Dialysis and Transplantation Open Access

Editorial *Volume 2; Issue 2*

Belatacept in Kidney Transplantation: Are We Ready for a Different Immunosuppression Backbone?

Ramesh K Batra[1]* and Elizabeth A Cohen[2]

[1]Assistant Professor of Surgery, Yale University, USA

[2]Department of Pharmacy, Yale University, USA

***Corresponding author:** Dr. Ramesh K Batra, Assistant Professor of Surgery, Yale University, USA, Email: drrkbatra@gmail.com

Received Date: August 12, 2019; **Published Date:** August 14, 2019

Introduction

Calcineurin inhibitors (CNIs), cyclosporine and tacrolimus, remain the backbone of immunosuppression after kidney transplantation since the 1990s. However, their Achilles heel remains the adverse effect profile which has to be accepted and closely monitored to prevent limitations to graft and patient survival. Chronic allograft nephropathy, a term defining late graft failure due to many factors is largely attributed to CNI related nephrotoxicity [1]. Amongst CNIs, tacrolimus-based regimens are more popular than cyclosporine due to less nephrotoxicity and greater potency [2]. But tacrolimus in turn is associated with more neurotoxic and gastrointestinal side effects and higher rates of post-transplant diabetes mellitus than cyclosporine [3]. Furthermore, there are several direct and indirect metabolic side effects of tacrolimus, affecting patient survival due to cardiac events, a risk potentially far greater than the risk of graft failure due to chronic allograft nephropathy.

In 2000, with the U.S. Food & Drug Administration (FDA) approval of sirolimus, the hope was that the mammalian target of rapamycin (mTOR) inhibitors would become the replacement to CNIs and prolong graft and patient survival by preventing the adverse effects of CNIs. However, mTOR inhibitors were found to have more adverse effects and were less tolerable than the CNIs which limited their use and thus failed to offer any change to the average graft survival [4]. Although, sirolimus and everolimus had a limited use in kidney transplant immunosuppression, as an anti-tumor agent, but they by no means were a replacement to the CNIs.

Keywords: Kidney Transplant; Belatacept; Tacrolimus; Calcineurin Inhibitors; Nephrotoxicity

Belatacept

Belatacept (Nulojix®), a costimulation blocker, was approved by the FDA in 2011 and was the first immunosuppressant drug approved for transplantation with a new mechanism of action in eleven years.

At that time, one-year results demonstrated an increased risk of rejection within the first-year post-transplant as compared to cyclosporine, but with improved GFR [5]. Since then, seven-year data has been released, demonstrating that early rejection with belatacept did not affect patient or graft survival and patients were shown to have better kidney function and lower rates of the development of donor specific antibody (DSA) [6]. The fact that patients had less DSA development is an interesting one, especially as it relates to prolonging graft survival. One hypothesis to the decreased rates of DSA

Citation: Ramesh K Batra and Elizabeth A Cohen. Belatacept in Kidney Transplantation: Are We Ready for a Different Immunosuppression Backbone?. Dialysis Trans OA 2019, 2(2): 180011.

development is the likely increased adherence to belatacept injections as opposed to a twice-daily, timing dependent, CNI dosing, as there is evidence that fluctuating CNI levels may contribute to DSA development [7]. This is of interest because adherence with belatacept is likely much higher than adherence to CNI or mTOR as reported in other studies [8].

Recipients of Extended Criteria Donor (ECD) kidneys inherently have a shorter graft survival due to donor factors. Therefore, the least nephrotoxic immunosuppression is essential for their longevity and also improves acceptance of ECD kidneys by transplant physicians for their patients. In this direction, BENEFIT-EXT, a 3-year, phase III study comparing belatacept with CsA was conducted to evaluate belatacept in the most vulnerable group of donor kidneys, ECD kidneys. GFR rates were slightly better with the belatacept group and comparable rejection rates to CsA. Alongside the renal protection offered by belatacept, there was improvement in the cardiovascular and metabolic risk profiles in patients treated with belatacept [9]. This added benefit to the metabolic and cardiovascular risk factors was also observed when belatacept was compared with CsA for living donor and Standard Criteria Donor (SCD) kidney transplants in the BENEFIT clinical trial [7]. It is important to note the evidence that CNI or mTOR inhibitor use in a patient with baseline cardiac disease, may increase the risk of cardiac death [10]. Belatacept lacks the negative cardiovascular side effects of CNI and mTOR inhibitors, and we would argue that this should be considered when determining long-term immunosuppressive medication in kidney transplant patients.

PTLD was a concern in both BENEFIT and BENEFIT-EXT trial. Although in BENEFIT trial, PTLD developed in high risk patients i.e. EBV negative patients or patient who received T-cell depleting therapy [7]. but such was not the case in BENEFIT-EXT trial [9]. PTLD, continues to remain a reason why some centers are hesitant to use belatacept; however, a Cochrane systematic review after reviewing 4 studies showed no change in the risk of PTLD with belatacept when compared to CNI treated patients in both EBV seronegative and seropositive states [11,12].

Another benefit of belatacept over CNI and mTOR inhibitor based regimens are the avoidance of drug interactions, specifically with cytochrome P450 3A (CYP3A), P-glycoprotein (P-gp), and OATP1B1 enzyme inducers and inhibitors, which lead to fluctuating levels of CNIs and mTOR inhibitors causing increased toxicity or alternatively, increased rejection if not monitored appropriately. Belatacept does not have any known drug interactions and can be used in patients requiring medications that can affect levels of CNI and mTOR inhibitors, such as patients with HIV requiring protease-inhibitor based antiretroviral therapy[13].

The above is sufficient evidence to support the safety profile of belatacept, along with its efficacy in prolonging graft and patient survival. However, the risk of early rejection with belatacept has limited its use as a denovo agent, and therefore used as a conversion therapy from CNI or mTOR [13]. But as belatacept is not FDA approved for conversion, there is no standard conversion dosing protocol, although some dosing strategies have been published [14,15]. Conversion studies are also underway by the manufacturer, Bristol Myers Squibb, and some centers have reported on their use of belatacept as conversion therapy from calcineurin inhibitors in select patient populations, reporting specifically on glomerular filtration rate (GFR)[14]. Many of these reports are converting patients due to concerns for calcineurin inhibitor nephrotoxicity. But there are an unmeasured yet large number of transplant patients accepting CNI related adverse effects, both in short and long term, an alternative medication is very much needed and timely.

Conclusion

Like most transplant programs, amongst CNIs, tacrolimus based immunosuppression is the standard of care for kidney transplant patients at our center. We however have started to be more liberal in considering belatacept over CNIs, but we strictly follow a need-based approach to minimize CNI related toxicities in the affected patients. We think that better conversion and also denovo protocols to include belatacept as an offered choice in the immunosuppression framework are needed, to avoid the accepted adverse effects of CNIs. Therefore, belatacept may very well be the replacement to CNIs that kidney transplant has been looking for.

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