximab, natalizumab, omalizumab) or in oncology (rituximab, bevacizumab, trastuzumab, cetuximab) therapeutic areas. Hundreds of investigational antibody-based and other protein therapeutics are currently under development at different stages, spanning discovery to phase III clinical investigations.

Owing to 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. Therapeutic proteins, however, have long been perceived to have a very low propensity for drug–drug interactions 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 noncatabolic pathways such as hepatic metabolism via cytochrome P450 (CYP), renal excretion, and biliary excretion. Though it has been known for decades that some cytokines such as interferons, tumor necrosis factor α (TNF-α), and
interleukin 6 (IL-6) can down-regulate CYPs, very few drug–drug interactions had been reported for biotherapeutics until 2007, when two review articles containing examples of drug interactions involving therapeutic proteins were published. The majority of reported drug interactions associated with therapeutic proteins seem to be indirect; however, a mechanistic understanding for many of the observed interactions is still lacking.

1.2 SCIENTIFIC/REGULATORY LANDSCAPE OF THERAPEUTIC PROTEIN–DRUG INTERACTIONS

To help assess the common practice of evaluating therapeutic protein–drug interactions across the biotech/pharma industry and to shed some light on how and when a sensible therapeutic protein–drug interaction assessment strategy should be incorporated into therapeutic protein drug development, a survey was conducted within the Biotechnology Industry Organization (BIO) member companies in 2010. It is not surprising that a majority of the responder companies did not have internal strategies for evaluating therapeutic protein–drug interactions at the time of the survey. Nevertheless, the most favored approach employed to address potential drug–drug interactions of therapeutic proteins at that time was a tailored and integrated (i.e., case-by-case) strategy that addressed the possibility of the therapeutic protein acting as either an initiator (perpetrator) or target (victim) of the interaction. Despite the fact that many of the companies responding to the survey reported drug–drug interactions involving therapeutic proteins, the majority of the clinical therapeutic protein–drug interactions studied did not warrant dose adjustment. In other words, most of the observed clinical therapeutic protein–drug interactions did not reach a clinically significant level. Routine in vitro screening and preclinical drug–drug interaction studies were not widely used for the evaluation of therapeutic proteins. For clinical development, dedicated clinical pharmacology drug–drug interaction studies were the most frequently used methodology, followed by population pharmacokinetics-based and clinical cocktail approaches.

The BIO survey results indicated that there was a pressing need to have a science-driven and risk-based assessment strategy for therapeutic protein–drug interactions (TP-DIs). A closer collaboration among scientists from the biotech/pharma industry, regulatory agencies, and academia appeared to be essential in reaching that goal. As a result, a TP-DI steering committee from industry, the FDA, and academia was founded in 2009 to address this challenge. The initial scope of this committee was focused only on pharmacokinetics (PK) and metabolism-based drug–drug interactions for the major classes of therapeutic proteins, including monoclonal antibodies, fusion proteins, cytokines (excluding antibody–drug conjugates). The committee intended to investigate the potential for therapeutic proteins to interact, either as initiators or targets, with drugs that are metabolized via CYP enzyme pathways. Two major focus areas the committee concentrated on were (1) to critically assess standard in vitro screening techniques and methodologies
(e.g., for cytokine-related drug–drug and drug–disease interactions) and (2) to provide guidance for study designs with consideration of specific disease area (e.g., oncology) issues and timings.

Several scientific knowledge gaps were identified from a 2010 American Association of Pharmaceutical Scientists (AAPS) workshop on Strategies to Address Therapeutic Protein-Drug Interactions during Clinical Development. One gap was associated with the relevance of in vitro systems to assess potential therapeutic protein–drug interactions, and another gap was a lack of best practices for using population PK-based approaches to assess potential therapeutic protein–drug interactions. The steering committee also identified similar gaps and consequently formed two working groups to specifically tackle them.

During the same time period, scientists from the FDA published two important review articles on TP-DI, but these were mostly from a regulatory perspective. In 2012, a draft of a new drug–drug interaction guidance document was made available by the FDA for public comments. That draft included a dedicated section on therapeutic protein–drug interaction to address specifically the newly emerging area of drug–drug interactions with therapeutic proteins.

The Workshop on Recent Advances in the Investigation of Therapeutic Protein Drug-Drug Interactions: Preclinical and Clinical Approaches was held on June 4–5, 2012. The workshop, co-sponsored by the FDA Office of Clinical Pharmacology and the Drug Metabolism and Clinical Pharmacology Leadership Group of the IQ Consortium, was intended to facilitate a better understanding of the current science, investigative approaches, knowledge gaps, and regulatory requirements related to the evaluation of therapeutic protein–drug interactions. The workshop also provided an opportunity to discuss the current views from the two (in vitro and population PK approaches) therapeutic protein–drug interaction working groups. The proceedings from this workshop are being compiled with the intent of issuing white papers in these subject areas. It is anticipated that the recommendations from both white papers will soon provide pharmaceutical scientists with sensible and scientifically sound best practices and an assessment framework for using in vitro and population PK-based approaches for evaluating therapeutic protein–drug interactions.

Our current understanding of the mechanisms of many therapeutic protein–drug interactions is still in its infancy. Much basic research needs to be conducted to verify several existing hypotheses related to therapeutic protein–drug interactions. Continued close collaborations among fellow scientists in industry, academia, and regulatory agencies will be vital to generate more plausible mechanistic hypotheses and collectively address the many challenges in this area. Through these collaborative efforts, the knowledge base on therapeutic protein–drug interactions will likely be largely expanded in the near future, and it is hoped and anticipated that over the next decade a similar level of mechanistic understanding and systemic assessment methodology will be achieved and developed for drug interactions with protein therapeutics as it has been established in the last two decades for small molecule drugs. The journey toward that goal has just begun.
REFERENCES

CHAPTER 2

PHARMACOKINETIC AND PHARMACODYNAMIC-BASED DRUG INTERACTIONS FOR THERAPEUTIC PROTEINS

DAN LU, SANDHYA GIRISH, FRANK-PETER THEIL, and AMITA JOSHI

2.1 INTRODUCTION

Therapeutic proteins (TPs) are protein products manufactured for pharmaceutical use. They include monoclonal antibodies (mAbs), antigen-binding fragments, antibody–drug conjugates (ADCs), cytokines, enzymes, growth factors, and miscellaneous proteins (e.g., fusion proteins and recombinant proteins). The development of therapeutic biologics, including TPs, is increasingly important in the pharmaceutical industry.\(^1\) To achieve greater clinical benefits, TPs are often being combined with other TPs and small molecule drugs (SMDs). Whether drug interactions (DI) in combination therapy result in an undesirable impact on efficacy and safety needs evaluation. To date, for the observed therapeutic protein–drug interactions (TP-DI) that affect the exposure of TPs, only a modest change in exposure is observed and no impact on safety or efficacy has been documented, suggesting a limited clinical relevance.\(^2\) This might be because most TPs have a relatively large therapeutic range compared to the majority of traditional SMDs. However, TP-DIs that affect the exposure of some drugs with a narrow therapeutic range (NTR), such as some SMDs and ADCs, may have an impact on efficacy and safety. The TP-DIs that result in enhanced toxicity due to undesirable pharmacodynamic (PD) interactions without a direct impact on exposures may also be clinically relevant. Thus the evaluation of TP-DIs is an important and evolving topic for the development of TPs in combination with other drugs.

This chapter reviews the major absorption, distribution, metabolism, and excretion (ADME) pathways of TPs, summarizes the potential mechanisms of
pharmacokinetic (PK) and PD-based TP-DIs, and recommends a question-based TP-DI risk assessment strategy during clinical development. The DIs for some nonprotein biologics such as nucleic acid–based derivatives are reviewed in other chapters.

2.2 DISTRIBUTION, CATABOLISM/METABOLISM, AND EXCRETION MECHANISMS OF THERAPEUTIC PROTEINS

ADME processes determine the PK properties of SMDs and TPs. In drug combinations, one drug may impact the ADME processes of another drug, leading to a change in its exposure. For SMDs, absorption is mainly mediated by the solubility and permeability of a SMD and its interaction with transporters. Distribution of SMDs is mediated by several key processes, such as blood perfusion, permeability across membrane barriers, and nonspecific binding. Metabolism of SMDs is mainly mediated by cytochrome P450 (CYP) and non-CYP enzymes (such as N-acetyl and glucuronyl transferase). Excretion of SMDs mainly occurs via renal filtration or renal and biliary secretion mediated by transporters. Figure 2-1a depicts the typical clearance pathways for SMDs.

For TPs, ADME processes are different from SMDs. Owing to high gastrointestinal enzyme activity and low permeability through the gastrointestinal mucosa, most TPs are not therapeutically active on oral administration. Consequently other routes of administration, such as intravenous, subcutaneous, and intramuscular routes of injection are used for TPs. For subcutaneous injections of TPs with large molecular weight, convective transport across local lymphatic vessels is the major mechanism of absorption from the injection site. The processes of distribution, catabolism, and excretion of TPs are reviewed in detail in this chapter. As illustrated in Figure 2-1b, the catabolism of TPs are mainly mediated by nonspecific clearance pathways. Target-mediated drug disposition (TMDD) and immunogenicity-mediated pathways also play roles in the clearance of some TPs. ADCs belong to a more complex group of TPs, made up of both a mAb and a small molecule cytotoxic agent. Their PK properties are also reviewed here.

FIGURE 2-1  Comparison of clearance mechanisms of (a) a SMD and (b) a TP. CYP: cytochrome P450; FcRn: neonatal Fc receptor; SMD: small molecule drug; TMDD: target-mediated drug disposition; TP: therapeutic protein.
2.2.1 Distribution of Therapeutic Proteins

Distinct from most SMDs that widely distribute to various tissues and organs after administration, distribution of mAbs and large TPs is usually confined by their large size; consequently the molecules have limited mobility through membranes. This often results in a relatively small volume of distribution. The volume of distribution of mAbs and ADCs at steady state is often a low multiple (1 to 2) of physiologic plasma volume (approximately 50 mL/kg). This is similar to the distribution characteristics for an endogenous immunoglobulin G (IgG). The distribution of TPs outside the systemic circulation is mediated by limited interstitial penetration in various organs, convection-dominated lymphatic drainage, specific and nonspecific binding to peripheral tissues, and target-mediated cellular uptake. For TPs with relatively low molecular mass, preclinical study results have demonstrated better tissue penetration. Unlike SMDs, transporters usually do not play a role in the distribution of large TPs.

2.2.2 Catabolism of Therapeutic Proteins

Most TPs are mainly catabolized by proteolytic degradation in cellular lysosomes through nonspecific pathways, resulting in peptides and amino acids that are reutilized for protein synthesis. It is generally believed that nonspecific catabolism of TPs may take place predominantly in the lysosomes of endothelial cells and the mononuclear phagocyte system (MPS). TPs, such as mAbs and some fusion proteins containing a fragment crystallizable region (Fc region), interact with neonatal Fc receptors (FcRn) similar to endogenous IgGs. In adults, FcRn is primarily expressed in the vascular endothelial cells. FcRn is also detectable on monocytes, tissue macrophages, and dendritic cells. The FcRn-mediated recycling protects IgG type of proteins (e.g., endogenous IgGs, mAbs, and Fc fusion proteins) from proteolytic degradation in lysosomes, consequently delaying their catabolism and prolonging their half-lives compared to other types of proteins that are not rescued by FcRn-mediated recycling. As a result, endogenous IgGs, mAbs, and Fc fusion proteins usually have relatively long half-lives, ranging from several days to weeks. The pathways of nonspecific clearance and FcRn-mediated recycling are typically low-affinity and high-capacity pathways, which are usually nonsaturable at therapeutically relevant doses. For mAbs, relatively constant values of nonspecific clearance are found in each species. In humans, this value is 3–6 mL/day/kg and is affected by multiple pathophysiological and demographical covariates.

In addition to the nonspecific clearance pathways, TMDD may also play a role in the clearance of target-binding proteins (e.g., mAbs, Fc fusion proteins, recombinant proteins). By this mechanism, a TP is cleared from the systemic circulation by binding to its target antigen followed by proteolytic degradation. The target antigens can be cell-surface receptors or soluble antigens. For targets that are cell-surface receptors, a TP is cleared after the TP–antigen complex is internalized and degraded in the lysosomes of target cells or when the TP-opsonized cell engages in immune effector function, which triggers apoptosis of the target cells by
complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity followed by degradation of the TP. For targets that are soluble antigens, a TP is cleared after the TP–antigen complex is eliminated via phagocytosis and proteolysis by endothelial cells and MPS. TMDD is typically a high affinity, low capacity and saturable process. When TMDD plays an important role in TP clearance, the PK parameters of the TP is concentration and dose dependent and may show a time-dependent decrease of clearance if receptor capacity is decreased after repeated treatment. For example, efalizumab\(^9\) and panitumumab\(^10\) show higher clearance at low concentrations and doses in clinical applications. The clearances of gemtuzumab and rituximab decrease after the second dose compared to the first dose, which may result from the decrease of target-mediated clearance after a reduction in target tumor cell number after the first dose of treatment.\(^11\) For most TPs with TMDD involvement, the TMDD pathway is usually more dominant at low doses and low concentrations of the TPs when this pathway is not saturated. At therapeutic doses of these TPs, the therapeutic protein is often in great excess compared to the expression level of the respective target antigen available for binding under equilibrium conditions; consequently, the nonspecific clearance pathways play a dominant role. For these TPs at their prescribing doses (e.g., pertuzumab,\(^12\) bevacizumab,\(^13\) and trastuzumab\(^14\)), changes of target antigen levels generally have a minimal impact on their clearance, and their PK parameters are concentration and dose independent.

The ability of TPs to elicit humoral responses, i.e., immunogenicity, can often modulate the clearance of TPs. The humoral response leads to the formation of antitherapeutic antibodies (ATAs), which may form immunocomplexes with TPs and consequently affect the clearance rates by affecting the binding of a TP to its target or affecting the nonspecific clearance pathways. For example, accelerated clearance of infliximab and adalimumab has been reported after development of ATA in rheumatoid arthritis (RA) patients.\(^15,16\)

### 2.2.3 Excretion of Therapeutic Proteins

Excretion mechanisms for TPs also differ from those for SMDs. Renal clearance is generally negligible when the molecular size of a TP exceeds the cutoff size for renal filtration of approximately 45 kDa.\(^17\) Tubular secretion does not occur to any significant extent for large TPs. The peptides resulting from TP catabolism may be partially reabsorbed in the proximal or distal tubule of the nephron or are further catabolized in kidney. Biliary excretion of TPs has been reported for only some fragment peptides and proteins such as immunoglobulin A and octreotide,\(^6,18\) which are subsequently degraded in the gastrointestinal tract.

### 2.2.4 Pharmacokinetic Properties of Antibody–Drug Conjugates

ADCs, as an emerging class of TPs, have the PK properties of both mAbs and SMDs. ADCs are composed of a potent cytotoxic agent conjugated to a mAb via various types of linkers.\(^19,20\) ADCs bind to their target receptors on the surface of tumor cells. The complexes are internalized and degraded and subsequently release
the cytotoxic agents to kill tumor cells. Usually the PK properties of multiple analytes, such as the conjugate and the unconjugated cytotoxic agent, are assessed after administration of an antibody–drug conjugate.

To date all ADCs are administered intravenously. The distribution of ADCs is similar to their unconjugated mAbs. For example, in a preclinical in vivo study, it was found that trastuzumab emtansine (T-DM1), an ADC for the treatment of human epidermal growth receptor 2 (HER2) positive solid tumors, had similar tissue distribution to that of trastuzumab, the mAb component of T-DM1, indicating that conjugation does not impact the distribution of trastuzumab. ADCs are catabolized by similar pathways as mAbs, including nonspecific proteolytic degradation and TMDD pathways. Immunogenicity may also play a role in ADC clearance.

In addition, the processes of linker chemistry-determined deconjugation in plasma and tissue are also involved in the catabolism and clearance of ADCs. The formation rate of the small molecule cytotoxic component by catabolism of the ADC is usually much slower than the elimination clearance of the small molecule cytotoxic component itself, resulting in formation rate-limited pharmacokinetics. Upon formation, these unconjugated cytotoxic molecules undergo typical clearance pathways of SMDs, such as hepatic metabolism and renal and biliary excretion, as mediated by CYP, non-CYP enzymes, and transporters. The low dose of the SMD component of an ADC and relatively slow formation rate combined with a relatively fast elimination rate of the unconjugated SMD molecules may explain the observed relatively low systemic exposure of the unconjugated cytotoxic agent. For example, the average maximal concentration of the derivative of maytansine (DM1) is \( \sim 5 \text{ ng/mL} \) after the administration of 3.6 mg/kg of T-DM1 every 3 weeks. The average maximal free monomethyl auristatin E (MMAE) concentrations are 5–7 ng/mL after the every-3-week administration of 1.8–2.7 mg/kg of brentuximab vedotin, a MMAE-containing ADC.

### 2.3 MAJOR MECHANISMS OF THERAPEUTIC PROTEIN–DRUG INTERACTIONS

We are categorizing DIs as either PK based or PD based. PK-based DIs are those resulting from direct competition, inhibition, or induction of drug ADME mechanisms without involvement of the therapeutic targets. PD-based DIs are those resulting from modulation of the systems or target biology via the PD effects of drugs in combination. Both PK- and PD-based DIs may result in relevant changes in exposure and lead to a potential impact on safety and efficacy outcomes, especially for drugs with a NTR. PD-based DIs may also cause undesirable toxicity without an impact on exposure. Unlike SMDs, which are often susceptible to PK-based DIs due to an alteration in CYP and transporter-mediated ADME processes by drug combinations, TP-DIs are often mechanistically different.
2.3.1 Impact of Pharmacokinetic-Based Therapeutic Protein–Drug Interactions on the Exposures of Therapeutic Proteins and Small Molecule Drugs

PK-based TP-DIs are not common because TPs and SMDs have distinct PK properties. The nonspecific clearance pathways for TPs are usually unsaturable at therapeutic concentrations. Likewise, these pathways are unlikely to be saturated by the combination of two TPs. For example, the clearances of trastuzumab and bevacizumab are dominated by nonspecific pathways at their clinically efficacious doses. No alteration in PK properties is observed when they are given in combination.26

When a TP is combined with a SMD, there is usually no direct overlap and competition in the metabolism and clearance pathways, thus PK-based DIs are unlikely. For example, chemotherapeutic agents such as irinotecan, 5-fluorouracil, and platinum-based therapy (i.e., cisplatin, carboplatin) do not affect the PK properties of cetuximab in cancer patients.27–29 Similarly, no PK-based DIs are observed between bevacizumab and any of the following agents: capecitabine, cisplatin, 5-fluorouracil, irinotecan, oxaliplatin, or paclitaxel.30 A dedicated study was conducted to evaluate potential TP-DIs for the combination of bevacizumab and irinotecan (as part of the FOLFIRI regimen containing irinotecan, fluorouracil, and leucovorin). This study demonstrated that the 90% confidence interval of geometric mean ratios for exposure of irinotecan and SN-38 (the active metabolite of irinotecan) in the absence of versus in the presence of bevacizumab were both within the prespecified no effect boundaries, indicating no clinically relevant TP-DIs for this combination.31 Additional examples of no TP-DIs for combinations of anticancer mAbs with chemotherapeutic and antineoplastic SMDs have been reviewed in recent publications.2,30,32–35

PK-based TP-DIs involving ADCs are theoretically possible because the cytotoxic component of the ADC, once deconjugated, may elicit PK-based DIs when the ADC is combined with other SMDs. The cytotoxic agent, which is often a CYP substrate, is likely a victim of DIs when combined with SMDs that are CYP inhibitors or inducers. However, the cytotoxic agent has a relatively low systemic exposure. Thus it is not expected to have any impact on CYP and transporter activities in clinical settings and is unlikely to be a perpetrator. Data for ADC-related DIs are limited to assessments for T-DM1 and brentuximab vedotin (Adcetris). When T-DM1 is given in combination with taxanes (paclitaxel or docetaxel), the PK properties of taxanes and DM1 remain unchanged because taxanes and DM1 are not potent CYP inhibitors or inducers at clinically relevant concentrations.36,37 A dedicated study of brentuximab vedotin found that it does not affect the PK parameters of midazolam, a CYP3A4 substrate. In the same study, the unconjugated MMAE exposure increased ~34% when brentuximab vedotin was combined with ketoconazole (a potent CYP3A4 inhibitor) and decreased ~46% when brentuximab vedotin was combined with rifampin (a potent CYP3A4 inducer). Therefore it is recommended that patients who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin should be closely monitored for MMAE-related adverse reactions. These results are expected because MMAE is a substrate of CYP3A4 but not a CYP inhibitor or inducer at clinically relevant concentrations.23
2.3.2 Impact of Pharmacodynamic-Based Therapeutic Protein–Drug Interactions on the Exposure of Therapeutic Proteins

Distinct from the less common cases of PK-based TP-DIs, there are several plausible mechanisms for PD-based TP-DIs that change the exposure of TPs. As shown in Figure 2-2, interaction between the biological systems or target biology with a TP may affect the TP’s exposure through immunogenicity-mediated clearance or target-mediated clearance pathways. The TPs or SMDs given in combination may modulate these clearance pathways by their PD effect, leading to DIs. For example, immunosuppressants such as methotrexate (MTX), mycophenolate mofetil, and azathioprine increase the exposures of infliximab, adalimumab, and basiliximab, possibly due to the effect of the immunosuppressants on decreasing the immunogenicity rate of these mAbs when they are given in combination. In another case, triple immunosuppressive agents may decrease target (CD11a+ T-cells) level, subsequently decreasing target-mediated clearance of efalizumab and thus increasing its exposure.

2.3.2.1 Pharmacodynamic-Based Therapeutic Protein–Drug Interactions Owing to Changes in Immunogenicity-Mediated Clearance of Therapeutic Proteins

Some immunosuppressive drugs may modulate the humoral immune response and decrease the immunogenicity of a TP, thus modulating its clearance. This is possible only for TPs that have a relatively high immunogenicity rate and when the clearances of TPs are impacted by immunogenicity. Examples include infliximab, adalimumab, and basiliximab, as listed in Table 2-1. Infliximab and adalimumab are both mAbs antagonizing tumor necrosis factor α (TNF-α) and are often given in combination with immunosuppressive agents.
<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Type of TP and Indication</th>
<th>Possible Mechanisms for TP-DIs</th>
<th>Change in PK Properties</th>
<th>Clinical Relevance</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Infliximab + MTX</td>
<td>Infliximab: anti-TNFα mAb</td>
<td>MTX may inhibit humoral response; ↓ immunogenicity of infliximab.</td>
<td>MTX ↓ CL of infliximab.</td>
<td>No dose adjustment is recommended.</td>
<td>38,39</td>
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<tr>
<td></td>
<td>Indication: RA</td>
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<tr>
<td>Adalimumab + MTX</td>
<td>Adalimumab: anti-TNFα mAb</td>
<td>MTX may inhibit humoral response; ↓ immunogenicity of adalimumab.</td>
<td>MTX ↓ CL of adalimumab by 20–44%.</td>
<td>No dose adjustment is recommended.</td>
<td>15,40</td>
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<tr>
<td></td>
<td>Indication: RA</td>
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<tr>
<td>Basiliximab + CsA + corticosteroids + mycophenolate mofetil or azathioprine</td>
<td>Basiliximab: chimeric mAb against IL-2Ra on T-cells</td>
<td>Mycophenolate mofetil or azathioprine may inhibit humoral response; ↓ immunogenicity of basiliximab.</td>
<td>Mycophenolate mofetil ↓ CL of basiliximab by 51%; azathioprine ↓ CL of basiliximab by 22%.</td>
<td>No dose adjustment is recommended.</td>
<td>41,42</td>
</tr>
<tr>
<td></td>
<td>Indication: prevent transplant rejection</td>
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<tr>
<td>Eflizumab + triple immunosuppressive agents (CsA, sirolimus, prednisone)</td>
<td>Eflizumab: humanized IgG1 anti-CD11a mAb</td>
<td>Triple immunosuppressive agents may ↓ TMDD of eflizumab by suppression of CD11a+ T-cells.</td>
<td>Triple immunosuppressive agents ↓ CL of eflizumab by 50% in transplant patients compared to psoriasis patients.</td>
<td>No dose adjustment is recommended.</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Indication: psoriasis, prevent transplant rejection</td>
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