# TDM of belatacept and other biologicals in transplantation.

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**Abstract**

In solid organ transplantation biologicals like recombinant therapeutic proteins, monoclonal antibodies, fusion proteins and conjugates are increasingly used for immunosuppression, desensitization, ABO incompatibility, antibody mediated rejections and atypical hemolytic uremic syndrome. For some of these drugs this represents off-label use; and the evidence to define their role in current therapies and the evidence for their clinical benefit may be sparse. Biologicals are large molecules compared to traditional drugs, and the processes that define their pharmacokinetics are different. Validated drug assays that can be applied in clinical routine are to a large extent available. Dosing is currently mostly standard -either fixed doses or adjusted according to body size; and when drug concentrations have been measured, large variability in distribution and elimination has been demonstrated. This opens for the proposal to identify optimal concentration ranges, establish PK/PD models for interpretation and guidance, leading to model informed precision dosing. Extrapolation of the results from use of these drugs on other indications may provide some of the necessary information. For drugs like alemtuzumab, eculizumab, rituximab, tocilizumab and belatacept there may be a potential for model informed precision dosing. However, for all of these the challenge is to perform studies that are properly designed to provide evidence for beneficial outcome related to the individualization of treatment. This calls for collaboration within the transplantation and TDM community.

## Introduction

Biologicals -in this context mostly drugs that are recombinant therapeutic proteins, monoclonal antibodies (mAb), fusion proteins and conjugates- have entered many therapeutic areas in the last couple of decades.

The pharmacokinetic characteristics of such drugs differ in several aspects from the traditional small molecule drugs. The route of administration is frequently intravenous (iv) only, occasionally formulations for subcutaneous (sc) administration are available and may introduce a source of variation in bioavailability. Still, the most important factor giving rise to variability within and between patients, is the elimination of biological drugs. The question is whether this leads to variations of a proportion suggesting that individualization of dosing is warranted. Currently, for most of the established therapies with biologicals, the dosage regimens are typically one recommended dose for all adults -or in some cases dose adjusted to bodyweight or body surface area.

In organ transplantation there are only a limited number of biologicals with immunosuppression after transplantation as the labelled indication. A few more may have labels relevant for treatment of conditions related to transplantation or the underlying disease. A number of biological drugs, however, are used off label on various indications in organ transplant recipients. Hopefully, in many cases it will serve the patient well, but unless this transforms into formal clinical studies of the new indication, it is difficult to aggregate experience with dosing versus response and toxicity and to optimize the treatment further by implementing therapeutic drug monitoring (TDM). Following a period of very few drugs reaching approval for the use in transplant recipients, there is currently a resurgence and a number of biologicals are in clinical testing, mostly for desensitization and treatment of antibody mediated rejections, but also for some other specific indications. Examples of such drugs are listed alongside drugs with approved indications in Table 1.

**Criteria for TDM**

When considering whether a drug should be a candidate for TDM, there are several criteria that should be assessed. The most important can be summarized as to whether there is: - an available, validated assay to measure the drug concentrations or an other relevant biomarker

- a known relationship between the obtained concentration in plasma (or other relevant matrix) and the effect or toxicity of the drug

- variability in plasma concentration large enough that some of the obtained concentrations will be outside a presumed optimal range; i.e. whether it is a narrow index drug

- evidence supporting an increased probability of successful treatment -effect without toxicity- if dosing is adjusted to obtain a suggested target concentration range

- a need for lower or higher exposure in special subpopulations (e.g. transplant recipients with high risk)

- issues with respect to adherence to prescribed treatment (not relevant for drugs administered iv)

- 'financial toxicity'; high prices may hamper availability of adequate treatment for patients, especially in lower economy regions. Personalized dosing can be used to explore whether lower doses or increased dose intervals can be effective, as has been demonstrated for immune checkpoint inhibitors in cancer treatment [1].

**Assays for measurement of biologicals**

The measurement of biologicals in clinical samples faces different challenges from traditional small molecules assays, some of which are obvious given their large and complex structures. Ligand-binding assays, both commercially available and in-house developed, have been used for quantifications of mAbs, including several among the ones relevant in transplantation [2-4]. These methods can also be adapted to or complemented with assays for the detection of anti-drug antibodies (ADA) [3, 5]. Recent technological advances in mass spectrometry based analysis (LC–MS/MS) have enabled the development of multiplex bioanalysis which means that several mAbs can be analysed in the same setup [6], as exemplified for some of the drugs that are discussed in the following [7-10]. The detailed discussion of the analytical challenges and pitfalls are beyond the scope of this paper, and readers are referred to the cited reviews for details.

**Pharmacokinetics of biologicals**

The pharmacokinetic characteristics of biologicals differ in important aspects from traditional small molecule drugs. The majority of biologicals are administered by iv infusion. This allows rapid delivery of sufficient amounts of drug and the required volumes that may be too large for other parenteral routes, while also securing complete bioavailability. Some biologicals have a formulation for subcutaneous (sc) administration, which may introduce variations in bioavailability but allows injections at home and also may provide less fluctuation in exposure if the dosing is split into more frequent administrations. Absorption from sc injection occur via the lymphatic system, but the biologicals with lower molecular weight can also be absorbed by blood capillaries [11]. The lymph fluid drains slowly into the circulation, therefore the absorption into blood may typically continue for days. Bioavailability after sc administration is influenced by physicochemical properties of the antibody, and it is suggested that for these characteristics there may be an inverse correlation between bioavailability and elimination [11-13]. The co-formulation of mAbs with hyaluronidase has facilitated the administration of larger volumes and amounts of drug by sc injections.

Concentrations of mAbs in tissue interstitial fluid are in general lower than in plasma. This is because the large and polar antibodies move slowly across the vascular endothelial cells, and the elimination from tissue can be fast compared to the convective uptake. In highly perfused tissues like bone marrow, spleen and liver, higher concentrations have been observed [11, 13].

The typical processes that determine the pharmacokinetics of biologicals are recycling mediated by the neonatal Fc receptor (FcRn), target-mediated clearance, ADA response and off-target binding [13].

When circulating IgG, albumin and other serum proteins are taken up by pinocytosis into endothelial cells or monocytes, they will bind to the FcRn in the acidic endosomes (pH[?] 6). This enables IgG to escape the degradation by lysosomes, and when IgG reaches the cell surface and a physiological pH, it is released back to the circulation. The IgG which is not bound to FcRn will be degraded by the lysosomes. This directed circulation provides regulation of IgG homeostasis. The drug mAb and antigen complexes are recycled in a similar manner as the native IgG. Clever modification of specific sites in the mAbs favours that the bound antigen is split from the mAb and destined to degradation while the mAb is rescued by the FcRn and recycled in a similar manner as native IgG. Increased half-lives of therapeutic mAbs have been achieved by increasing their binding to FcRn at pH 6 while also maintaining or increasing release at pH 7.4 [14]. As an example, eculizumab has a relatively short half-life in the circulation of about 11 days. The introduction of two selected amino acid substitutions in the Fc region, to increase the affinity to FcRn, increased the half-life several fold (as in ravulizumab) [14, 15].

An important feature of the target-mediated clearance (or target mediated drug disposition, TMDD) is that it is non-linear. The binding of drug to its target, whether receptors, enzymes or transporters, and the subsequent dissociation and degradation of the drug-target complex, is dose dependent. At low concentrations of mAb the TMDD contributes significantly to overall elimination of the drug. With increasing mAb concentrations TMDD is gradually saturated and clearance decreases. At the higher mAb concentrations the first-order elimination via FcRn will dominate and eventually the nonlinear pathway becomes negligible [13]. The TDMM is mostly relevant for drugs that target surface antigens but may also be important versus soluble antigens. To appreciate these effects, one must be aware that the nonlinearity of elimination may be masked in clinical practice for drugs that are given in doses that saturate the target.

The repeated administration of biologicals like mAbs can be highly immunogenic. While the development from chimeric to humanized and fully human mAbs has reduced immunogenicity, the development of ADA may still occur. In various studies the frequencies of ADA development across a range of mAbs have been reported from zero up to 70%. The mechanisms for ADA development are not fully understood; both drug and patient characteristics as predisposing factors have been identified [16]. In addition to the risk of adverse immune reactions, the development of ADAs can lead to reduced or loss of treatment response. The ADA that develop in patients are characterized as either neutralizing antibodies which directly block the ability of the drug binding to its target, or the non-neutralizing ADA that bind to sites of the drug which does not interfere with target binding. Although the effect may be retained in the latter situation, these non-neutralizing ADA may reduce bioavailability and accelerate the drug clearance [17].

Off-target binding of mAbs may also contribute to altered pharmacokinetics, including tissue distribution and drug elimination. Specific pre-clinical screens as well as sophisticated modelling have been applied in order to identify mAbs with a higher risk of fast clearance [18, 19]. There are examples where mAbs with identical Fc regions but slightly different variable regions appear to have diverging elimination rates that could be attributed to off-target binding [18]. Obviously these are aspects of biologicals PK variability that need to be investigated in the pre-clinical development of biologicals. However, it is difficult to decipher to what degree the off-target binding contributes to PK variability of a biologic drug when used in the clinical setting.

**Model informed precision dosing**

If the criteria for TDM are met, the application in the clinical setting can be improved by the use of population PK/PD models to facilitate model informed precision dosing (MIPD). Such models have been developed, validated and applied in research for decades -for small molecule drugs and increasingly also for biologicals. However, the implementation of such tools into the clinical use of biologicals has been limited, which may also reflect the sparse evidence for the role of TDM in this setting. There are examples especially in the therapy of inflammatory bowel disease and some other immune diseases where MIPD has been explored to guide personalization [20-23]. Also for a drug like alemtuzumab a PK/PD model was developed for patients treated for chronic lymphocytic leukaemia (CLL) [24]. Although the model performed well in this setting, the study highlighted the nonlinear and time-dependent pharmacokinetics due to changes in WBC count for the CLL

patients, which again illustrates that models may not be applied in other patient populations like transplanted patients. A lot of work has been invested to better understand the contributions of physiological processes and drug characteristics that govern the PK and PD and hence can guide the model development. The more complex descriptions may be more relevant in the process of mAbs development [19, 25], however there may also be lessons to learn for models. How the application of a PK/PD model can improve the personalization of a biologic like eculizumab, has been elegantly demonstrated by the work of a group at Cincinnati Children's Hospital. The treatment of transplant-associated thrombotic microangiopathy (TA-TMA) in children and young adults undergoing hematopoietic stem cell transplantation (HSCT) was prospectively individualized by support of a model that was proven effective for eculizumab versus outcome of these severe adverse effects of the HSCT [26, 27].

**Belatacept**

Belatacept is a soluble fusion protein combining the human IgG1 Fc domain with the modified extracellular domain of cytotoxic T lymphocyte–associated antigen 4 (CTLA4). As a CD28 homolog it binds to CD80 and CD86 on the antigen-presenting cells, thus inhibiting CD28-mediated T cell co-stimulation and thereby selectively preventing the activation of T cells. Belatacept is approved for rejection prophylaxis in renal transplant recipients as an alternative to calcineurin inhibitors (CNI) and in combination with basiliximab, mycophenolate and glucocorticoids. Further clinical trials have tested alternative approaches like belatacept plus mTOR inhibitor, weaning of glucocorticoids and the replacement of basiliximab with alemtuzumab in a belatacept based regimen. A common finding in these studies is a somewhat increased incidence of acute rejections but the decline in renal function and other typical CNI related adverse effects has been avoided.

*Variability*

Based on available reports from the early belatacept trials (see refs in [28]), we concluded in a previous review that the variability in belatacept concentrations seemed to be low -in itself an argument against the need of TDM for this drug [28]. The quoted papers mostly reported geometric means and coefficients of variation of the concentrations and the pharmacokinetic parameters from the applied PK-modelling. However, to get insight into the variability in belatacept PK between individuals, one may re-examine the actual observed individual concentrations in the period (32-52 weeks after first dose) when dosing was similar in the two arms LI ('less intensive') and MI ('more intensive'). Here trough concentrations ranged from less than 0.1 to around 20 µg/L, and although the authors concluded that *'model-predicted time-varying distributions of trough concentrations were in excellent agreement with observed values ... and interindividual variability in PK was low, illustrating that belatacept exposure is predictable and suggesting that the need for therapeutic drug monitoring of belatacept may not be needed for KTRs* ', one could still argue that the interindividual variability on this dosing was quite large when compared to therapeutic ranges for other narrow index drugs that are monitored in transplantation. In a couple of later publications similar ranges of observed belatacept concentrations has been reported as part of the validation of new assays for belatacept concentrations [4, 7]. The patients in both of these reports, n=5 [4] and n=108 [7] were followed in the stable phase of belatacept maintenance following switch from tacrolimus.

*TDM of belatacept*

The inter-individual variability in belatacept exposure seems large enough that a potential for optimized treatment by TDM should be considered. Also, although the switch from CNI based immunosuppression to belatacept in renal transplant recipients has been proven non-inferior with respect to long term graft and patient survival, there is still an increased incidence of rejection episodes and the incidence of severe adverse effects is not negligible. So far, none of the reported analyses of a potential association between belatacept concentrations and treatment failure or side effects have found correlations that could indicate a therapeutic range. A weak point in this argumentation, is that studies with the aim to elucidate a PK-PD relationship for belatacept have been hampered since the drug has been unavailable in periods due to manufacturing problems. All considered, the conclusion remains that based on the data currently available, there is not evidence to recommend TDM of belatacept when used in transplantation.

**Other biologicals used in transplantation**

Some of the drugs listed in Table 1 are used in very short courses in organ transplantation. According to definition (FDA https://www.fda.gov/files/drugs/published/Biological-Product-Definitions.pdf), anti-thymocyte globulin preparations (ATG) are biological drugs although not designed and produced like current biologicals. In the US immunosuppressive protocols frequently include ATG for induction therapy, while in most of Europe the specific IL-2R antagonist basiliximab is preferred. In these regimens only one or two doses are given, leaving limited space for personalized dosing except if one would try to individualize the initial dose more than current practice. In steroid resistant rejections ATG is an important treatment option. To reverse the rejection repeated doses will often be required, and in this setting the dosing intervals are adjusted based in part on the absolute CD3 cell counts –which may be considered a form of pharmacodynamics monitoring [29].

Imlifidase is an enzyme which rapidly degrades and depletes IgG from circulation. This drug is approved for desensitization in highly sensitized patients awaiting kidney transplantation. It is also in trials for treatment of ABMR [30]. For desensitization a single dose is recommended pretransplant while a small study also explored the use of one repetition [31]. Dosage is BW adjusted, otherwise no further personalization has been discussed. Of specific note is that several other mAbs may be degraded by imlifidase if administered concurrently.

*Abatacept*

Abatacept was the predecessor of belatacept; in the latter two amino acid substitutions provided a more potent binding of its ligands CD80 and CD86. This led to the approval of belatacept for use in kidney transplantation while abatacept is used in rheumatoid arthritis. While belatacept is available for intravenous use only, abatacept can also be given by subcutaneous injections. This led a French group to test the replacement of belatacept by abatacept sc in stable transplant recipients, as a feasible alternative to belatacept to reduce their need to visit the hospital during the initial stay-at-home order in France under the COVID-19 pandemic. Data on the use of abatacept in kidney transplantation are scarce, patients in the study were switched from abatacept after three months. In this perspective the treatment was successful with only two rejection episodes (n=176) while 19 patients (11%) had abatacept discontinued for various reasons. In this study the abatacept dosage was 125mg sc every week for all patients [32].

This study raises questions whether abatacept sc could be an alternative to belatacept in stable kidney transplant recipients long term. Another alternative, if feasible, would be to have a formulation of belatacept for sc administration. If these options should be further explored, it could also provide an opportunity to investigate the potential for a more individualized dosing. So far this has not been advocated for abatacept on any of its indications [33].

*Rituximab*

Rituximab induces a depletion of blood CD20+ B cells followed by reconstitution over subsequent

months and reduces the number of these cells in spleen and lymph nodes. In kidney transplantation, rituximab has been tested for reduction of blood group antibodies in blood group incompatible transplantation, in reducing the concentration of DSA in highly immunized recipients and to treat AMBR [30]. In an early trial using rituximab in renal transplant recipients the authors concluded that a single dose of rituximab, as opposed to repeated doses, was sufficient for sustained depression of B cells in peripheral blood. In that study all patients received 375mg/m2 [34]. In contrast to what was suggested by retrospective studies, later clinical trials using similar rituximab dose have not been able to confirm a significant benefit of rituximab on AMBR [30]. From the perspective of personalized dosing, it is of interest that in the study by Sautenet et al [35], 1-2 extra rescue administrations of rituximab was allowed. In the control group and in the rituximab group, this occurred for 42% and 32% of the patients respectively. Also, adverse reactions from rituximab are frequent, therefore one hypothesis would be that the introduction of MIPD might better predict the effective dose regimen already from the start –however this has not been addressed for transplanted populations.

Since rituximab has been used in several years for other diseases like rheumatoid arthritis, cancers and more, the PK/PD studies in these areas might indicate if and how personalized dosing could be introduced. A recent review on TDM of biologicals in rheumatoid arthritis [33] concluded that for rituximab the evidence was insufficient, but still that rituximab concentrations could predict the occurrence of ADAs and also in retrospect that lower rituximab levels preceded flares [36]. Studies in patients with lymphomas revealed log-fold inter-individual variability in rituximab concentrations indicating that median levels are not representative [37] and that time-changes in clearance could serve as a predictive marker of response [38]. This has also been suggested from recent trials of rituximab in multiple sclerosis [39]. Although different from the transplantation setting, these experiences with rituximab in divergent diseases, dosing regimens and drug combinations may be relevant for further trials were the potential benefit of MIPD could be explored.

*Alemtuzumab*

The approved indication for alemtuzumab is relapse-remitting multiple sclerosis. Alemtuzumab is a humanized, monoclonal IgG1 antibody directed against CD52 that is expressed on T and B

lymphocytes, as well as on natural killer (NK) cells and monocytes. In renal transplantation the drug is used off-label both for induction and as antirejection therapy. Although PK data exist from the use of this drug in chronic lymphocytic leukemia (CLL), this is an example where target-mediated clearance will differ between these two indications due to the much higher load of CD52-positive cells in patients with CLL, hence the extrapolation of PK data cannot be precisely extrapolated. The PK of alemtuzumab has been investigated in renal transplant recipients from a clinical trial where all patients received alemtuzumab sc immediately before and 24hrs after transplantation for induction of immunosuppression [40]. A large between-patient variability in distribution and elimination was observed, and a PK model was developed which showed an adequate concordance of the observed and population and individual predicted alemtuzumab concentrations. The PK variability was to a large degree explained by body size and the authors suggested that lean BW-adjusted dosing can be applied to correct for this phenomenon, showing potential as a marker to reduce between-subject variability in alemtuzumab exposure.

Another recent study presented a model predicting the response to alemtuzumab for acute kidney transplant rejection [41]. From the 115 patients a set of clinical and histological characteristics were collected and logistic regression modelling was used to construct a prognostic score enabling the accurate prediction of response which was even further improved by including a set of targeted gene expressions. This study did not include measurement of alemtuzumab concentrations. Taking into account the efficient depletion of immune cells following an alemtuzumab dose and the associated risk of infections, malignancy and autoimmunity, and the fact that a single 30mg dose is used, it is conceivable that many patients may be overdosed when treated for acute rejection.

Taken together these recent studies suggest that follow-up studies on the relation between alemtuzumab PK, lymphocyte dynamics and clinical outcomes are warranted to further substantiate the clinical potential

and rationale for personalized alemtuzumab therapy in kidney transplantation [40]. And as pointed out in an editorial [42]: the combination of clinical and histologic data with molecular analysis of renal allograft biopsies and pharmacokinetic data of the drug of interest is the way forward.

*Daratumumab*

Daratumumab is directed against CD38 and it has been suggested that it may be effective in reducing preformed antibodies and desensitizing patients, given its effect on plasma cell elimination. Only case reports have been published so far, and there has been concerns whether this drug could cause depletion also of regulatory B cells and thus induce a T cell mediated rejection [43]. Currently two clinical trials are in progress including highly HLA-sensitized patients awaiting kidney transplantation. From the summaries of study plans (ClinicalTrials.gov ID NCT05145296 and NCT04204980) it is not clear whether samples to estimate PK will be collected. Obviously this would be of particular interest in the situation where one may expect toxicity to be a limiting factor.

*Tocilizumab and Clazakizumab* The currently approved indications for tocilizumab are rheumatoid arthritis and some other autoimmune diseases as well as the treatment of Covid-19 for selected patients. This drug is acting via inhibition of the IL-6 receptor. Tocilizumab has shown some promising results both in the treatment of AMBR and in desensitization, and the potential for such treatment both in kidney, lung and heart transplantation has been discussed in several recent papers [30, 44-47]. More rigorous and sufficiently large trials are needed to clarify the role for tocilizumab as well as other IL-6 or IL-6R inhibitors in these settings. Meanwhile there are also studies that indicate large variability in the PK of tocilizumab. Such data have been collected for tocilizumab when used on its label indications, however there are also recent studies in transplant recipients showing the significant variability in PK. A few of these studies have also used PK models in order to characterize the parameters in detail and even indicated association between tocilizumab concentrations and effects like reduction in anti-HLA antibodies [9] and albuminuria [48] while others did not find such correlations [49]. It is a challenge to arrange prospective studies that are able to provide evidence for the benefit of TDM. One opportunity that could be pursued, is to involve the measurement of drug concentrations as a sub-protocol in clinical trials that are planned to demonstrate effectiveness by clinical endpoints. Clazakizumab is an IL-6 antagonist which has also been suggested for the treatment of AMBR. So far only small studies have been reported [30]. However a large phase 3 multicentre clinical trial is ongoing, and according to the protocol (IMAGINE-trial: ClinicalTrials.gov identifier: NCT03744910) samples will be collected during the first three weeks to provide individual pharmacokinetic parameters. The anticipated study population of 350 patients should guarantee that these data will be of great interest for clazakizumab as well as for the discussion of the personalization of biologicals in general in the post-tx setting.

*Eculizumab*

Eculizumab binds to complement component C5, thereby blocking its cleavage and the subsequent formation of the C5b-C9 membrane attack complex, the final common pathway effector of the complement system. Approved indications for eculizumab are paroxysmal nocturnal hemoglobinuria,

atypic hemolytic uremic syndrome (aHUS), myasthenia gravis and neuromyelitis optica spectrum disorder. Besides the prevention and treatment of aHUS and thrombotic microangiopathy (TMA), in organ transplantation there are reports from its use for desensitization, prevention and as supplement in the treatment of AMBR [30, 50-52]. Although these studies are too small to provide definitive conclusions on the role of eculizumab in these situations, there is already an example of how eculizumab concentration measurements combined with a PK/PD model can be used for model-informed precision dosing in the treatment of TMA in children undergoing HSCT [27].

Although no formal economic cost-benefit analysis was reported, for an expensive drug like eculizumab it is worth to notice the remarks from the authors that by using MIPD in their study each patient only received the required therapy course which minimizes the risk of over treating and reduces the clinical and financial burden of eculizumab therapy [26]. The approach that was used in this study could also serve to suggest how to tailor the application of eculizumab and other biologicals in solid organ transplant recipients.

## Conclusion

The use of biologicals like recombinant therapeutic proteins, monoclonal antibodies, fusion proteins and conjugates is expanding. Many of these can be extended to off-label indications within the field of solid organ transplantation based on available experience from their use on other, labelled indications. However, pharmacokinetic characteristics of these large, partly also immunogenic molecules differ from those of traditional small molecules, and the variability may depend on factors like target mediated elimination which complicates extrapolation from one disease to another. So far the studies that have explored individualization by concentration measurements and modelling have been proof-of-concept or feasibility studies that lack the power to provide evidence for eventual improvement in clinical outcome.

For some drugs like alemtuzumab, eculizumab, rituximab, tocilizumab and belatacept the inter-individual variability in pharmacokinetics has been demonstrated. The option for subcutaneous administration may reinforce the need and the potential for individualization by TDM. A few of the drugs mentioned -probably

also for some in the pipeline- there is an economic aspect of appropriate dosing that needs to be pursued. Available assays and models to refine interpretation are in place, the obstacles are in the challenges to perform trials of adequate size to document the usefulness of TDM and model informed precision dosing.

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**Table 1.**

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