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Tolerance protocol of living kidney transplant for developing countries through basic strategy of lymphocyte depletion

Suhail SM *et al*, Tolerance by lymphocyte depletion

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Abstract

End-stage kidney failure (ESKD) is a global issue where kidney replacement therapy imposes enormous economic burden to people of developing countries, in addition to the severe limitations to the availability of haemodialysis and peritoneal dialysis technique. The best option of kidney transplantation also requires lifelong combination immunosuppressive medicines, the cost of which is equally comparable to lifelong dialysis. A strategy of achieving transplant tolerance that requires minimum immunosuppressive medicines, although in experimental stage, also requires state-of-art technology with costly medicines and interventions. This is evidently beyond the reach of ESKD patients of developing countries. Hence, globally in developing countries, a need for an innovative but cost-effective tolerance protocol is a burning need for a successful transplant program. In brief, transplant tolerance is defined as a state of donor-specific unresponsiveness to the allograft antigens without the need for ongoing pharmacologic immunosuppression or with a minimal need. Current state-of-art techniques involves: (1) A state of haematological chimera, for complete tolerance; (2) Prope or partial tolerance where immune-reactive T-lymphocytes are inhibited using

monoclonal antibodies; and (3) Chimeric antigen receptor for T-regulatory (T-reg) cell therapy using genetically engineered T-reg cells targeting specific T-lymphocyte receptors for inducing anergy. From our experience in real world transplant management in post-transplant lympho-proliferative disorders (PTLD), we noticed frequently a drastic reduction in the need of immunosuppressive medicines following lympho-ablative therapy for PTLD. We recently published a case study on a real-world experience transplant case where we explained a partial or prope tolerance that developed after lymphocyte ablation therapy, following which the allograft was maintained with low dose dual standard immunosuppressive medicines. Based on this publication, we propose here an innovative tolerance protocol for living related low risk kidney transplantation for developing countries, in this opinion review.

Key Words: Renal allograft; B and T lymphocytes depletion; Tolerance protocol; Immunosuppressive medicines; Living renal transplant

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Core Tip: In this opinion review that is based on our recent publication, the core tip concentrates on achieving a partial or prope tolerance in renal allograft through sequential B and T lymphocyte depletion in an approved and in-practice strategy, for living related and low risk kidney transplantation. The allograft would require a half dose dual immunosuppressive therapy subsequently.

INTRODUCTION

Renal allograft, unlike autograft or isograft, would invoke rejection process though cellular and humoral immune mechanism by the nonself-antigen mediated alloimmune response. This results in rejection of the grafted organ unless immunosuppressive medicines targeting the donor T and B lymphocytes are in place. As opposed to the

rejection process, tolerance is a state of unresponsiveness to the allograft, where the graft can be maintained without or with minimal immunosuppression. This is achieved by the use of effective innovative and aggressive immunosuppressive protocols[1].

Even though, safe and reliable strategies of achieving transplant tolerance is not in place, anecdotal reports and experimental animal studies targeting T and B lymphocyte ablation, offer hope[2]. However, these need cost and state of art infrastructures which are beyond the reach of end-stage renal failure patients in developing countries. Finding an innovative but cost-effective tolerance protocol remains an allusive goal for a successful transplant program for low economic zones.

In real-world experience (RWE) of transplant management when transplanted patients develop post-transplant lympho-proliferative disorders (PTLD), we noticed frequently a drastic reduction in the need of immunosuppressive medicines following lympho-ablative therapy for PTLD. Recently we published a case study of a living kidney transplant who achieved immunologic tolerance requiring low dose calcineurin inhibitor (CNI) with minimal prednisolone after the patient was treated by lympho-ablative therapy for Lymphoma that he developed during the post-transplant period[3]. Based on this publication and our RWE with PTLD cases management[3], we would propose in this opinion review a partial or prope tolerance protocol that can be achieved through depletion of lymphocytes pre-emptively in low risk kidney transplant recipients. The added advantages being considered is the reduced requirements of stat-of-the-art technologies and reduced cost that are needed for achieving current desensitisation and immunosuppressive protocols required for tolerance.

WHAT ARE THE CURRENT EVIDENCES OF TOLERANCE IN ALLOGRAFT?

In anecdotal case reports, complete tolerance was achieved in subsequent renal allograft where bone marrow transplant was done in case of Multiple myeloma (MM) patients with lymphocyte ablation done by radiation and chemotherapy prior to kidney transplantation from the marrow donor. The grafted kidney did not require immunosuppressive medicines afterwards[4]. This is a kind of tolerance obtained

because of a form of hematologic chimera thus developed during treatment of MM through allogeneic bone marrow transplant where host immune system was replaced by donor marrow.

WHAT ARE THE MECHANISMS OF TOLERANCE AND REJECTION?

A brief outline of gross immunology physiology in foetal life and life after birth is presented in Figure 1A. Immune reactive cells undergo apoptosis on exposure of foetal self-antigens, thus leaving behind the cells which are naïve to any other foreign antigens. In life after birth, immune response shifts to proliferation and activation state in contrast to foetal state of apoptosis[5].

Thus immune cells shows immune response by proliferating and reacting to foreign antigens and allograft, as shown in figure 1B. This induces T-cell proliferation and results in cell mediated cytotoxicity and inflammation that results in acute rejection unless immunosuppressive therapies are not imposed[6].

Figure 1C summarizes the current research based adoptable protocol for achieving anergy (tolerance). Firstly, achieving a state of hematologic chimera. In other wards, complete tolerance; Second, a state of partial or prope tolerance, where immunoreactive T-lymphoytes are depleted or suppressed; And third, the newer, CAR-T (Chimeric Antigen Receptor for T-reg therapy). T-reg cells are genetically manipulated to express co-stimulatory receptors on their surfaces, that results in blocking of signal-2. This causes ablation of T-cell immunoreactivity resulting in anergy or tolerance.

WHAT ARE THE CURRENT PRACTICES OF TOLERANCE PROTOCOLS IN RENAL ALLOGREAFT?

Road to complete tolerance has not opened yet because of lack of available protocols.

Transplantation among monozygote twins does not require immunosuppressive medications, hence is an example of complete tolerance[7].

Partial or Prope tolerance is available using of Campath-1H where allograft could be maintained with minimal immunosuppression with Low dose Cyclosporine-A (CSA)

alone. CAMPATH-1H is monoclonal antibody (mAb) against CD52 antigen present on surface of all lymphocytes. Anti CD52 mabadministration causes ablation of all lymphocytes that lasts for long period. The new lymphocyte that are subsequently produced from lymphoreticular tissues are naive to the grafted kidney inducing tolerance[8]. This was demonstrated in 3C, INTAC and other studies, showing promising evidences to tolerance[9]. This is costly and requires infrastructures where infections and patient safety protocols can be monitored. In many low economic zones, expected to be not feasible.

Current approach to tolerance is focused on inducing anergy to the reactive host or graft T lymphocytes by blocking the co-stimulatory signal to CD-3 T lymphocytes either by unique mAb against receptors for T-lymphocyte co-stimulation [CTLA-4 (cytotoxic T-lymphocyte associated antigen 4), CD28, B7, CD137] the so called signal-2 co-stimulation inducing T-lymphocyte anergy, or CAR-T therapy targeting T-regulatory lymphocyte's CTLA-4 antigen mentioned, to block co-stimulation of CD3-lymphocytes; inducing tolerance (anergy) for all T lymphocytes.

BENEFIT study used belatacept, a selective co-stimulation blocking mAb against CTLA-4 mentioned above for inducing anergy, to show a partial tolerance[10]. But the results were not promising.

Most recently, research on CAR-T therapy targeting CTLA-4 co-stimulatory receptor on the CD-3 T-lymphocytes for induction of T-lymphocyte anergy, produced promising results in pancreatic islet cell graft, as well as cuteneous graft[11,12]. Furthermore, these therapies are exceedingly costly.

HOW RECIPIENT AND DONOR FACTORS AFFECT IMMUNOSUPPRESSION AND TOLERANCE?

Highly sensitized recipients and marginal donors would impact the outcome of immunosuppression and concepts of tolerance.

A higher immunosuppressive protocol for graft survival is required for recipients with preformed antibodies against donor antigens that includes pre-transplant

desensitization[13]. ABO incompatible recipient and recipient with donor specific antibodies requires desensitisation protocol. Recipients with multiple blood transfusion recipients, multigravida, cases of repeat transplant, are highly immunogenic showing frequent cross-match positive results for both B and T-lymphocyte [14]. Consequently, tolerance protocols may not be appropriate for these groups of highly immunogenic recipients.

Organ donors with high immunogenicity are ABO incompatible and HLA mis-match donors, deceased donors, and harvested kidney with long cold ischemia time. These requires increased immunosuppression[15,16]. In addition, may require desensitization protocol with cascade plasmapheresis and immuno-adsorbtion techniques. This is combined with use of various anti-lympfocyte and combination of potent immunosuppressive medicines. These protocols are available to be practised in targeted high risk kidney transplantation. Obviously achieving a successful protocol of tolerance could be a matter of ingenuity here and trough levels, 300 and 50 mcg/L respectively). Over time, Prednisolone to be reduced to 5 mg daand mycophenolate mofetil (MMF) to be[17].

HOW SHOULD BE THE PARADIGM SHIFT TO TOLERANCE FROM CONVENTIONAL IMMUNOSUPPRESSION?

The objectives of tolerance protocol are: (1) minimum acute rejections; (2) minimum use of immunosuppressive medicines; (3) normal graft function; and (4) reduced short term and long term complications.

Shift to tolerance from conventional immunosuppression should be planned for minimally and normally immunogenic kidney donors and recipients, as described above. ABO compatible, better HLA matching, closer family members and matching body parameters are important considerations. All other donor recipient relationships are not appropriate for any tolerance protocol.

Available protocols for partialtolerance involves depletion of lymphocytes at the initial period of tranplant surgery. The examples are, 3C, INTAC studies, where

lymphocyte depletion was achieved using CAMPATH-1H mAb[8,9]. Sadly, lack of generalisation and limiting factors of higher incidences of sepsis and malignancy limits their application[10]. Use of CAR-T therapy against T-lymphocyte receptors is also in infancy for renal transplantation[11,12]. For low socio-economic zones, nonetheless, they are irrelevant.

WHAT COULD BE THE TOLERANCE PROTOCOL FOR DEVELOPING COUNTRIES WHERE BURDEN OF END-STAGE KIDNEY FAILURE ALSO EQUALLY HIGH?

In RWE in cases of PTLD, the point to note is depletion of lymphocytes with use of R-CHOP cycles for PTLD as described in earlier sections. Profound lymphopenia and neutropenia that resulted from these R-CHOP therapy, required stopping withdrawal of some immunosuppression like mycophenolate mofetil. The grafted kidney was subsequently maintained with a small dose of prednisone and a low dose of CSA[3].

Thus we summarise the protocol in Figure 2: The protocol starts with selection of donor and recipient, as shown in Figure 2A—the donor would be living ABO compatible donor with maximum possible HLA match and with negative for B and T lymphocyte cross match. The recipient needs to be of low immunologic risk with Panel Reactive Antibody titre less than 26%.

The subsequent steps are shown in Figure 2B as follows: First step is elective bone marrow suppression with a few R-CHOP cycles as described, each cycle consisted of IV Rituximab, IV Cyclophosphamide, IV Doxorubicin and IV Vincristine. This is followed by oral Prednisolone 50 mg daily for 5 days. This cycle is repeated 3 to 6 times tilled the desired depletion of Lymphocytes is achieved as mentioned earlier[3].

Second step: For low risk renal transplant, induction with Anti-CD25 mAb first with MMF, CNI and IV hydrocortisone (or solumedrol) at standard doses till stable graft function is achieved. We used 2 doses of IV basiliximab as anti-CD25 mAb 20 mg IV at interval of 4 d at induction. We used CSA as CNI with a target Peak level of 1000 to 1200 μg/L at the beginning with reduction to 600 to 800 μg/L at stability of the graft

function. MMF was used at 12 mg/kg body weight twice a day during this period. We used Prednisolone 30 mg daily for 4 wk, then reduction by 2 mg every week until maintenance dose of 10 mg is reached.

Third step: After achieving stable graft function that might require between 13 to 26 wk, to reduce CNI to half of the existing dose (target peak level and trough levels, 300 and 50 mcg/L respectively). Over time, Prednisolone withdrawn slowly over 12 wk, monitoring the graft function.

HOW COULD THIS TOLERANCE PROTOCOL FOR LOW RISK LIVING TRANSPLANT BE VALIDATED?

Firstly, the use of R-CHOP therapy is validated as B lymphocyte depleting therapy in Lympho-proliferative diseases as a standard therapy[3]. This was used in our RWE scenario for treating the PTLD that developed later. Subsequently, the allograft was maintained with low dose dual immunosuppression with stable graft function for long time. Following this practical experience, use of this B lymphocyte depletion regime is aimed to achieve predominant B-lymphocyte depletion prior to transplant surgery. Subsequently following the transplant of the allograft, the recipient's marrow would produce B-lymphocytes (now new host B lymphocytes) that are naïve to the renal allograft antigens (resident antigens). Consequently, as the new host B lymphocytes are naïve to the grafted resident antigens, it would not display humoral immune response against the graft tissue.

Secondly, the validity for using MMF and CNI at the beginning is to avoid incidence of acute cellular rejection by depleting resident and host T-lymphocytes at the engraftment period post-transplant[18]. New batch of T-lymphocytes are produced by lymphoreticular system that are naive to the renal graft. Thus, the newer lymphocytes (host T lymphocytes), appears to take the allograft antigens (resident antigens); as self, thus do not cause cellular immune rejection.

Thirdly, B-lymphocyte depletion in a sequential manner as above before transplant surgery followed by immediate post-transplant T-lymphocyte depletion by anti CD25

mAb with CSA and MMF, enables the host acquire a state of prope tolerance to the renal allograft that we observed in the RWE scenario. The dual immunosuppressive medicines at lower dose maintain the graft and avoids long and short term complications of currently used medicines[19].

Lastly, risk of infection post-lymphocyte depletion, as described, would be similar to current existing strategies used in high risk renal transplant programmes as well as same as lymphoablative therapies used in Lymphoma. Paradoxiclly, the risk of infection would be rather reduced following the cycle of lymphocyte depletion strategy as mentioned, because the strategy is time limitted. This therapy would be followed by rather a reduced and dual immunosuppressive low CNI trough level therapy to maintain the renal graft. In practical situations of Lymphoma treatment, infection and recurrent malignancies are rather infrequent. In our case and several other similar sitautions, recurrent malignancies and infections were not of frequent impediments.

HOW WILL THIS TOLERANCE PROTOCOL IMPACT CURRENT TRANSPLANT PROGRAMME?

Current transplant protocols with newer monoclonal antibodies, desensitization procedures and newer drugs, may may impact disastrously in many programs of transplantation[18]. Nevertheless, kidney transplant is considered best renal replacement therapy in End-stage kidney failure (ESKD).

For a sustainable transplant programme guideline-based immunosuppressive regimens and opinion based protocols are required for highly immunogenic donor-recipient relationship. The parody lies in the disparity of the economics and infrastructures for provision, and extent of ESKD cases in developing regions. In such situation, an alternative approach may be considered.

This tolerance protocol could be suitable and applicable in RWE situations for low risk transplant scenario. In developing countries ethics committee may contribute to the feasibility of low risk living renal transplantation for maintaining a reasonable

transplant programme to reduce the burden of ESKD at lower cost and feasible infrastructures.

HOW THIS TOLERANCE PROTOCOL DIFFERS FROM EXISTING TOLERANCE PROTOCOLS?

We aimed at a sequential lymphocyte depletion therapy rather than an ablative therapy. The sequence starts with B lymphocyte depletion with cycles of R-CHOP therapy to achieve the target Neutrophil and lymphocyte levels, pre-transplant. Following living kidney donation (LKD) transplant with a low immunogenic donor-recipient risk-relation, standard tripple immunosuppressive protocol with CNI, MMF and prednisolone will resume for achieving stable graft function. This will be followed by step wise and monitored reduction of immunosuppression to a half trough level CNI and minimum alternate day Prednisolone regimen. Thus, episodes of immediate acute rejections are minimised and a prope or partial tolerance with low dose dual immunosuppressive startegy is achieved.

The strategy of CNI half trough level as described, and alternate day low dose prednisolone is described as prope or partial tolerance. The monitoring of this tolerance would be the regular monitoring of graft function by serum creatinine levels and hematuria and proteinuria levels. In essence, is the equivant monitoring of a standard graft kidney.

This strategy to induce partial or prope tolerance, even though is meant for facilitating low risk LKD transplant is developing countries for reasons explained in the epilog, in fact, it will benefit the recipient world-wide. I would rather think that developed countries are better equipped with ancilliary supportive infrastructure to consider this proposed protocol.

In the abstract, a detailed background introduction, was mentioned in order to simplify the understanding of issues related to scope of transplant needs, especially in developing countries with marked limitations in infrastructure, finance, and scarcity of dialysis facilities for an increasing population of ESKD. To maintain a universal

understanding of different stakeholders of chronic kidney disease, the article did a little elaboration before focusing on the strategy of partial tolerance.

CONCLUSION

In our recent publication[3], we discussed the real world experience scenario renal transplant case who achieved prope or partial tolerance requiring a low dose dual immunosuppression following B lympho-ablative therapy for PTLD. In this opinion review, we extrapolate that B lymphocyte depletion protocol to living kidney transplant of low immunogenic risk. Considering the impact of ESKD burden in developing nations, respective transplant societies with their corresponding ethics committee, would consider our proposed protocol for low risk living kidney transplant programme.

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