

Opinion

Belatacept dosing in Lung Transplantation: is there a Method to the Madness?Christine Pham ^{1,*}, Brett J Pierce ¹, Simon W Yau ², Georges J Youssef ², Ahmad Goodarzi ², Howard J Huang ²

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Received: July 09, 2021**Accepted:** August 25, 2021**Published:** August 30, 2021**Abstract**

Data supporting the use of belatacept in non-abdominal organs are limited to case series and small cohorts involving patients requiring conversion due to CNI intolerance or contraindication. Review articles summarizing the efficacy of belatacept salvage therapy in lung transplantation have previously been published, however, dosing regimens are highly variable and uniform guidance is lacking. In this article, indications and considerations for belatacept use in lung transplant recipients are reviewed with a specific focus on dosing regimens. Utilization of standardized dosing protocols to guide belatacept conversion will both improve the ability to directly assess outcomes and provide the opportunity to improve future patient care. A suggested framework for dosing selection and timeline for cross titration is proposed herein.



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Keywords

Lung transplantation; belatacept; immunosuppression; dosing

1. Introduction

Belatacept is commonly used in kidney transplantation for maintenance immunosuppression as an alternative to calcineurin inhibitors (CNI) due to its more favorable metabolic profile, reduced chronic allograft nephropathy and incidence of *de novo* donor specific antibodies (DSAs), preservation of renal function, and improved long term patient and graft survival [1]. Belatacept was approved in 2011 by the US Food and Drug Administration (FDA) for use in combination with basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids for prevention of rejection in adult kidney transplant recipients seropositive for Epstein-Barr virus (EBV) [2]. The immediate post-transplant labeled dose is 10 mg/kg intravenous (IV) on days 1 and 5, and weeks 2, 4, 8, and 12 post-transplantation, followed by 5 mg/kg every four weeks thereafter. This dosing scheme was used in the BENEFIT and BENEFIT-EXT studies, leading to its approval for *de novo* use. While both of these studies showed superior renal and metabolic outcomes, they also found that belatacept was associated with higher rates of acute cellular rejection within the first year post-transplant [3, 4]. Subsequently, alternative non-FDA approved belatacept-based maintenance regimens were explored including: (1) later post-transplant conversion from CNI to belatacept; (2) combination of belatacept plus a mammalian target of rapamycin inhibitor (MTORI); (3) belatacept plus transient CNI; and (4) T cell-depletive induction followed by belatacept plus MMF and early corticosteroid withdrawal [1]. All these strategies were described in a kidney transplant population. Belatacept carries multiple black box warnings (BBW). The first BBW concerns increased risk of development of post-transplant lymphoproliferative disorders (PTLD) in those seronegative for EBV. As such, EBV seropositive status should be confirmed in all patients in whom belatacept is considered. The second BBW advises against use in liver transplantation due to an exploratory phase II study showing increased risk of death and graft loss within 6 months post-transplant [5]. The mechanism explaining this association in liver transplantation remains unclear and has not been observed within the other transplanted organ populations.

Data supporting the use of belatacept in non-abdominal organs are limited to case series and small cohorts involving patients requiring conversion due to CNI intolerance or contraindication. Clinical trials evaluating *de novo* use of belatacept in lung transplantation are currently underway [6]. Robust review articles summarizing the efficacy of belatacept salvage therapy in lung transplantation have previously been published, however, there exists little guidance on dosing selection [2]. This article reviews published belatacept dosing regimens to provide a framework for dosing selection in lung transplant recipients (LTRs) requiring conversion.

2. Indications for Salvage Therapy in Lung Transplant

Belatacept has no FDA approved indications for use in LTRs. However, belatacept has been used in LTRs for the purpose of renal sparing when alternative therapies were ineffective or when contraindications to CNIs exist. Additionally, the utility of belatacept in patients with donor specific

antibodies (DSAs) and chronic antibody mediated rejection (AMR) has been explored within the kidney transplant literature.

2.1 Renal Sparing

While CNIs are standard of care for prevention of rejection, they are associated with chronic renal dysfunction through constriction of the afferent renal artery. Prevalence of chronic kidney disease stage ≥ 3 is 22.4% at one year and ~50% at five years post-lung transplant [7, 8]. When compared to kidney transplant recipients, LTRs are maintained at higher CNI goals due to increased immunologic risk [9]. Post-transplant tacrolimus goals at our center are 10-15 ng/mL for the first 90 days, 8-12 ng/mL for days 91-365, 5-10 ng/mL for years 1-3, and tapered to 5-8 ng/mL thereafter. In kidney transplantation, MTORIs are recommended for renal sparing either through replacement of CNI or combination therapy with minimized CNI. Recommendation of belatacept over MTORIs for the purpose of renal sparing cannot be provided due to lack of efficacy data. However, MTORIs are poorly tolerated due to issues with impairment of wound healing, proteinuria, hypertriglyceridemia, cytopenias, peripheral edema, or pneumonitis. In the event an LTR cannot tolerate MTORI, belatacept may be an appropriate option to consider.

2.2 CNI Intolerance

In thrombotic thrombocytopenia purpura (TTP), hemolytic uremic syndrome (HUS), or posterior reversible encephalopathy syndrome (PRES), re-challenging a CNI may not be ideal [10-12]. These complications generally occur in the immediate post-transplant phase, during which MTORI cannot be utilized. Reliance on belatacept for maintenance immunosuppression within the early post-transplant period compromises increased rejection risk. During instances of CNI contraindication, concurrent timely withdrawal of the CNI with up titration of the replacement agent is ideal.

2.3 Donor Specific Antibodies/Antibody Mediated Rejection

Post hoc analysis of data from the BENEFIT and BENEFIT-EXT trials have demonstrated both significantly lower *dn*DSA formation in patients receiving belatacept versus cyclosporine, and better control of persistence of preexisting DSAs posttransplant as determined by MFI [13, 14]. These findings spurred further exploration into the utility of belatacept in patients with DSAs/AMR [15, 16]. Specifically, Kumar et al. reported a reduced rate of decline in renal function and a numerical nonsignificant decline in mean immunodominant DSA post-belatacept conversion in 19 kidney recipients with chronic active AMR [17]. DSA incidence at any time post-transplant in LTRs (26-47%) is significantly higher than in kidney transplantation (2-5% per year) [18-20]. Conversion to belatacept for treatment of DSAs/AMR is not directly supported within the literature. However, LTRs who are unable to tolerate augmented CNI goals due to chronic kidney disease, full dose MMF due to cytopenias, or immune-depletive therapies due to infections may benefit from a more targeted/alternative maintenance immunosuppression regimen.

2.4 Absorption Concerns

LTRs commonly experience post-transplant gastroesophageal reflux disease (GERD) and gastroparesis. These abdominal complications are associated with decline in lung function, and have

been identified as possible causes of CLAD [21]. Unique subsets of patients transplanted for either interstitial lung disease or pulmonary hypertension include those with connective tissue disorders (i.e. scleroderma or sarcoidosis). Because both scleroderma and sarcoidosis are autoimmune disorders, lung transplantation is not curative, but rather, provides patients with functional respiratory reserve and subsequent improvement in mortality. Post-transplantation, these patients are at exquisitely high risk for chronic aspiration, malnutrition, and absorption concerns. It is possible that use of belatacept may be advantageous in patients with absorption concerns who have difficulties maintaining stable CNI levels. However, this hypothesis requires further exploration.

3. Precautions for Use

Given the paucity and heterogenous nature of existing data, it is unclear what long-term safety concerns may exist with use of belatacept in lung transplantation. Recent studies in kidney transplantation have highlighted the risk of CMV infections with belatacept. One study found high-risk (donor CMV IgG seropositive, recipient CMV IgG seronegative) kidney transplant recipients treated with a belatacept-based regimen experienced a higher incidence of CMV viremia, and a non-significant trend towards higher risk of graft loss [22]. A second study found that CMV disease occurred in 18% of kidney transplant recipients converted to belatacept (median nine months post-conversion, median 30 months post-transplant) with 73% of these cases occurring in low (both donor and recipient CMV IgG seronegative) or intermediate risk (recipient CMV IgG seropositive) patients [23]. However, 38/40 patients who developed CMV disease were not receiving prophylaxis at time of disease diagnosis (median time from prophylaxis discontinuation to CMV disease of 26 months). It may be reasonable to continue CMV prophylaxis in LTRs receiving belatacept, or utilize CMV T-cell immunity panel monitoring to guide prophylaxis duration.

Belatacept resistant rejection (BRR) episodes have been described in kidney transplant recipients, and warrants precaution. The exact mechanism of resistance has yet to be elucidated and appears to be multifactorial. One theory behind BRR is that even with intensive loading and high-dose maintenance regimens, inhibition of T-cell proliferation is unlikely to exceed 70%. Though significantly diminished, low level proliferation, differentiation, and development of memory T-cells continues to occur. Secondly, belatacept exposure may induce CD28 downregulation and increase production of memory T-cells which are not susceptible to co-stimulation blockade. These memory T-cells may also have a higher inclination for allograft infiltration due to increased expression of cellular adhesion molecules [24]. Certain populations of memory T-cells have been implicated in the development of BRR and novel, targeted therapeutics are currently under development in an attempt to abate the deleterious effects attributed to belatacept resistant memory T-cells [25].

4. Dosing Schemes

Belatacept dosing is comprised of an induction (or initial) and maintenance phase. The most common induction doses are 10 mg/kg IV or 5 mg/kg IV x 3-6 doses, given on specific post-transplant days. Belatacept demonstrates linear pharmacokinetics with steady state achieved by week eight in the induction phase and by month six in the maintenance (i.e. without induction phase) [26]. Induction doses for belatacept are recommended to reach >90% CD86 receptor occupancy (% occupied-CD86) for maximal inhibition of lymphocyte proliferation and cytokine interferon- γ production in vitro; this was specifically studied using a dosing scheme of 10 mg/kg x ten doses

within the context of *de novo* use to prevent acute rejection during allograft engraftment [27]. The *in vitro* difference in % occupied-CD86 between the 10 mg/kg x ten doses, 10 mg/kg x four doses, and 5 mg/kg loading doses x four doses was not directly compared, however, the 10 mg/kg dosing scheme achieved trough concentrations two to three times greater than the 5 mg/kg scheme. The % occupied-CD86 receptors over time decreased to 94, 88, 86, 75, 67% at post-transplant days 5, 14, 28, 84, 168, and 184, respectively, during the maintenance phase. It is important to note that there is no recommended minimum % occupied-CD86 corresponding with adequate level of immunosuppression. This *in vitro* data demonstrates that increasing belatacept exposure and dosing regimen does not protect against acute rejection within kidney transplant recipients in the immediate post-transplant phase. Use of the higher dosing regimen (i.e. ten loading doses) was also associated with an increased risk of serious adverse effect [28]. Specifically, administration of higher cumulative doses (greater than 20 mg/kg per single dose) or higher frequency (more frequently than monthly following the initial loading period) should be avoided based on observed higher incidence of central nervous system (CNS) adverse reactions including PTLD, progressive multifocal leukoencephalopathy (PML), and serious infections. While these adverse effects occurred more frequently in EBV seronegative patients—ultimately leading to the inclusion of the BBW—total burden of immunosuppression remains an overall risk factor for PTLD and should be considered.

Across all solid organ transplant patients being converted to belatacept, there is concern for both under- and over-immunosuppression. Ensuring the timely discontinuation of the intended agent without excessive or inadequate overlap appears to be more art than science at this point. The previously published belatacept induction and maintenance doses are compiled in Table 1 and Table 2 respectively. Even within the same indications, dosing schemes varied.

Table 1 Published belatacept induction doses.

Indication	Study	Organ	N	Induction Dose
<i>Non-Abdominal</i>				
Renal Rescue	Timofte et al. [29]	Lung	8	10 mg/kg x 4 doses
CNI Failure (TTP, PRES, HUS)	Iasella et al. [30]	Lung	11	<u>Conventional</u> : 10 mg/kg x 6 doses <u>Transitional</u> : 5 mg/kg every 2 weeks x 6 doses
	Hui et al. [31]	Lung	1	10 mg/kg IV x 1 dose
Non-adherence	Enderby et al. [32]	Heart	1	10 mg/kg x 4 doses
<i>Abdominal</i>				
De novo	Vincenti et al. [3, 4]	Kidney	686	<u>Moderate intensity</u> : 10 mg/kg x 10 doses <u>Low Intensity</u> : 10 mg/kg x 4 doses
<6 months from TXP	Grinyo et al. [33]	Kidney	162	5 mg/kg x 5 doses
Prolonged DGF	Nair et al. [34]	Kidney	16	10 mg/kg x 4 doses
	Le Meur et al. [35]	Kidney	25	5 mg/kg every 2 weeks x 6 doses
	Wojciechowski et al. [36]	Kidney	20	10 mg/kg x 3 doses
CNI Failure (TMA)	Brakemeier et al. [37]	Kidney	70	5 mg/kg x 5 doses <u>CNI-induced TMA</u> : 10 mg/kg x 4 doses

Conversion	Schulte et al. [38]	Kidney	20	5 mg/kg every 2 weeks x 4 doses
	Gupta et al. [39]	Kidney	6	5 mg/kg x 5 doses
	Rostaing et al. [40]	Kidney	173	5 mg/kg x 5 doses

CNI, calcineurin inhibitor; TTP, thrombotic thrombocytopenia purpura; PRES, posterior reversible encephalopathic syndrome; HUS, hemolytic uremic syndrome; TXP, transplant; DGF, delayed graft function; TMA, thrombotic microangiopathy

Table 2 Published belatacept maintenance doses.

Indication	Study	Organ	N	Maintenance Dose
<i>Non-Abdominal</i>				
Renal Rescue	Timofte et al. [29]	Lung	8	10 mg/kg + CNI goal 2-6 ng/mL
CNI Failure (TTP, PRES, HUS)	Iasella et al. [30]	Lung	11	<u>Conventional</u> : 5 mg/kg monthly <u>Transitional</u> : 5 mg/kg monthly
	Hui et al. [31]	Lung	1	5 mg/kg every 4 weeks
	Ong et al. [41]	Lung	1	5 mg/kg every 2 weeks
Non-adherence	Enderby et al. [32]	Heart	1	5 mg/kg every 4 weeks
<i>Abdominal</i>				
De novo	Vincenti et al. [3, 4]	Kidney	686	<u>Moderate intensity</u> : 5 mg/kg every 4 or 8 weeks <u>Low Intensity</u> : 5 mg/kg every 4 weeks
	Grinyo et al. [33]	Kidney	162	5 mg/kg every 4 weeks + CNI discontinued by day 29
	<6 months from TXP	Nair et al. [34]	Kidney	16
Le Meur et al. [35]		Kidney	25	5 mg/kg every 4 weeks + CNI withdrawn over 15-30 days
Prolonged DGF	Wojciechowski et al. [36]	Kidney	20	5 mg/kg monthly + FK 8-12 on D0-13, then 50% on day 14, then off by day 28
CNI Failure (TMA)	Brakemeier et al. [37]	Kidney	70	5 mg/kg every 4 weeks + CNI off by day 180
Conversion	Schulte et al. [38]	Kidney	20	5 mg/kg every 4 weeks + CNI off by day 180
	Gupta et al. [39]	Kidney	6	5 mg/kg every 4 weeks then CNI off by day 42
	Rostaing et al. [40]	Kidney	173	5 mg/kg every 4 weeks + CNI off by day 29

CNI, calcineurin inhibitor; TTP, thrombotic thrombocytopenia purpura; PRES, posterior reversible encephalopathic syndrome; HUS, hemolytic uremic syndrome; TXP, transplant; DGF, delayed graft function; TMA, thrombotic microangiopathy

5. Four Drug Maintenance Versus Replacement

An important decision to make when transitioning to belatacept in lung transplant recipients is determining which agent to discontinue. Four drug maintenance regimens can be used in patients at high immunologic risk, but there is little evidence to recommend this in lung transplantation due to significant infection risk. Because infection is the leading cause of mortality within the first year post-lung transplant [42], avoiding overimmunosuppression with a four drug maintenance regimen is advised, but can be considered in patients with recurrent rejection. While chronic allograft dysfunction and chronic rejection supplant infection as the leading cause of death beyond the first year [43], the relative risk between rejection and infection should take into account patient-specific post-transplant courses. When determining which agent to discontinue, the indication for salvage therapy should also guide selection.

6. Proposed Dosing Selection Algorithm

With the abundance of varying published dosing protocols, our center has developed an algorithm to assist in selection of belatacept dosing (Figure 1). Through a series of three questions, the transplant clinician evaluates a patient’s immunologic versus infection risk.

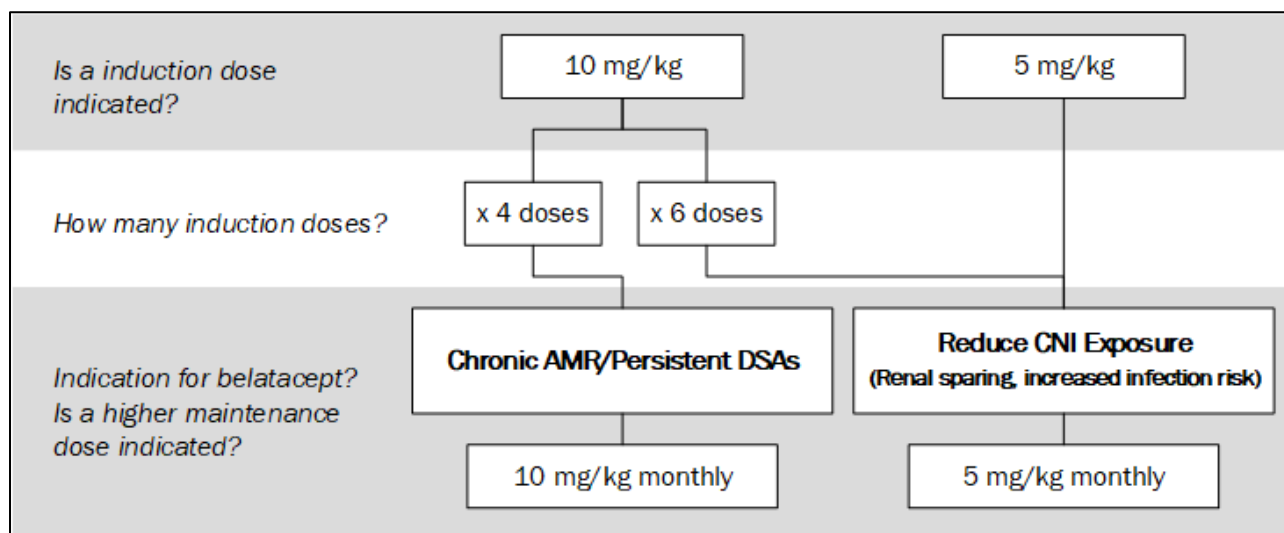


Figure 1 Belatacept dosing selection algorithm.

The questions to consider are:

1) Is an induction dose indicated? Consider the patient’s immune risk (rejection history, persistence of DSAs) versus infection risk (frailty, infection history). Can this patient tolerate a brief period of time where they may be over immunosuppressed?

2) If an induction dose is indicated, how many should the patient receive? If a patient will be maintained on a higher monthly dose (i.e. 10 mg/kg), they will likely only need four induction doses.

3) What is the indication for belatacept? Is a higher maintenance dose indicated? Consider the patient’s long term goals (i.e. better control of immune outcomes versus reduction in CNI exposure).

Other general conversion considerations include:

- The agent intended to be discontinued must be tapered off slowly to prevent subtherapeutic immunosuppression.

- The agent intended to be discontinued should be stopped after all induction doses have been given.

At this point in time, there are no data to compare efficacy between three drug maintenance regimens with (1) prednisone, (2) belatacept, and (3) an antimetabolite, CNI, or MTORI. Our center has elected to continue minimized CNI in combination with belatacept, unless the CNI is contraindicated. We are hesitant to completely withdraw CNIs due to the superior rejection protection they provide. Additionally, given the aforementioned incomplete inhibition of T-cell proliferation and persistence of memory T-cell activity, our approach has been to minimize but not remove CNI from our maintenance regimen outside of clinical trial or absolute intolerance of CNI.

To both conceptualize the conversion schedule and provide a framework for consistent conversion, we developed dosing guidance schematics (Figures 2-5). Depending on the desired induction and maintenance doses, the time frame for conversion and overall state of immunosuppression varies.

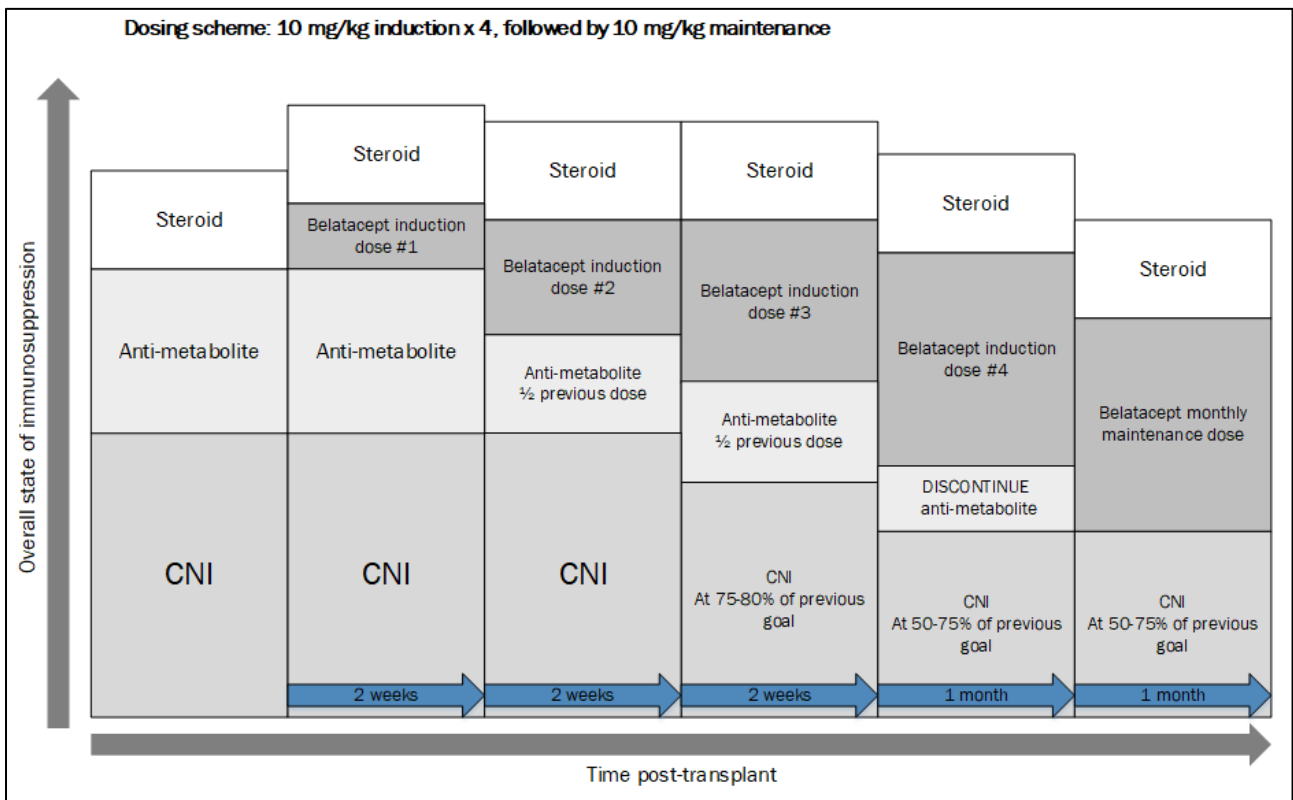


Figure 2 Conversion schematic—10 mg/kg induction x 4, followed by 10 mg/kg maintenance.

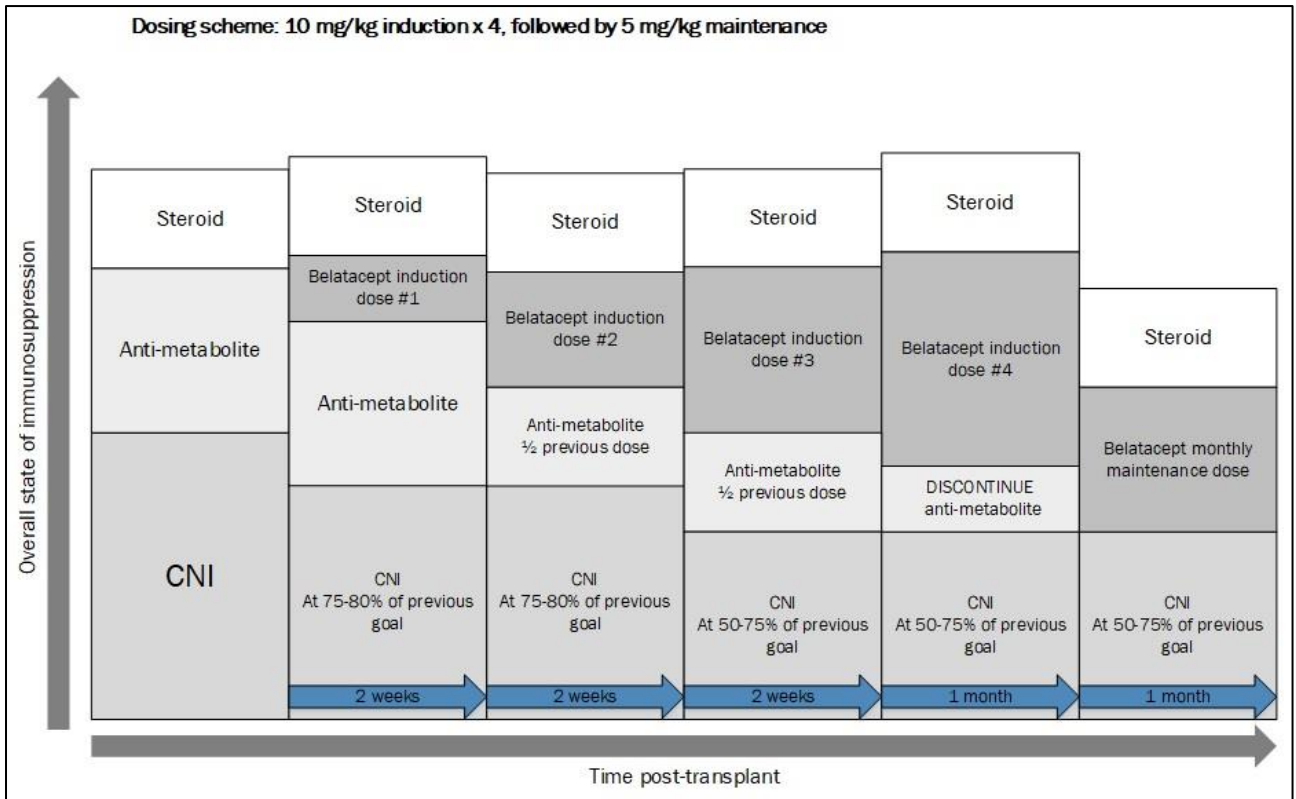


Figure 3 Conversion schematic—10 mg/kg induction x 4, followed by 5 mg/kg maintenance.

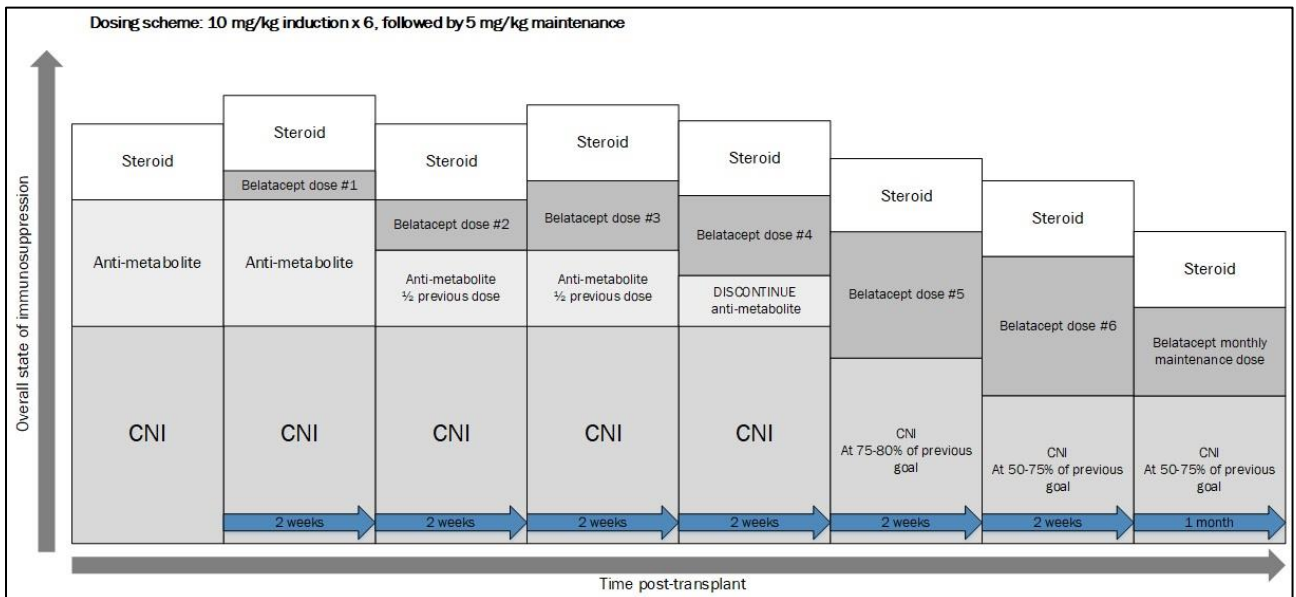


Figure 4 Conversion schematic—10 mg/kg induction x 6, followed by 5 mg/kg maintenance.

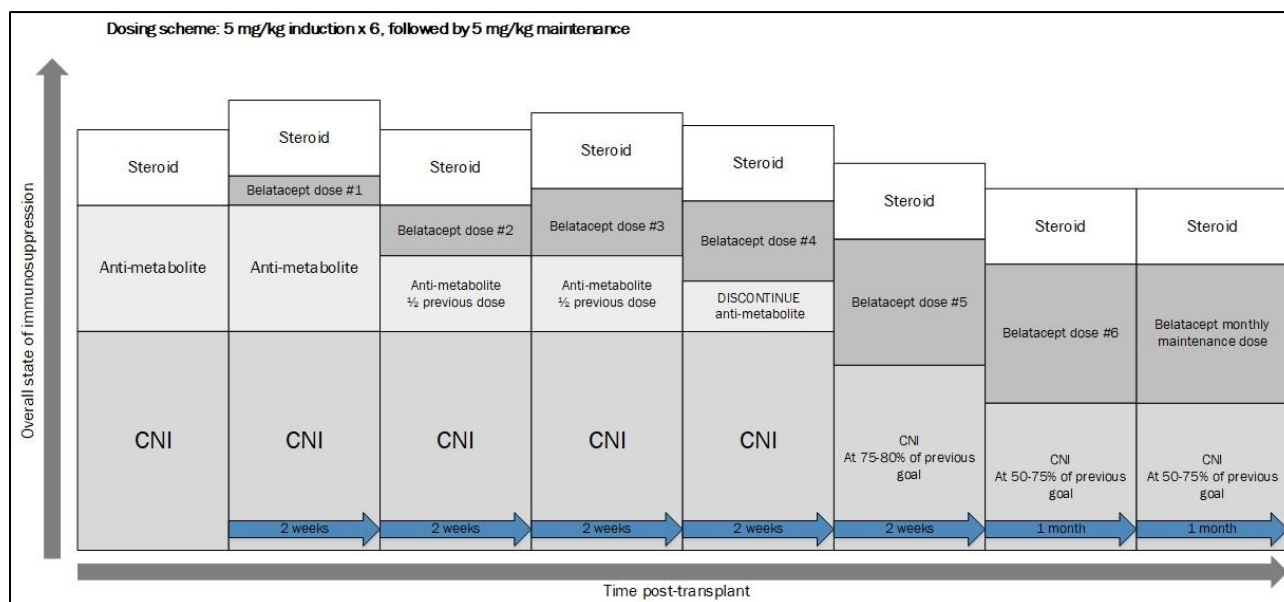


Figure 5 Conversion schematic—5 mg/kg induction x 6, followed by 5 mg/kg maintenance.

If an absolute contraindication to CNI exists, the CNI should be discontinued immediately and selection of a belatacept dosing scheme with induction doses should be considered in order to achieve steady state quicker. The MTOR1 or antimetabolite should be continued at full dose in conjunction with belatacept and a steroid as part of a CNI-free maintenance regimen.

7. Future Directions

Prospective randomized controlled trials evaluating belatacept dosing schemes are needed. Only one retrospective study has been published characterizing 13 belatacept conversion protocols in 78 kidney transplant recipients across a single integrated health care organization [44]. The authors evaluated rejection within 6 months post-belatacept conversion, then analysed for baseline characteristics associated with rejection. Although efficacy and safety of the numerous conversion protocols was not directly assessed, the authors noted no observed association of rejection with any specific protocol, tacrolimus tapering regimen, presence of DSA, or pre-conversion rejection.

As belatacept utilization continues to increase in non-kidney transplant recipients, long term outcomes will need to be reported upon. Other possible avenues for assessing appropriateness of immunosuppression between dosing schemes include in vitro testing to compare CD86 receptor occupancy, belatacept therapeutic drug monitoring, or measurement of donor derived cell-free DNA. In addition to direct assessment of dosing, research centered on clinical outcomes after belatacept conversion (i.e. renal function, rejection, DSAs, longitudinal lung function) are of top priority. Ultimately, consistent belatacept dosing using conversion protocols will improve the ability to directly assess outcomes and improve patient care.

Author Contributions

C Pham and B Pierce participated in conception of work, compilation of prior published literature, writing of manuscript, and revision of work. SW Yau, A Goodarzi, GJ Youssef, and HJ Huang participated in revising of work for important intellectual content.

Competing Interests

The authors have declared that no competing interests exist.

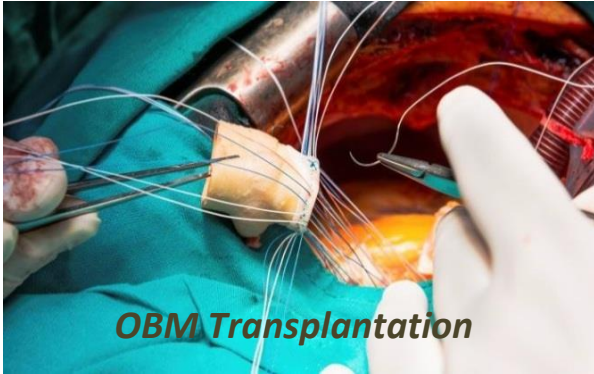
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