Immunosuppression in Sensitized Patients

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Following organ transplantation, sensitized patients have higher rates of antibody-mediated rejection (AMR) compared to those who are non-sensitized. More stringent donor matching is required for these patients. Current approaches for sensitized patients focus on reducing preformed antibodies that preclude transplantation; however, this type of desensitization does not modulate the primed immune response in sensitized patients. Thus, an optimized maintenance immunosuppressive regimen is necessary for highly sensitized patients, which may be distinct from non-sensitized patients.

sensitization immunosuppression induction B cell plasma cell

1. Introduction

Immunosuppressive strategies for sensitized patients are largely borrowed from those used in non-sensitized patients. However, variability in outcomes reveals the insufficiency of current immunosuppressive regimens in sensitized patients. Sensitized patients with a negative crossmatch (no donor-specific antibody) showed comparable graft survival to non-sensitized patients in the current organ allocation system [1] even though these patients might have individual center-driven immunosuppressive regimens which are different from non-sensitized patients (i.e., thymoglobulin with higher Tac trough level, etc.). However, immunologically high-risk transplants occurring in sensitized patients, particularly for crossmatch positive, incompatible transplants, require enhanced immunosuppression. Innovation in this field has largely focused on ‘desensitization’ prior to transplantation, or early post-transplant therapies to reduce the risks of acute antibody-mediated rejection (AMR) [2][3][4][5][6][7][8][9][10][11]; however, there has been little examination of the optimal maintenance regimen post-transplant. Furthermore, even with currently available desensitization therapies, both acute AMR and acute cellular rejection (ACR) rates were significantly higher in sensitized/desensitized patients compared to non-sensitized patients [12][13][14]. Recently, changes in deceased donor allocation in the US in particular [15], as well as improvements to living kidney donor sharing schemes [16], have demonstrated that fewer sensitized patients require the need for cross-match positive living transplantation [17]. Nonetheless, patients with pretransplant or de novo donor-specific antibody (DSA) are at greater risk of graft rejection.

2. Choice of Induction Therapy in Sensitized Kidney Transplant Recipients

Induction therapy reduces rates of acute rejection, delayed graft function (DGF), and death after kidney transplantation, and there is a wide variety of induction agents available and used in clinical practice today [18].

Rabbit antithymocyte (rATG) polyclonal antibody or interleukin-2 receptor monoclonal antibodies are the most common agents used for induction in non-sensitized patients. Sensitized patients with preformed HLA antibodies are at greater risk of cellular and humoral rejection, and outcomes can be optimized by using polyclonal induction agents, such as ATG or alemtuzumab, that are associated with a lower risk of rejection and better graft survival [19][20][21][22]. However, the impact of different induction approaches on sensitized patients has not been fully elucidated and the variability in induction therapy can be largely attributed to transplant center choice and clinician preference rather than patient or donor characteristics [20][21][22][23].

2.1. Basiliximab

Basiliximab (Simulect) is a non-depleting chimeric anti-CD25 monoclonal antibody against the interleukin-2 (IL-2) receptor on activated T lymphocytes [24]. It is comparable to rATG in patients with low risk of acute rejection, though less effective in high-risk kidney transplant patients, defined as being at risk of DGF or having panel reactive antibody (PRA) > 20% [24][25][26]. Even though activated B cells express CD25 and IL-2 mediated signaling has a critical role for its further differentiation into plasma cells [27], our data in a highly sensitized nonhuman primate model demonstrated a clear limitation of basilliximab in controlling robust memory T and B cell immune responses [28]. Additionally, basiliximab was associated with a greater risk of biopsy-proven acute rejection (BPAR) than rATG in sensitized (HLA class I and II mismatch) kidney transplant recipients without pre-existing DSA [29].

2.2. Thymoglobulin

Thymoglobulin, or rATG, is a polyclonal gamma immunoglobulin and the preferred choice in sensitized patients at high risk for acute rejection or delayed graft function [18][19]. rATG targets T cells via antibody dependent cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC), but it also depletes B cells and plasma cells since thymus also contains these cell populations. In moderately sensitized patients (positive DSA and negative flow crossmatch), induction with ATG resulted in reduced occurrence of de novo DSA (dnDSA) and AMR compared to basiliximab [30]. In simultaneous heart and kidney transplants, sensitized patients (with PRA > 10%) treated with rATG induction had lower mortality [31].

2.3. Alemtuzumab

Alemtuzumab is a depleting anti-CD52 antibody that targets T and B cells resulting in lymphocyte depletion and prolonged immunosuppression [32]. Low-dose alemtuzumab is used as an induction agent in sensitized patients undergoing kidney transplantation and, when combined with triple maintenance immunosuppression, is well tolerated and has shown favorable patient and allograft outcomes (death-censored graft survival: 79.2%) [32]. A prospective study found that the rate of biopsy-confirmed acute rejection in low-risk patients was lower with alemtuzumab when compared with basiliximab, but among high-risk patients, there was no significant difference between alemtuzumab and rATG [33]. However, alemtuzumab is associated with prolonged lymphocyte depletion [32][34] and increased rates of infection [32][35].

2.4. Rituximab

Rituximab is an anti-CD20 monoclonal antibody that targets B cells, suppresses preformed alloantibodies and reduces peripheral B lymphocytes prior to transplantation [36][37]. A retrospective study of highly sensitized kidney transplant recipients (XM-positive or DSA positive) treated with IVIG and rituximab induction therapy found increased rates of AMR in sensitized recipients compared to low-risk recipients, but similar long-term patient or graft survival at 6 year follow-up [38].

3. Choice of Maintenance Immunosuppression in Sensitized Patients

3.1. Triple Immunosuppression

Maintenance immunosuppressive therapy prevents acute rejection and increases allograft survival following kidney transplantation. The standard maintenance regimen varies by center or clinician preference, but the KDIGO Transplant Work Group guideline recommendations include triple therapy immunosuppression consisting of a calcineurin-inhibitor (CNI), such as tacrolimus, an antimetabolite, such as mycophenolate mofetil (MMF), and a glucocorticoid, such as oral prednisone, in kidney transplant recipients [39]. Tacrolimus inhibits activation of T lymphocytes by binding to an intracellular protein, FKBP-12, and inhibiting calcineurin while MMF inhibits T and B cell proliferation. It has been shown that CNIs (cyclosporine and tacrolimus) inhibit antibody production in T and B cell cultures but fail to inhibit immunoglobulin (Ig) production when B cells are cultured with primed T cells [40]. According to the most recent Scientific Registry of Transplant Recipients (SRTR) registry data, over 60% of patients are discharged from the hospital on tacrolimus, MMF, and prednisone triple therapy due to its success as a maintenance immunosuppressive regimen [41][42].

3.2. Limited Efficacy of Standard Maintenance Immunosuppression in Sensitized Patients

Graft function was similar between groups at 1 year follow-up with no graft loss, and both groups were treated with thymoglobulin induction and standard maintenance triple therapy [43]. A study in which all patients were maintained on standard triple therapy found an increased incidence of acute AMR in patients with pretransplant DSA than those without (41.7% vs. 1.6%, $p < 0.001$) and that higher levels of pretransplant DSA had a detrimental effect on 5 year graft survival [44]. These studies highlight the limitations of standard triple maintenance immunosuppressive therapy and the need for different therapeutic regimens in the sensitized, DSA positive, CDC-crossmatch negative patient population, particularly in light of the experimental evidence highlighted regarding the inability of CNI to prevent antibody production during cognate T–B cell interactions [40].

3.3. Replacing Tacrolimus

The mammalian target of rapamycin (mTOR) controls the T cell response (activation and proliferation) and is a valuable immunosuppressant in clinical transplantation. mTOR inhibitors, such as rapamycin (sirolimus) and everolimus, promote the differentiation and function of various helper T cells and suppress the differentiation of

memory CD8+ T cells [45]. Furthermore, unlike CNIs, mTOR inhibitors are able to prevent Ig production from B cells when cultured with primed T cells, which suggests their direct impact on B cells [40][46]. Rapamycin has also shown its superiority over tacrolimus with respect to inhibiting B cell to plasma-cell differentiation [47]. In mice sensitized by prior skin graft, preoperative rapamycin increased the expression of regulatory T cells, but did not prolong the survival of mice after cardiac allotransplantation [48]. In donor skin-sensitized mice, those with mTOR deletion in T cells had longer mean survival time (MST 19.5 days) versus wild-type recipients (MST 5.4 days) [45]. Mice sensitized by skin transplant and treated with rapamycin induction therapy were found to have altered frequencies of splenic and intragraft neutrophils, macrophages, and natural killer (NK) cells [49].

4. Newly Available Agents for Sensitized Patients

4.1. Costimulation Blockade

4.1.1. Belatacept

Belatacept, a CTLA4-Ig fusion protein that binds to cluster of differentiation (CD) 80 and CD86 receptors on antigen presenting cells (APC), prevents binding to CD28 on T cells, thereby reducing the T cell–dependent immune response [50]. Belatacept has been shown to selectively reduce the humoral response in sensitized, maximally HLA-mismatched non-human primates (NHPs) by suppressing the peripheral and germinal center follicular helper T cell (Tfh) response [51]. Translational studies in highly sensitized NHPs found that desensitization with belatacept in combination with bortezomib or carfilzomib therapy led to significantly reduced AMR, DSA, and plasma cells leading to prolonged graft survival, although it should be noted that these animals received tacrolimus-based triple therapy as maintenance [52][53]. Preliminary studies in animals receiving belatacept in addition to triple therapy indicate a further prolongation of survival, even in a highly sensitized NHP model [54].

4.1.2. Anti-CD40mAb

The CD40/CD154 pathway is important for activating T cell differentiation and B cell isotype switching and was found to be important in both the humoral and cell-mediated immunologic response pathways [55]. CD4+ helper T cells are mandatory for generating both naïve and memory DSA responses [56]. Thus, targeting helper T cells in maintenance therapy may lead to decreased AMR and prolonged allograft survival in kidney transplant recipients. Much of the existing evidence is in large animal models as clinical studies blocking the CD40/CD154 pathway have been halted due to the development of thromboembolic complications and direct platelet activation [57][58]. Thromboembolic complications were found to be primarily due to blocking interactions with CD154, which is important for thrombus stability [59]. However, similar events were not observed in antibodies targeting CD40 [60][61][62], so this may be a more promising therapeutic target. A novel blocking, non-depleting Fc-silent anti-CD40 mAb, iscalimab (CFZ533), has been found to prolong renal allograft survival in NHP in the absence of B cell depletion with no evidence of thromboembolic events [63].

4.1.3. Anti-CD154mAb

An initial study found that anti-CD154 monoclonal antibodies prevent acute renal allograft rejection in non-sensitized NHPs [64]. A study in donor skin-graft-sensitized mouse recipients of cardiac allografts found that naïve CD8+ T cells depend on CD154 signaling to differentiate into effector T cells, while primed/memory CD8+ T cells remain intact [65].

4.2. Adjuvant Therapies

4.2.1. Targeting IL-6 or IL-6R

Interleukin (IL)-6 is a pleiotropic cytokine involved in a variety of pathways regulating immune responses, with an important role in the induction of follicular helper T cells which stimulate B cells to differentiate into memory B cells and IgG-secreting plasma cells [66]. The IL-6 receptor (IL-6R) exists as a membrane-bound protein, expressed mostly on hepatocytes and immune cells, and a soluble protein that can bind IL-6 and transmembrane gp130, termed trans-signaling, on nearly all cell types [67][68]. Interactions between IL-6 and IL-6R lead to the activation of transmembrane protein gp130, eliciting signals to downstream JAK and MAPK pathways and the subsequent activation of inflammatory genes [67]. IL-6 is a proinflammatory cytokine that plays a pathologic role in chronic immune disorders, cancer, and transplant rejection [68]. IL-6 also promotes Th17 differentiation and inhibits Treg differentiation, suggesting targeting IL-6/IL-6R may have clinical applications in treating autoimmune disease and organ rejection [67][69].

4.2.2. Anti-BAFF

B cell activating factor (BAFF, also known as BLyS) and a proliferating inducing ligand (APRIL) are cytokines that belong to the tumor necrosis factor family whose primary function is to enhance B cell survival and differentiation into plasma cells [70]. Both are currently used in treating autoimmune diseases such as systemic lupus erythematosus (SLE) and Sjogren's, but several studies have found that high levels of serum BAFF are associated with the formation of anti-HLA DSA, increased risk of AMR, and poor renal graft survival [71][72][73][74][75]. BAFF is highly expressed in the membrane and renal tubule epithelial cells of transplanted kidneys with acute rejection, and high pretransplant BAFF has been found to predict risk of graft rejection [76].

4.2.3. Targeting PC

Conventional PI

Bortezomib was the first proteasome inhibitor (PI) to be FDA-approved for the treatment of malignant plasma cell diseases [77]. Proteasome inhibitors, including bortezomib, carfilzomib, oprozomib (ONX 0912), and ONX 0914 (immunoproteasome inhibitor), reduce proliferating B cells and antibody production conceivably by inducing apoptosis of activated B cells [78]. Bortezomib has been shown to be effective in preventing AMR and ACR, as well as reducing DSA in kidney transplant recipients [79]. Since then, bortezomib has been studied in combination therapy with plasmapheresis (PP) and IVIG with or without rituximab or steroid as plasma cell–targeted therapy in sensitized kidney transplant recipients, showing success in reducing DSA, treating acute or late AMR [80][81] as rescue or primary treatment [82][83][84], and reducing plasma cell rich acute rejection [85][86]. Recently, six patients

who developed acute AMR received bortezomib and belatacept combination therapy, which led to the reversal of AMR and reduction in circulating DSA [87].

5. Concluding Remarks

Conventional maintenance immunosuppression with tacrolimus, MMF, and steroids after lymphocytic depletion has been widely used for managing sensitized patients with incompatible organ transplants considered to be at increased immunological risk of rejection. Despite the fact that these T cell centric approaches are effective in non-sensitized patients, they fail to control the post-transplant humoral response of sensitized patients. Given the known challenges of the primed immune system of the sensitized patient, targeting B cell or T cell interactions with B cells should be considered as part of an optimal maintenance immunosuppression for this patient population. Due to the rapid evolution of agents targeting individual steps of humoral responses, as well as advances in our understanding of AMR, it is possible to design a mechanistically rational approach for the sensitized patient.

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