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Pharmacometric Applications and Challenges in the Development of Therapeutic Antibodies in Immuno-Oncology

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Abstract

Purpose of review—Monoclonal antibodies targeting key checkpoints in immune stimulatory pathways have over the last years become the mainstay of cancer immunotherapy. This article provides a brief review of the application and key impact of pharmacometrics and quantitative clinical pharmacology approaches in the development of these novel biologics.

Recent findings—The clinical development and selection of optimal dosing regimens for monoclonal antibodies used in immune-oncology has been facilitated by an extensive application of pharmacometric approaches to characterize the exposure-response relationship for major efficacy and safety endpoints. These analysis techniques were applied for the anti CTLA-4 antibody ipilimumab, as well as the anti PD1/PD-L1 antibodies nivolumab, pembrolizumab, avelumab, atezolizumab and durvalumab. The utilization of quantitative clinical pharmacology, including model-based analyses, did not only support the identification of efficacious doses with acceptable safety limits, but was also able to address complicating challenges such as time- and response-dependent changes in antibody clearance as observed for most compounds.

Summary—A widespread and systematic application of pharmacometric approaches has provided key aspects in elucidating, interpreting and integrating preclinical, biochemical and clinical data in support of the development of safe and efficacious dosing regimens of monoclonal antibodies used in immuno-oncology, thereby facilitating the clinical use of this promising new class of biologics in cancer patients with unmet medical needs.

Keywords

Immuno-oncology; monoclonal antibody; quantitative clinical pharmacology; pharmacometrics; PD1; PDL1

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Conflict of Interests:

LD is an employee of Bristol-Myers Squibb, the manufacturer of nivolumab and ipilimumab.

Introduction

Cancer immunotherapy is the use of the immune system to attack tumor tissue. In 2013, Science magazine declared that, all sciences considered, cancer immunotherapy had been the major breakthrough of the year [1]. Five years later, cancer immunotherapy has largely held its promises. The surprisingly durable tumor responses have turned into significant gains of overall survival for various cancer indications. Dramatic differentiations on the tails of Kaplan-Meier survival curves have been observed for immuno-oncology monoclonal antibodies (mAbs) compared with standard of care in several cancer types, and the lifted plateau on the tail of the survival curve is the signature feature of cancer immunotherapy [2]. One antibody against cytotoxic T-lymphocyte antigen-4 (CTLA-4), ipilimumab, two antibodies specific for the programmed cell death receptor 1 (PD-1), nivolumab and pembrolizumab, and three specific for programmed cell death-ligand 1 (PD-L1), atezolizumab, avelumab, and durvalumab, have been approved by the US Food and Drug Administration (FDA) for the treatment of various tumor types, including metastatic melanoma, non-small-cell lung cancer, and bladder cancer [2].

Tumors may modulate and evade the host immune response through a number of mechanisms, including downregulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T-cell checkpoint regulators such as CTLA-4 and PD-1 are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades that downregulate T-cell activation and proliferation. Therapeutic T-cell checkpoint inhibitors derive antitumor activity through breaking of the immune tolerance to tumor cell antigens. While CTLA-4 inhibits T-cell clonal expansion, PD-1 contributes to T-cell exhaustion in peripheral tissues [3].

Cancer immunotherapy is a new treatment paradigm that quickly evolves further. In traditional oncology drug development, dose selection has been based on the maximum tolerated dose (MTD) paradigm, which might not be an appropriate and acceptable approach for selecting the optimal dose for immuno-oncology agents [4]. Immunotherapies have a distinct adverse event profile compared to classic small molecules and other biologic anti-cancer agents, their exposure-safety relationships are not well understood yet, and there is no strong rationale to assume that the highest tolerable dose is the optimal dose [5]. For immunotherapies, the typical 4-week period that is used to identify dose-limiting toxicities may not be sufficient as immune-related adverse events are often not observed until 8–10 weeks of therapy [6]. Furthermore, it is almost impossible for most trials to identify a maximum tolerable dose, and often only a maximum feasible dose is defined [5, 6]. In addition, it is difficult to determine the optimal dose, dosing frequency, and duration of treatment for a maximum benefit-risk ratio. For example, questions still remain whether cancer immunotherapies should be given as continuous therapy or whether a limited number of administrations would be sufficient to trigger a durable immune response [6].

Pharmacometrics, or Quantitative Clinical Pharmacology, is a quantitative analysis approach employed in drug development to characterize drug response and its determinants through integrated mathematical representation based upon pharmacokinetics, pharmacodynamics,

and knowledge about the disease process [7–9]. A key role of pharmacometrics in drug development is dose selection [8]. To identify the optimal dose in pivotal clinical trials and ultimately for clinical use, a variety of pharmacometric tools have been applied to this novel class of immune-oncology mAbs including population pharmacokinetics (PK), mechanistic PK-pharmacodynamic (PD) preclinical-clinical translational modeling, and exposure-response (efficacy and safety) modeling of clinical Phase 1 and 2 trial data [10, 11]. These analyses contributed essential quantitative information for optimal dose selection of immune-oncology mAbs, particularly in the early clinical development stage when there is still very limited survival data available as primary efficacy endpoint [11, 12]. The following paragraphs provide select published examples of where pharmacometric approaches have been utilized in the development of therapeutic mAbs in immuno-oncology.

Ipilimumab

Ipilimumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody targeting CTLA-4, which is a key immune checkpoint molecule that downregulates T-cell activation [13]. Some of the earliest exposure-response analyses for immune-oncology agents were performed with ipilimumab using Phase 2 data containing doses at 0.3, 3, and 10 mg/kg by logistic regression models (for tumor response and safety) or Cox proportional-hazards models (for overall survival) [14]. The objective of these analyses was to characterize the exposure-response relationship of ipilimumab for efficacy and safety as basis for understanding its risk-benefit profile. These analyses suggested a clear exposure-response relationship: higher exposure was associated with improved tumor response, longer survival, but also a higher incidence of immune-related adverse event. Ultimately, the clinical benefit of ipilimumab was confirmed in a Phase 3 trial in patients with previously treated metastatic melanoma at a dose level of 3 mg/kg every 3 weeks for up to 4 doses [15]. The dose-response relationship for ipilimumab has been further confirmed in a Phase 3 clinical trial [16] that was a post-marketing requirement to better characterize the risk/benefit profile in patients with advanced melanoma. In this study, ipilimumab 10 mg/kg resulted in significantly longer overall survival than did ipilimumab 3 mg/kg, but with increased treatment-related adverse events [16].

Nivolumab

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that targets PD-1 with no antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) [17]. Nonclinical data indicated an efficacious dose in the range of 1–10 mg/kg in humans through allometric scaling, and a first-in-human starting dose of 0.3 mg/kg was supported by nonclinical pharmacology and toxicology data [5]. In a Phase 1 study, peripheral receptor occupancy reached saturation at a dose of 0.3 mg/kg [18]. Therefore, peripheral receptor occupancy data did not differentiate activity across dose levels and may not provide much value in understanding the clinical dose-response relationship. The utility of peripheral PD is also limited by the lack of a thorough understanding of the relationship between peripheral receptor occupancy and intra-tumoral receptor occupancy, as well as the immune-modulating activity in the tumor environment. In order to support dose selection, pharmacometrics-based dose-response and exposure-response analyses were performed on

phase 1a/1b efficacy and safety data in multiple different cancer indications. Observed activity and exposure-response analyses for various efficacy response measures (e.g. objective response rate [19] and tumor growth dynamics) indicated that higher nivolumab doses/exposures are required for low-immunogenic tumor types [5]. For example, ORRs were similar across 1–10 mg/kg for melanoma and renal cell carcinoma. For non-small cell lung cancer (NSCLC), however, higher ORRs were observed at 3 mg/kg and 10 mg/kg than at 1 mg/kg Q2W. Therefore, high ORR and longer progression free survival were achieved at lower dose levels for highly-immunogenic tumor types such as melanoma and renal cell carcinoma.

With regard to safety, the probability of adverse events leading to discontinuation (AE-DC) appeared to be lower in the 1 mg/kg compared to the 3 and 10 mg/kg dose levels. The probabilities of both grade ≥3 treatment-related adverse events and AE-DC were similar between the 3 and 10 mg/kg dose levels. Therefore, the exposure-response relationship for efficacy suggested that nivolumab at 1 mg/kg Q2W might be active for high-immunogenic tumor types of melanoma and renal cell carcinoma while 3 mg/kg Q2W may be needed for the less-immunogenic tumor types such as NSCLC [5]. Nivolumab 3 mg/kg Q2W was selected as the monotherapy dose for further evaluation across all tumor types, which was shown to provide long-term survival benefit across multiple tumor types.

A population PK model was developed to support the clinical pharmacology section in the prescribing information using data from 1,895 patients who received 0.1–20.0 mg/kg nivolumab in 11 Phase 1–3 clinical trials [20]. The analysis showed that nivolumab pharmacokinetics are linear within the studied dose range and similar among patients across different tumor types including NSCLC, melanoma, renal cell carcinoma, and others. Renal function, hepatic function status, and PD-L1 expression did not have a significant impact (<20%) on nivolumab clearance. Importantly, this analysis identified a time-variant clearance with a non-stationary sigmoid-E_{max} function form, with a mean maximal reduction from baseline values at initiation of therapy of approximately 24.5% after 4–5 months. This decrease in clearance, however, was not considered clinically relevant [20].

It was hypothesized that the decrease in nivolumab clearance over time may be associated with the improvement of disease status, and the associated decreased cachexia. The magnitude of individual clearance change was found to be associated with the patient response status evaluated based on the Response Evaluation Criteria In Solid Tumors (RECIST) criteria. Patients with complete response or partial response showed the larger average decrease of clearance over time, while patients with stable disease or progressive disease showed the smaller average decrease of clearance over time [21].

Pharmacometrics also played a key role in the switch of body weight based dosing to flat dosing for the currently approved indications in 2016. 3 mg/kg IV every two weeks was replaced with 240 mg IV every two weeks as the label recommended dosing regimen for renal cell carcinoma, metastatic melanoma, and non-small cell lung cancer. The approval was based on population PK analyses and dose/exposure-response analyses demonstrating the comparability of the PK exposure, safety and efficacy of the flat dosing with the previously used body weight-based dosing [22]. The benefits of flat dosing include the

elimination of excess drug waste, convenience to health care providers, and reduced concerns regarding accurate dosing in patients with weight fluctuations. In 2018, the FDA approved a Supplemental Biologics License Application adding a 4-week dosing schedule for nivolumab and a shorter 30-minute infusion for a majority of approved indications.

Combination immunotherapies may offer synergistic effects in efficacy by targeting multiple mechanisms in the cancer-immunity cycle. FDA approved the combination of nivolumab and ipilimumab for the treatment of melanoma in 2015. The increased efficacy, however, came at the cost of increased adverse effects. Pharmacometrics may play an even more important role in the dose selection for combination therapies because of the inability to explore all possible combinations of dosing regimens in clinical trials [19]. Therefore, the increased application of model-based analyses to facilitate better understanding the therapeutic window of combination therapies in immune-oncology seems highly desirable.

Pembrolizumab

Pembrolizumab is a humanized IgG4 monoclonal antibody against PD-1 with no ADCC/CDC activity. PK, PK-PD and exposure-response evaluations played an important role throughout the clinical development of pembrolizumab [23].

Pembrolizumab was initially approved by FDA for the treatment of unresectable or metastatic melanoma through a single expanded Phase 1 study (N=411) with the recommended dose of 2 mg/kg every 3 weeks. Modeling and simulation played a key role in support of identifying an appropriate dosing regimen in lieu of extensive dose-finding studies. A recent perspective summarized the modeling and simulation strategy in melanoma [23]. Two approaches were utilized to identify the appropriate dosage regimen balancing benefits and risks. The first approach characterized the PK-PD relationship with an exploratory *ex vivo* peripheral blood mononuclear cell biomarker IL-2 stimulation ratio, which is a surrogate for target engagement, and PK data obtained in the initial cohorts of the clinical study [24]. A key design feature was the inclusion of doses substantially lower than those expected to demonstrate PD activity and intrapatient dose-escalation (0.005-0.3-2.0 mg/kg, 0.02-0.3-2.0 mg/kg, 0.06-1.0-10 mg/kg), allowing for precise assessment of the PK-PD relationship [25]. Peripheral PK-PD characterization through the *ex vivo* IL-2 assay provided the information that 95% saturation was reached at ~1 mg/kg Q3W. Further modeling suggested that at 1 mg/kg Q3W the probability of achieving full target engagement was 64%, and at ≥2 mg/kg the probability was 90% or higher (including 10 mg/kg) [24]. Therefore, a dose of 2 mg/kg was assumed to likely fall near the plateau of the underlying exposure-response relationship achieving near-maximal clinical efficacy and was proposed as the efficacious dose.

The second analysis used a translational PK-PD modeling approach based on integration of available preclinical PK data, PD-1 receptor occupancy, and anti-tumor efficacy data from a syngeneic mouse model [26]. Translational PK-PD modeling is a unique approach in translational research to integrate diverse preclinical information to predict either human biomarkers or exploratory early clinical endpoints. The results suggested a minimal increase in efficacy for doses higher than 2 mg/kg. Therefore, the dosing regimen carried forward in

the pivotal trial, 2 mg/kg Q3W, was based on multiple data sources and pharmacometric analyses including translational modeling, *ex-vivo* IL-2 data and observed clinical data [23]. In the pivotal trial, the flat exposure-efficacy (ORR) and exposure-safety relationships across the AUC range observed with doses of 2 mg/kg and 10 mg/kg Q3W supported an optimally efficacious dose of 2 mg/kg Q3W. Therefore, both translational PK-PD modeling and exposure-response analyses contributed to the identification of the optimal dose for pembrolizumab.

Similarly as for nivolumab, a flat dose of 200 mg every 3 weeks recently replaced body weight based 2 mg/kg Q3W dosing for pembrolizumab in the label based on post-approval population PK analyses demonstrating their equivalence in exposure [27]. Pembrolizumab clearance is also approximately 20% lower at steady state than that after the first dose. Similar to nivolumab, this decrease in pembrolizumab clearance with time was not considered clinically important [28].

Avelumab

Avelumab is a fully human IgG1 monoclonal antibody that specifically binds PD-L1 with a native Fc region capable of inducing ADCC, in contrast to other mAbs targeting PD-1/PD-L1 which lack the ability to trigger ADCC due to belonging to the IgG4 subclass or possessing a mutated Fc region [29]. The half-life of avelumab (3.9 – 4.1 days) is relatively short compared with other anti-PD-1/PD-L1 monoclonal antibodies, including nivolumab (12–20 days), pembrolizumab (14–22 days), and atezolizumab and durvalumab (both approximately 21 days) [30]. Similar to nivolumab and pembrolizumab, avelumab exhibited a decrease in clearance over time during prolonged therapy [31].

A starting dose of 1 mg/kg for dose-escalation in humans was utilized based on toxicology studies in Cynomolgus monkeys, which was further supported by preliminary data showing that this dose level had pharmacological activity including target occupancy and T-cell activation [30]. In a Phase 1a dose-escalation trial, mean PD-L1 target occupancy on CD3+ T-cells at the end of cycle 1 (day 15) before the second dose was greater than 90% at doses of 3 mg/kg and 10 mg/kg [30]. The dosing regimen of 10 mg/kg every 2 weeks was selected for further development in Phase 3 trials based on the totality of the data including the safety and tolerability in the Phase 1a study, pharmacometric modeling, and target occupancy. *In vitro* studies have previously shown that 1 μg/mL was the serum level required to ensure more than 90% target occupancy, and data analysis and model-based simulations indicated that trough levels at 10 mg/kg, but not at 1 and 3 mg/kg, were sufficient for >95% target occupancy at all dosing occasions [30, 32, 33].

Atezolizumab

Atezolizumab is a humanized Fc-engineered IgG1 monoclonal antibody that specifically binds PD-L1 on tumor in ltrating immune cells and tumor cells, and inhibits its interaction with its receptors PD-1 and B7.1 [34]. The Fc region of atezolizumab is modified in such a way that it induces neither ADCC nor CDC [34]. The approved dosing regimen of atezolizumab in metastatic urothelial carcinoma and metastatic NSCLC is fixed (non-

weight-based) at 1,200 mg every 3 weeks, which is the same as that utilized in the pivotal trials [34]. In the dose escalation part of the Phase 1 study, atezolizumab was dosed based on body weight at doses ranging from 0.01 to 20 mg/kg. A maximum tolerated dose was not achieved during that escalation. In the dose expansion part of the Phase 1 study, atezolizumab was dosed on a weight-based (mg/kg) dose of 15 mg/kg as well as a fixed dose of 1,200 mg. Pharmacometric analyses did not identify a statistically significant exposure-response relationship based on the available data [34]. A lack of exposure-safety relationship in addition to an assessment of the PK profile of atezolizumab in relation to the target serum concentration of 6 μg/mL led to the adoption of a 1,200 mg fixed dosage Q3W (equivalent to an average body weight-based dose of 15 mg/kg) for later clinical trials, including the pivotal trials [34]. This dosing regimen provided acceptable safety and efficacy data. Furthermore, this dosing regimen can reach a projected target steady-state trough concentration of 6 μg/mL based on nonclinical tissue distribution data in tumor-bearing mice and the desired receptor occupancy in the tumor [35].

Durvalumab

Durvalumab is also a humanized Fc-engineered IgG1 monoclonal antibody that specifically binds PD-L1, but induces neither ADCC nor CDC [36]. Durvalumab does not bind to PD-L2, which may help avoid potential immune-related toxicity due to PD-L2 blockade. In a posthoc population pharmacokinetic analysis, durvalumab clearance was found to decrease slightly over time, with a mean maximal reduction from baseline value of 15.5% [37]. The proposed dosing regimen of 10 mg/kg Q2W in urothelial carcinoma patients is based on a manageable safety profile, clinically meaningful efficacy in patients with locally advanced or metastatic urothelial carcinoma, and achievement of desired target trough concentrations of 50 μg/mL for target occupancy in the majority of the patients [37]. An exposure-efficacy and exposure-safety analysis of durvalumab in patients with urothelial carcinoma and other solid tumors indicated no relationship of PK exposure with either the efficacy or safety following a 10 mg/kg IV Q2W regimen [38]. Model-based simulations indicated similar overall PK exposures following weight-based (10 mg/kg Q2W) and fixed dosing regimens (1,500 mg Q4W or 750 mg Q2W), demonstrating the feasibility of switching to a fixed dose regimen [39].

Challenges in the Exposure-Response Analysis

The assessment and definition of the exposure-response relationship for immune-oncology agents by pharmacometric approaches has been complicated by time-dependent changes in the pharmacokinetics of these therapeutic mAbs, whereby the clearance is decreasing over time during prolonged therapy, on average between 20–40% over a time frame of 2–6 months. This time-dependent change in clearance seems to be a class effect of anti-PD-1/PD-L1 mAbs as it has so far been reported for at least nivolumab [20], pembrolizumab [28], avelumab [31], and atezolizumab [35].

While the mechanistic basis for this time-varying clearance has so far been undetermined, it has been suggested that the change in the clearance of these antibodies is secondary to a general change in protein turnover in the body, including endogenous immunoglobulin

turnover [40]. Elevated whole body protein turnover of up to 50–70% is a well described phenomenon in cancer patients and is assumed to be caused by a chronic inflammatory status in these patients [41]. In line with these observations, concentrations of serum albumin, as endogenous protein, have frequently been reported as an inversely correlated covariate for mAb clearance, where increased albumin levels are indicative of decreased mAb clearance [9, 42]. Changes in the endogenous protein turnover over time due to either the natural progression of the disease or the therapeutic effect of the mAb would then result in time-varying clearance for therapeutic mAbs [20, 40].

While the occurrence of time-variant pharmacokinetics can be well addressed with model-based pharmacometric approaches, as exemplified for nivolumab [20], the situation for exposure-response analyses is further complicated by the fact that the magnitude of the time-dependent change in clearance seems to be linked to treatment response.

The observation that the change in clearance was higher in patients with complete response or partial response according to RECIST criteria compared to those with stable or progressive disease was not only made for nivolumab as previously mentioned, but has also been described for pembrolizumab and avelumab. It is also not limited to a specific type of cancer, but has been observed in a variety of cancer indications, including NSCLC, renal cell carcinoma, melanoma and Merkel cell carcinoma [21, 28, 31]. As systemic exposure is, in these cases, not an independent predictor for response but rather a function of response, application of classic exposure-response methodologies may lead to misinterpretations and artificial exposure-response relationships, particularly if only one dose level is considered [40]. To minimize the impact of response effects on clearance and identify the causal exposure-response relationship, approaches such as use of early exposure/baseline clearance, i.e., trough concentrations ($C_{trough1}$) or area-under-the concentration-time curve (AUC_1) after the first dose, have been utilized in the exposure-response analyses, as well as the reliance on dose-response assessments over a wide range of dose levels.

The notion that the magnitude of change in mAb clearance is correlated with treatment response has also triggered considerations that change in mAb clearance may potentially even serve as an early biomarker for response to therapy in this class of compounds.

Conclusions

In summary, extensive application of pharmacometric and quantitative clinical pharmacology approaches has substantially contributed to the characterization of the dose-exposure-response relationships for currently approved immune-oncology mAbs, thereby facilitating the selection of optimal dose levels for efficacious cancer therapy with acceptable safety in a variety of cancer indications.

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