



Identifying Safety Thresholds for Immunosuppressive Drugs: Applying Insights from Primary Antibody Deficiencies to Mitigate Adverse Events in Secondary Antibody Deficiencies Using Mathematical Modeling of Preclinical and Early Clinical Data

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Abstract

Immunosuppressive drugs can alleviate debilitating symptoms of autoimmune diseases, but, by the same token, excessive immune suppression can result in an increased risk of infection. Despite the dangers of a compromised immune system, clear definitions of what constitutes excessive suppression remain elusive. Here we review the most common infections associated with primary antibody deficiencies (PADs), such as agammaglobulinemia, common variable immunodeficiency (CVID), and IgA deficiency, as well as infections that are associated with drug-induced or secondary antibody immunodeficiencies (SADs). We identify a number of bacterial, viral, and fungal infections (e.g., *Listeria monocytogenes*, *Staphylococcus* sp., *Salmonella* spp., *Escherichia coli*, influenza, varicella zoster virus, and herpes simplex virus) associated with both PADs and SADs, and suggest that diagnostic criteria for PADs could be used as a first-line measure to identify potentially unsafe levels of immune suppression in SADs. Specifically, we suggest that, based on PAD diagnostic criteria, IgG levels should remain above 2–3 g/L, IgA levels should not fall below 0.07 g/L, and IgM levels should remain above 0.4 g/L to prevent immunosuppressive drugs from inducing mimicking PAD-like effects. We suggest that these criteria could be used in the early stages of drug development, and that pharmacokinetic and pharmacodynamic modeling could help guide patient selection to potentially improve drug safety. We illustrate the proposed approach using atacept as an example and conclude with a discussion of the applicability of this approach for other drugs that may induce excessive immune suppression.

Key Points

The occurrence of similar infections in patients with primary (PADs) and secondary (SADs) antibody deficiencies suggests there may be value to using diagnostic criteria for PADs to increase the safety of SADs.

Atacept can be used as a retrospective example to demonstrate the potential of the mathematical modeling of early clinical data to increase drug safety by refining the inclusion criteria for patient selection.

1 Introduction

Disease management for severe autoimmune disorders, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and myasthenia gravis, frequently relies on the use of immunosuppressive drugs that both reduce symptoms and attempt to short circuit the disease cycle [1]. For instance, in SLE, immunosuppressive drugs such as atacept and belimumab are administered to prevent B cell maturation, while drugs such as anifrolumab are designed to interfere with the signaling of inflammatory cytokines such as IFN- γ [2]. While these approaches may alleviate some of the disease symptoms, they can also result in significant immune suppression, especially when administered in addition to non-specific immune suppressants such as corticosteroids, which is often the standard of care [3–5]. This oversuppression can cause immune deficiency, increasing patient susceptibility to opportunistic infections [2].

There are two recognized types of immunodeficiencies: primary and secondary. Primary antibody deficiencies (PADs) are the most common form of primary antibody

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deficiency. PADs are typically caused by genetic defects that result in either loss of immunoglobulins (Ig) or their malfunction due to the disruption of B cell differentiation. PADs include common variable immunodeficiency (CVID) and pan-agammaglobulinemia (the absence of IgM, IgG, and IgA), among others. A detailed review of PADs can be found in the literature [6–9]. Unfortunately, there are currently no cures for these conditions, so therapeutic interventions are primarily palliative, aimed at managing infections and boosting the immune system [6, 8, 10].

Secondary antibody deficiencies (SADs) are acquired as a result of disease (e.g., HIV) or drug treatment, such as chemotherapy or immunosuppressive drugs. Mechanisms of action of the latter can involve the depletion of B cells, which occurs for example when rituximab [11] is used for the treatment of lupus nephritis [12, 13] or milatuzumab is used for the treatment of non-Hodgkin lymphomas, multiple myeloma, and chronic lymphocytic leukemia [14–16]. Other mechanisms of action include inhibition of B cell survival (this occurs with, for example, belimumab [17] and atacept [18]), inhibition of B cell activation (this occurs with imatinib for chronic myelogenous leukemia [19] or with bortezomib for multiple myeloma [20], for example), as well as inhibition of T cell/B cell interactions (this occurs with, for example, abatacept for rheumatoid arthritis [21]). A detailed review of SADs can be found in [22–24].

Both PADs and SADs are associated with increased infection risk, particularly of the upper respiratory tract. Despite this increased susceptibility to infections of patients undergoing immunosuppressive therapy, the exact identification of safety thresholds with regards to acceptable levels of immune suppression remain elusive, due in particular to high interpatient variability. While some adverse events can only be discovered in late-stage clinical trials, many can be identified in preclinical or in early-stage clinical studies when new drugs are first tested on healthy subjects or in patients to assess safety. If it was known and benchmarked earlier in the drug discovery/development process, this information could be quite beneficial, as it could be factored into the quantitative analysis of the drug before it is introduced to clinics.

Here we propose using diagnostic criteria for PADs to inform safety thresholds for SADs. We first summarize known common diagnostic criteria for PAD patients, placing a particular focus on CVID and agammaglobulinemia as diseases that are symptomatically closest to drug-induced antibody deficiencies. We suggest that preclinical pharmacokinetic and pharmacodynamic modeling could be used to guide patient selection to improve drug safety. We illustrate the proposed approach using atacept as an example. We conclude with a discussion of how this approach could be used to potentially increase the safety of future immunosuppressive drugs.

2 Primary Antibody Deficiencies

PADs are a heterogeneous group of disorders characterized by various degrees of dysfunctional antibody production resulting from a disruption of B cell differentiation at different stages of B cell development [25, 26]. Clinical manifestations range from an almost complete absence of B cells and serum immunoglobulins to selectively impaired antibody responses to specific antigens in the presence of normal total serum immunoglobulin concentrations. All of these disorders lead to an increased susceptibility to infections that predominantly affect the respiratory tract [25].

2.1 Agammaglobulinemia

Agammaglobulinemias are rare antibody deficiencies caused by defects during early B cell development [24]. They are characterized by low to undetectable numbers of B cells and significantly decreased concentrations of immunoglobulins. At the time of diagnosis, most patients have low serum immunoglobulin concentrations; specifically, IgG concentrations below 2 g/L, IgA concentrations below 0.15 g/L, and IgM concentrations below 0.4 g/L [27]. Furthermore, almost all patients have markedly decreased B cell numbers, with under 2% CD19- or CD20-positive lymphocytes in the blood [25, 27]. Agammaglobulinemia patients are often prone to serial bacterial and viral infections [27].

2.2 Common Variable Immunodeficiency (CVID)

CVID is a disorder of B cell differentiation and maturation with dysfunctional antibody production [25, 28]. According to the immunologic analysis of a European multicenter cohort of CVID patients [28], usually several immunoglobulin classes—particularly IgG and IgA—are reduced. Hypogammaglobulinemia [29] is typically defined as a serum IgG level below 6 g/L; it is further stratified into mild (4–5.99 g/L), moderate (2–3.99 g/L), and severe (0–1.99 g/L). For CVID patients, serum IgG concentrations are in the range of 2.1 ± 1.65 g/L (normal range 7–17 g/L), IgA concentrations are 0.2–0.7 g/L (normal range 0.7–4 g/L), and IgM concentrations are below the norm of 0.4–2.3 g/L. T cell numbers and function are also reduced in some patients. Furthermore, reduced numbers of switched memory B cells (less than 2% of total B cells) have been shown to correlate with disease-associated complications such as splenomegaly and granulomatous disease [25, 28]. Patients often come to medical attention due to acute or chronic bacterial and, less frequently, viral infections [25].

2.3 IgA Deficiency

Selective IgA deficiency occurs when concentrations of serum IgA fall below 0.07 g/L in the presence of normal serum concentrations of IgG and IgM; it is diagnosed after other causes of hypogammaglobulinemia have been ruled out [25, 30]. Notably, the IgA deficiency is often compensated for by increased concentrations of IgM. Some IgA-deficient patients progress over time to CVID. A subset of IgA-deficient patients develop recurrent pulmonary and gastrointestinal infections [25].

2.4 Commonly Occurring Infections in PAD Patients

Pneumonia is a common infection in PAD patients. For instance, at least two-thirds of CVID patients had one or more episodes of pneumonia prior to diagnosis. In fact, almost all patients with PADs suffer from upper and lower respiratory tract bacterial infections. *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are present in the nasal cultures of the majority of patients, and frequently more than one pathogen is present [25]. Chronic lung disease and gastrointestinal complications are frequently observed in these patients. PAD patients sometimes also get chronic infectious arthritis, chronic enteroviral meningoencephalitis, acute and/or recurrent bacterial conjunctivitis, and occasional cutaneous infectious complications [25].

3 Infections Commonly Associated with Immunosuppressive Therapy (SADs)

Orlicka et al. [31] summarized the infections commonly associated with immunosuppressive therapy. These include *Listeria monocytogenes*, *Staphylococcus* sp., *Salmonella* spp., *Escherichia coli*, influenza, varicella zoster virus, and herpes simplex virus, among others. The most common of these infections are summarized in Fig. 1.

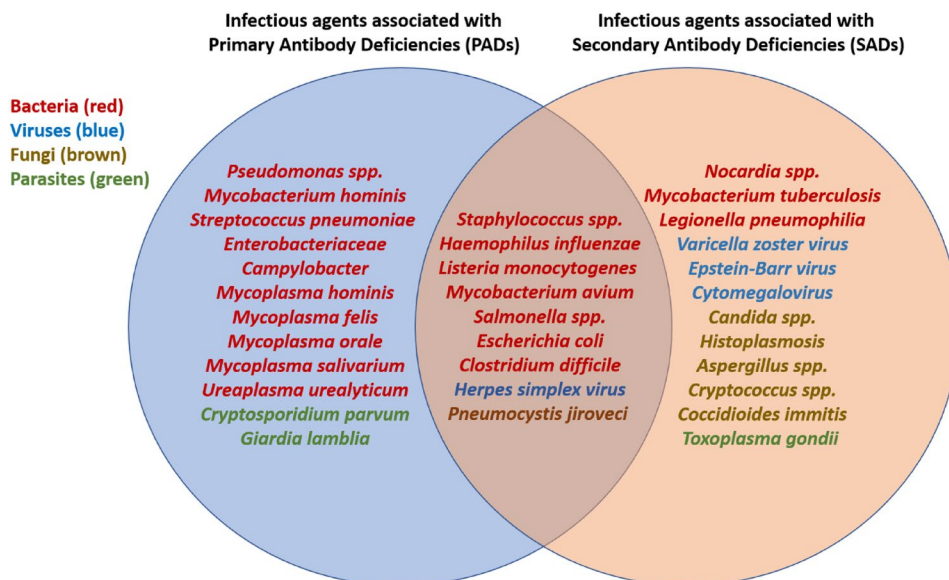
A summary of criteria that correlate with increased infections in PADs patients is given in Fig. 2.

Due to the fact that both PAD and SAD patients succumb to similar infections associated with a suppressed immune system, in the absence of a more rigorous understanding of SADs, the levels of immune cells and immunoglobulins commonly observed in PAD patients could be used to inform potential safety thresholds for immunosuppressive therapies.

4 Using Safety Thresholds in Predictive Pharmacokinetic and Pharmacodynamic Modeling

An understanding of safety thresholds for immunosuppressive drugs can be particularly useful in preclinical and early clinical pharmacokinetic and pharmacodynamic (PKPD) modeling. To illustrate this approach, we first describe a general PK model that describes the key mechanisms that drive the absorption, distribution, metabolism, and elimination of a drug upon its administration into the body. The PK model is then coupled with an indirect response PD model, which captures the impact of the change in drug concentration over time on a biomarker, in this case an immunoglobulin. We

Fig. 1 Infections that are commonly associated with secondary antibody deficiencies [SADs] (data adapted from [31]), and infections that are also common in primary antibody deficiencies [PADs] (data adapted from [25]). Bacterial infections are colored *red*, viral infections are in *blue*, fungal infections are in *brown*, and parasitic infections are in *green*. The occurrence of similar infections in patients with PADs and SADs suggests there may be value to using diagnostic criteria from PADs to inform safety thresholds for SADs



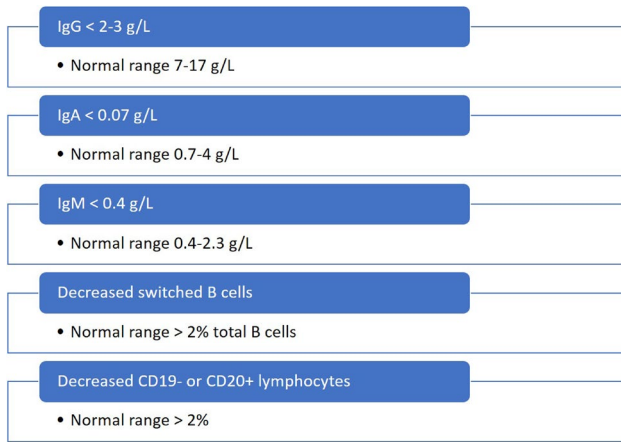


Fig. 2 Summary of criteria that correlate with increased infections in patients with primary antibody deficiencies, as described in Sect. 2; it is proposed that these criteria could be used as safety thresholds for secondary antibody deficiencies

then illustrate how such a model can be used to increase drug safety, using the immunosuppressive drug atacept as an example.

First, consider the following two-compartment model that describes the dynamics and interactions over time of the drug, its target, and the drug–target complex:

1. Drug D_{dose} is absorbed at a rate k_{01} into the plasma.
2. Once in the plasma, drug $D_p(t)$ can be distributed into the tissue; it can also be cleared from the plasma, or the drug can redistribute between tissue and plasma.
3. Once in the tissue, the drug $D_T(t)$ can interact with its target $S(t)$.
4. The dynamics of the drug–target complex $D_S(t)$ are governed by association/dissociation reactions between $D_T(t)$ and $S(t)$; the drug–target complex can also be cleared.
5. Finally, the target $S(t)$ has natural turnover rates of synthesis (k_{syn}) and degradation (k_{deg}) to allow for the maintenance of the steady-state concentration of the target.

These dynamics can be captured using the following system (Eq. 1) of ordinary differential equations that allow the concentrations of the drug in plasma and in tissue as well as the kinetics of the target and the drug–target complex to be tracked over time:

$$\begin{aligned}
 \underbrace{D_{\text{dose}}(t)'}_{\text{drug administration}} &= \underbrace{-k_{01}D_{\text{dose}}(t)}_{\text{absorption}} \\
 \underbrace{D_p(t)'}_{\text{free drug in plasma}} &= \underbrace{k_{01}D_{\text{dose}}(t)}_{\text{absorption}} - \underbrace{k_{pT}D_p(t)}_{\text{tissue distribution}} - \underbrace{k_{cP}D_p(t)}_{\text{elimination from plasma}} + \underbrace{k_{TP}\frac{V_T}{V_P}D_T(t)}_{\text{inflow from tissue}} \\
 \underbrace{D_T(t)'}_{\text{free drug in tissue}} &= \underbrace{\frac{V_P}{V_T}k_{pT}D_p(t)}_{\text{dose distribution}} - \underbrace{k_{TP}D_T(t)}_{\text{drug distribution}} - \underbrace{k_{on}D_T(t)S(t)}_{\text{binding to target}} + \underbrace{k_{off}D_S(t)}_{\text{dissociation}} \\
 \underbrace{D_S(t)'}_{\text{drug + target}} &= \underbrace{k_{on}D_T(t)S(t)}_{\text{bound to target}} - \underbrace{k_{off}D_S(t)}_{\text{dissociation}} - \underbrace{k_{TP}D_S(t)}_{\text{clearance}} \\
 \underbrace{S(t)'}_{\text{free target}} &= \underbrace{k_{\text{syn}}}_{\text{synthesis}} - \underbrace{k_{\text{deg}}S(t)}_{\text{degradation}} - \underbrace{k_{on}D_T(t)S(t)}_{\text{binding to drug}} + \underbrace{k_{off}D_S(t)}_{\text{dissociation}}
 \end{aligned} \tag{1}$$

A summary of the parameters used in system (1) is given in Table 1. The initial conditions are $D_{iv}(0) = \text{dose}/V_p$, $D_p(0) = D_T(0) = D_S(0) = 0$. The initial concentration of the target $S(0)$ is determined by its baseline level such that $k_{\text{syn}} = S(0) \times k_{\text{deg}}$. A detailed investigation of such models—called site of action (SoA) models—and their properties is provided in, for instance, [32]. A schematic of the processes described by system (1) is given in Fig. 3.

This baseline model can be used to quantify the effect of the drug on a particular biomarker, such as a generic immunoglobulin, here denoted as IgX. This is typically done using indirect response models [33], which capture increases or decreases in the level of a particular biomarker over time under the influence of the concentration of the drug. These drug interactions occur either in the plasma or at the SoA [32, 34]. A schematic representation of the output of such a PKPD model is shown in Fig. 4.

As an example, consider the turnover dynamics of IgX, which, in their simplest form, can be described as a difference between IgX production and clearance resulting in a baseline (steady-state) IgX concentration, as shown in the following equation (Eq. 2):

$$\underbrace{I'(t)}_{\text{IgX}} = \underbrace{k_{\text{in}}}_{\text{IgX production}} - \underbrace{k_{\text{out}}I(t)}_{\text{IgX clearance}} \tag{2}$$

where $I(t)$ is concentration of IgX, and k_{in} and k_{out} are the IgX synthesis and clearance rates, respectively. In disease, the IgX concentration could be elevated if either k_{in} is too high or k_{out} is too low. Therefore, some mechanisms of therapeutic intervention could involve decreasing the production of IgX, which can be captured as follows (Eq. 3):

Table 1 Summary of the parameters used in system (1)

Parameter	Description	Units
<i>Physiological parameters</i>		
V_P	Volume of the plasma compartment	L
V_T	Volume of the tissue (site of action) compartment	L
<i>Drug pharmacokinetics</i>		
CL_P, CL_T	Rate of drug clearance from the plasma and tissue compartments	L/day
k_{01}	Rate of drug absorption	1/day
k_{TP}	Drug distribution rate from tissue to plasma	1/day
k_{PT}	Drug distribution rate from plasma to tissue	1/day
k_{eP}	Rate of drug elimination from plasma, $k_{eP} = \frac{CL_P}{V_P}$	1/day
<i>Target properties</i>		
K_D	Equilibrium dissociation constant for drug–target binding	nM
k_{on}	Second-order rate constant of drug–target binding	nM/day
k_{off}	First-order rate constant for drug dissociation; $k_{off} = K_D k_{on}$	1/day
S_0	Homeostatic baseline target concentrations (determined experimentally or obtained from the literature)	nM
k_{int} or k_{deg}	Rate of target internalization, degradation, or clearance (this can also be calculated from the half-life of the target as $k_{deg} = \ln(2)/(\text{target half-life})$)	1/day
k_{syn}	Target synthesis rate ($k_{syn} = S(0) \times k_{deg}$), where $S(0)$ is the target-specific baseline target concentration	nM/day

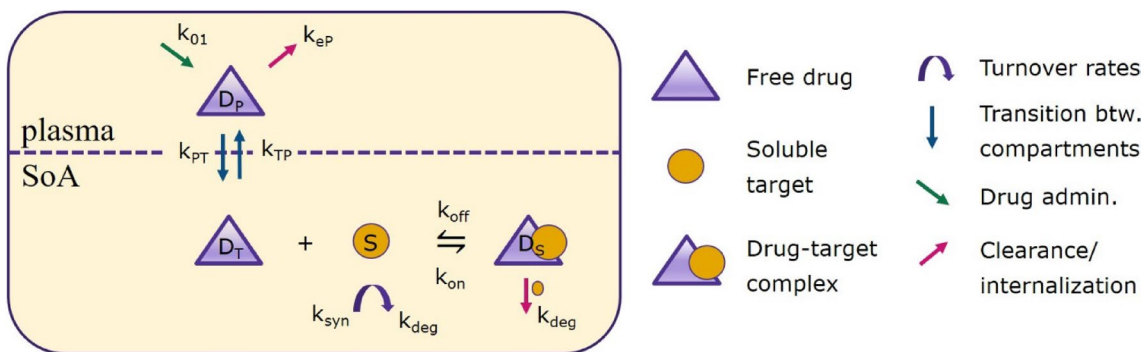
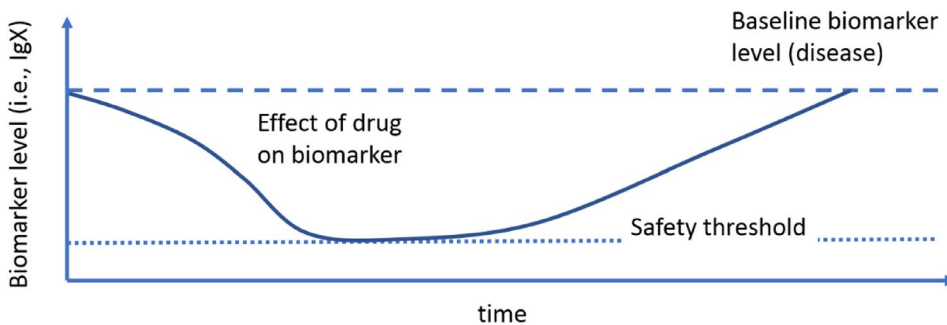


Fig. 3 A schematic diagram of the sample model described in system (1). Parameter descriptions and units are given in Table 1

Fig. 4 A schematic representation of the effect of a drug on a biomarker, such as a generic immunoglobulin IgX, as captured by indirect response models (note that the graph does not depict a specific compound; it is used for illustrative purposes)



$$I'(t) = \underbrace{k_{in}}_{\text{IgX}} \left(1 - \frac{I_{max} D_T(t)}{IC_{50} + D_T(t)} \right) - \underbrace{k_{out} I(t)}_{\text{Ig clearance}}, \quad I_{max} \in [0, 1]$$

indirect response model: drug decreases Ig production

(3)

It is clear that larger values of $D_T(t)$ as calculated from system (1) will cause the overall term $k_{in} \left(1 - \frac{I_{max} D_T(t)}{IC_{50} + D_T(t)} \right)$ to decrease, resulting in lower IgX production and thus lower IgX levels.

Correspondingly, the effects of increasing the clearance of IgX can be captured by the following equation (Eq. 4):

$$\underbrace{I'(t)}_{\text{IgX}} = \underbrace{k_{\text{in}}}_{\text{baseline IgX production}} - \underbrace{k_{\text{out}}I(t)\left(1 + \frac{S_{\text{max}}D_{\text{T}}(t)}{SC_{50} + D_{\text{T}}(t)}\right)}_{\text{indirect response model: drug increases IgX clearance}} \quad (4)$$

In this case, if $D_{\text{T}}(t)$ is large, the overall clearance term $k_{\text{out}}I(t)\left(1 + \frac{S_{\text{max}}D_{\text{T}}(t)}{SC_{50} + D_{\text{T}}(t)}\right)$ is increased, thereby increasing the clearance of IgX. Both of these mechanisms would produce the curve depicted in Fig. 4, even though the mechanisms of action are different. Notably, terminology I_{max} and S_{max} correspond to maximum inhibition and stimulation, respectively; in the context of this work, either the inhibition of drug production or the stimulation of drug clearance. A thorough description of indirect response models can be found in [33].

These types of indirect response models can be useful for predicting the effect of a drug on biomarker concentrations and thus preventing them from dropping below potentially unsafe levels (Fig. 4). Having a priori guidelines for safety thresholds can thus help us to predict the dose and frequency of administration that will keep immunoglobulin concentrations above unsafe levels, potentially improving the drug safety profile. We propose the following steps to achieve this goal:

1. Identify the impact of the drug on the biomarker levels; in the analysis presented below, percent reductions were obtained from clinical data (from the phase IIb atacept study ADDRESS II [35]), but they could also be obtained from preclinical models.

2. Simulate the predicted human PK and the expected impact on biomarker levels from step 1 to identify the minimum acceptable baseline biomarker levels needed to ensure that the thresholds summarized in Fig. 2 are not crossed during treatment.
3. Introduce variability using population PKPD modeling with the minimum acceptable baseline concentrations from step 2 to refine patient selection criteria to minimize adverse events associated with immune suppression.

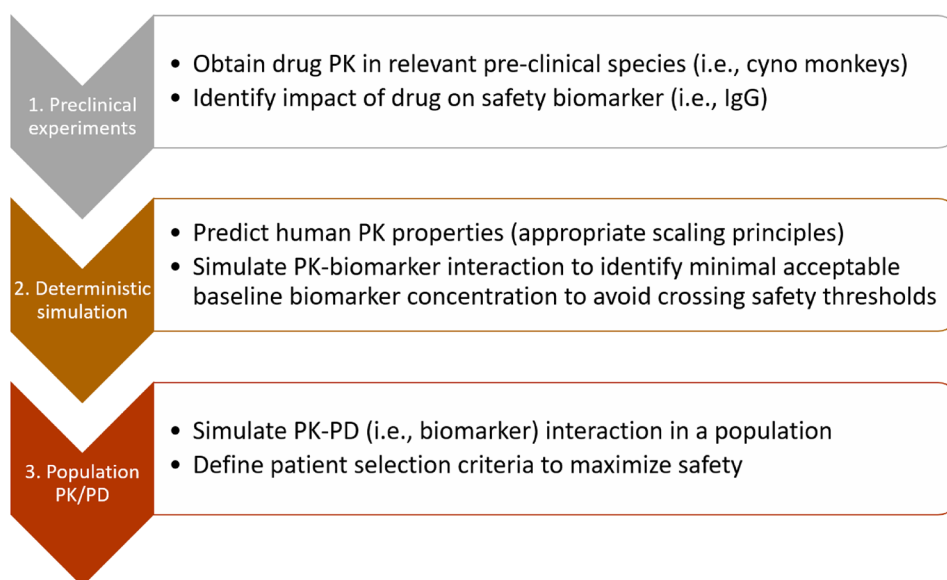
This approach is summarized in Fig. 5.

5 Example: Atacept

Consider the following example, which focuses on the immunosuppressive drug atacept, a fully human, recombinant, soluble fusion protein that targets the B cell stimulating factor (BLyS, also known as BAFF [36]) and a proliferation-inducing ligand (APRIL). Atacept showed evidence of efficacy in SLE in the phase II/III study APRIL-SLE and the phase IIb study ADDRESS II [18, 35]. A summary of the PK parameters for atacept as estimated from data are provided in the Supplementary Information; analysis of three clinical trials with the population PK model for atacept can additionally be found in [37, 38].

ADDRESS II included 306 participants ($n = 100$ received placebo, $n = 102$ received atacept 75 mg, $n = 104$ received atacept 150 mg), and the treatment duration was 24 weeks. Median reductions in baseline serum IgG were reported to be ~ 25 and 30% with atacept 75 and 150 mg, respectively, with a maximum IgG reduction of approximately 40% [31]. Additionally, the median percentage reductions in the serum

Fig. 5 Using modeling and safety thresholds to guide initial patient selection to minimize the risk of adverse events associated with immunosuppressive drugs. *PK* pharmacokinetic(s), *PD* pharmacodynamic(s)



levels of IgA (~ 45% with 75 mg and ~ 50% with 150 mg) and IgM (~ 60% with 75 mg and ~ 70% with 150 mg) compared with the baseline were reported. With regards to treatment-emergent adverse events, the most common adverse events were increases in upper respiratory infections, including nasopharyngitis (4.9% for the 75 mg group and 6.7% for the 150 mg group), bronchitis (1.0% for the 75 mg group and 3.8% for the 150 mg group), and influenza (2.9% for the 75 mg group and 2.9% for the 150 mg group). Pneumonia occurred in 1 patient (1.0%) in each atacept group.

The proposed approach can be applied to this example as follows.

For step 1 outlined in Fig. 5, consider the following system, which describes an indirect response model with inhibition of IgG production:

$$\frac{d\text{IgG}(t)}{dt} = k_{\text{in}} \left(1 - \frac{I_{\text{max}} C_{\text{tot}}(t)}{\text{IC}_{50} + C_{\text{tot}}(t)} \right) - k_{\text{out}} \text{IgG}(t) \quad (5)$$

$$k_{\text{in}} = k_{\text{out}} \text{IgG}_0$$

where $\text{IgG}(t)$ is the concentration of immunoglobulin G, C_{tot} is the concentration of total atacept, IgG_0 is the baseline IgG concentration, k_{in} is the zero-order IgG production rate, k_{out} is the first-order elimination rate of IgG, I_{max} is the maximum effect of the drug on IgG synthesis as estimated from the data, and IC_{50} is the concentration of total atacept that is required to produce 50% of the maximum effect atacept can induce. In the model, the decrease in IgG synthesis was related to the (total) plasma atacept concentration as shown in Fig. 6.

For step 2 outlined in Fig. 5, we couple system (1) with Eq. (5), simulating the PK for a 150 mg dose of atacept administered weekly for 24 weeks (to match the duration of

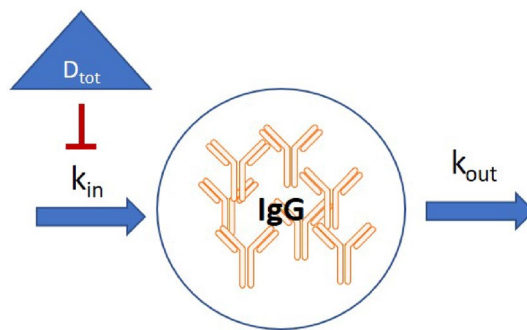
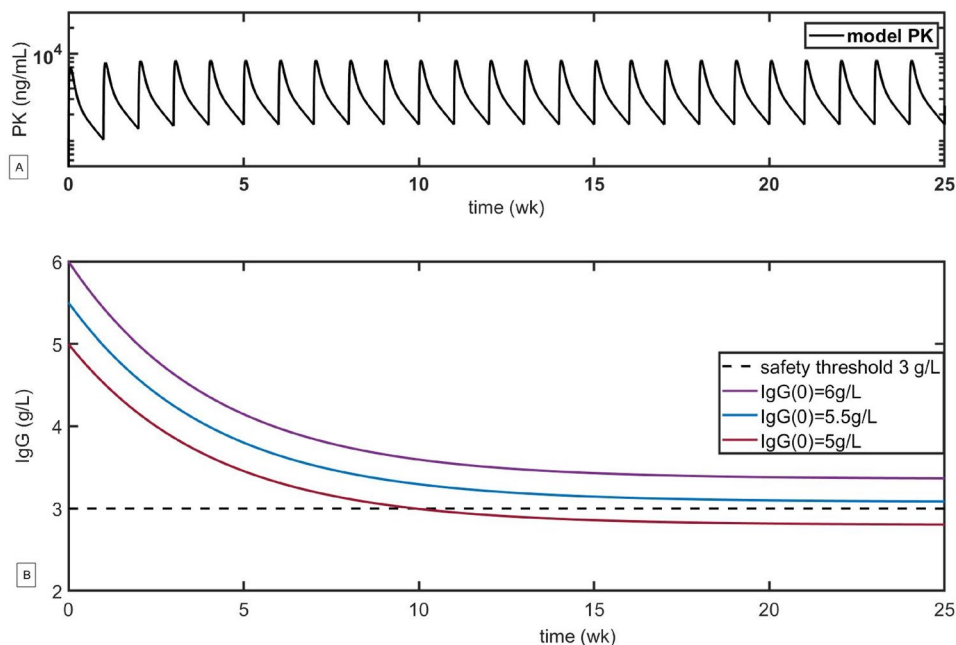


Fig. 6 Schematic representation of the IgG indirect response model used to model the effect of atacept on IgG production

the trial) as well as the projected reductions in IgG for various initial levels of IgG (see Fig. 7). Different baseline levels of IgG reflect the fact that SLE therapy is often administered to a pretreated patient population, resulting in lower initial IgG levels. As one can see in the scenario analysis reported in Fig. 7B, the IgG concentrations of individuals with baseline levels of IgG below 5.5 g/L are predicted to fall below the threshold of 3 g/L after 12 weeks, potentially increasing the risk of adverse events (the threshold of 3 g/L was taken as a tentative safety threshold because it is a mid-range value for moderate hypogammaglobulinemia as defined in [29]). Similar analyses can be performed for IgM and IgA.

This type of initial analysis can be performed at the pre-clinical stage to identify patient eligibility criteria, which in this case corresponds to the lowest baseline level of IgG that still allows the risk of infection due to immune suppression to be mitigated. Notably, no preclinical values of I_{max} (the maximum fractional IgG reduction due to the drug) were available for these simulations, so we estimated that I_{max}

Fig. 7 Scenario analysis of the variation in the drug concentration and IgG concentration with the administration of 150 mg of atacept weekly for 24 weeks. Pharmacokinetic parameters are defined in Table 1. The treatment schedule and the maximum IgG reduction of up to 40% were obtained from [35]. **A** Simulated pharmacokinetics (PK) of 150 mg of atacept administered weekly for 24 weeks (to mimic the design of the ADDRESS II clinical trial of atacept). **B** Simulated dynamics of the safety biomarker IgG for various baseline levels



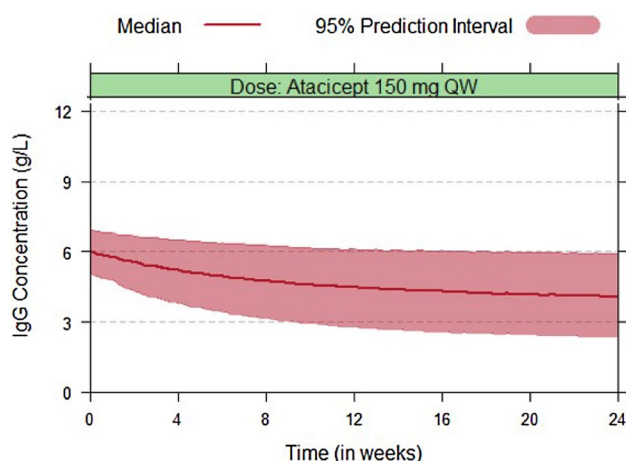


Fig. 8 Simulated IgG profiles following 150 mg weekly (QW) administration of atacept in systemic lupus erythematosus (SLE) subjects for 24 weeks. The baseline IgG was taken to be between 5 and 7 g/L, with a median concentration of 6 g/L. The proportion of subjects for whom IgG is predicted to drop below the safety threshold of 3 g/L at any time point is 3.8%

corresponds to an approximately 40% reduction in IgG, as observed in phase 1 trials. In the absence of preclinical estimates, phase 1 data can be used to evaluate the maximum IgG reduction in healthy subjects, which can then be used to refine the patient selection criteria for subsequent clinical trial phases.

Notably, while the results of simulations of systems (1) and (5) suggest that the average IgG concentration at baseline should be no lower than 5.5–6 g/L in order to minimize the possibility of crossing the IgG safety threshold, these results are deterministic and do not capture interpatient variability. To address this, a population PKPD model was used to simulate predicted IgG concentrations in a population treated with atacept (step 3 in Fig. 5). While the baseline IgG levels in healthy individuals are in the 7–17 g/L range [38, 39], with typical values in the 10–12 g/L range, patients undergoing standard of care treatment can have significantly lower baseline IgG levels. Modeling is a simple way to implicitly take this variability into account by changing the initial level of IgG at the beginning of the simulation. A detailed description of the PKPD model of atacept and the corresponding model parameter values can be found in the Supplementary Information.

A simulation of the PK and IgG profiles of 4000 SLE subjects was performed for weekly administration of a 150 mg flat dose of atacept for 24 weeks, replicating the setup of the clinical trials. The covariate information used for the simulation (body weight, baseline BlyS, and ethnicity) corresponded to the combined APRIL-SLE and ADDRESS II modified intention-to-treat populations, from which over 1500 subjects with a baseline between 5 and 7 g/L (median

concentration 6 g/L) were sampled with replacement. Simulated IgG profiles are shown in Fig. 8; these include median profiles together with the corresponding 90% prediction intervals for the entire simulated population. The proportion of subjects for whom IgG is predicted to drop below the safety threshold of 3 g/L at any time point is 3.8%; additional simulations can be found in Supplementary Materials.

Notably, in the ADDRESS II clinical trial of atacept, an exclusion criterion of IgG < 6 g/L was instituted to minimize the possibility of adverse events. The analysis presented here, which was conducted using only preclinical and early clinical data applied to simple PK and PD models, was able to rediscover this criterion.

Notably, with the 6 g/L threshold exclusion criterion in place in the long-term extension (LTE) part of the ADDRESS II study [35] (which was designed to gather long-term safety and tolerability data), 6 participants (approximately 2% of all patients) developed severe hypogammaglobulinemia (IgG < 3 g/L) during or after week 12.

Overall, the proposed analysis corresponds well with the results observed in clinical trials of atacept, highlighting the value of implementing this analysis from the earliest stages. Specifically, these results suggest that incorporating safety thresholds into indirect response models and combining them with population simulations can help guide initial patient selection to potentially minimize the risk of adverse events associated with immunosuppressive drugs from the earliest stages of clinical development.

6 Discussion

It is proposed in this work that using diagnostic criteria for PADs can help guide the establishment of safety thresholds for immunosuppressive therapies to ensure that these therapies do not oversuppress the immune system, resulting in SADs. These criteria can be used with PKPD modeling to improve patient safety by decreasing the likelihood of SAD development.

The main premise of this approach is to maximize the utility of preclinical and early clinical data (however sparse) to improve compound safety in the clinical setting by refining the criteria for patient selection in relation to baseline biomarker levels. For the initial assessment, only two pieces of data are necessary: the longitudinal PK and the data that connect the PK to biomarker reduction. For biomarkers with short half-lives, *in vitro* assays, which are typically run in the early stages of drug development, could provide an initial estimate of this link. In the case of immunoglobulins, with a half-life measured in days, this link can realistically only be estimated from longitudinal *in vivo* studies in nonhuman primates or phase I clinical studies that report maximum

levels of biomarker inhibition, as in the aforementioned case of atacept.

The key assumption that must hold for this approach to work is that the relationship between drug concentration (PK) and its effect on biomarker levels translates between species, or that there is a known factor by which this relationship translates. One can then use simulations to assess the impact of the projected human PK on biomarker levels and to identify baseline IgG (or other biomarker) levels that can serve to identify exclusion criteria aimed at preventing excessive IgG reduction. Notably, since the key to this analysis is the relationship between PK and biomarker reduction, any PK model that appropriately describes the pharmacokinetics of the drug can be used. Since the underlying indirect response model is correlative and nonmechanistic, it can be applied to a variety of biomarkers and indications. The projections should of course be refined as clinical PK data become available to improve the utility of the output.

The proposed approach could also be adopted for other compounds that can reduce IgG levels and therefore mimic primary antibody deficiencies. For instance, the administration of rituximab, an anti-CD20 B-cell-depleting monoclonal antibody used for lymphoma and rheumatoid arthritis, has resulted in clinically significant hypogammaglobulinemia; according to a meta-analysis conducted by Roberts et al. [40], out of 288 patients who received rituximab, 56% had IgG hypogammaglobulinemia during follow-up, with IgG levels falling below 5 g/L in 22% and below 3 g/L in 4% of patients and IgM \leq 0.3 g/L observed in 58% of patients. Furthermore, IgG concentrations prior to and at the time of treatment correlated with the IgG nadir post rituximab, which predictably confirms the need to refine patient inclusion criteria before the trials begin so that patient safety is improved with regards to excessive immunoglobulin depletion during the trials. Notably, the results also apply to pediatric populations [41], where applying a similar approach to similar drugs might improve safety profiles as those drugs move into the clinical setting.

Another example of a drug that has resulted in significant immunoglobulin reductions is tabalumab, a B-cell activating factor (BAFF) inhibitor. Administration of this drug led to a twofold drop in IgG levels from baseline in end-stage renal disease patients [42]; if the approach proposed in the present work had been implemented for tabalumab, the safety of this treatment may have been improved. Yet another example is blisibimod, a selective BAFF inhibitor [43] that induced a relatively modest IgG reduction (10%) and thus would not necessitate patient selection criteria refinement based on baseline IgG levels. While the application of the proposed methodology to these particular drugs is no longer necessary given that they are at advanced stages of development, they do highlight the relevance of this approach to compounds

beyond atacept that can significantly affect immunoglobulin levels.

7 Conclusions

We have described a complementary tool that can help leverage preclinical data for a drug to maximally improve patient safety using a totality of evidence approach before the drug enters clinics. The proposed guidelines are preliminary, and a more rigorous understanding of SAD-related infections is needed. Notably, drug-induced immune suppression is of course not solely dependent on concentrations of various immunoglobulins or any individual subsets of immune cells. Patients with SADs often have complex underlying diseases and conditions, in contrast to PAD patients, so focusing solely on these biomarkers would be insufficient to avoid all the potential issues that come with the administration of immunosuppressive drugs. Nevertheless, the aforementioned application of early-stage PKPD modeling can be helpful in the quantitative analysis of immunosuppressive drugs, which has the potential to increase patient safety.

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Declarations

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