NARRATIVE REVIEW

Problem to solution; from mammalian skin grafts to renal allograft rejection: a tale of 66 years of evolution of our understanding

Murtaza Dhrolia, Aasim Ahmad

Abstract

The first successful kidney transplant was done in 1954, and it remains the best option for those with failed kidneys. However, the recipient's immune system remains the most formidable barrier to transplantation, leading to rejection. Rejection continues to be the most important reason of graft malfunction and chronic renal allograft dysfunction and remains a challenge to date for successful transplant survival. The current narrative review was planned to find the best possible solution to the problem from among the different solutions presented in literature related to allograft rejection since 1954.

Keywords: Evolution, Renal transplantation, Allograft rejection, Immunosuppressant.

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Introduction

To achieve the best solution to renal allograft rejection, the current narrative review adopted the system of classifying and grabbing the problem, finding alternatives, and picking the finest solution, registering directions to resolve the problem, and to evaluate the solution based on the evolution of our understanding of renal allograft rejection since 1954 when the first successful kidney transplant was done.

Step 1: Classifying the problem

Diagnosing renal allograft rejection; Evolution of Banff classification:

Until the 1990s, few individual classifications with heterogeneous characterisation for renal allograft rejection had been developed.[1] In 1991, all those associated with transplants, like pathologists, nephrologists and transplant surgeons, gathered in Banff, Canada, and developed a schema to standardise the international classification of renal transplanted (RT) biopsies, which was finally published in March 1993.[2]

Thereafter, Banff Classification has been updated bi-annually in the light of latest evidence. After the initial meeting in 1991, there have been 15 meetings targeting expansion of understanding in the field of renal transplantation. The last meeting was held in 2019 in Pittsburgh, Pennsylvania, in the United States of America (USA).[3]

Step 2: Understanding the problem

Evolution of understanding related to the mechanism of renal allotransplant rejection:

The acquired immune system comprises two response mechanisms, cytotoxic T-cells and antibodies. Sir Peter Medawar, in 1943 and 1944, did revolutionary work in transplant immunology by showing that a second skin graft was rejected more quickly and easily because of active immunisation from the initial graft.[4, 5]

Billingham and Medawar[6] observed that the skin allografts given to rodents that did not have T-cells were not rejected, and giving them the T-cells reinstated the rejection. This led to the notion that T-cells were the only reason for the allotransplant rejection. Formation of antibodies after transplantation was initially reported in 1938.[7] In the early 1970s, the occurrence of already formed donor-specific antibodies (DSAs) established as a high-level risk for hyperacute rejection[8] and the development of DSAs post-transplantation caused poorer outcomes and showed lesions of vascular obliteration now called allograft vasculopathy.[9]

Our current understanding: Based on observations and continued research in the field of transplant immunology,[10-23] the understanding about the mechanism of rejection is that alloimmune responses are initiated in well-defined stages[10] and T- and B-cells are the chief modes of the adaptive immune response, as they not only contribute a significant part to the acute phase, but also have a part in the healing phases of ischaemia-reperfusion injury (IRI).[11]

Department of Nephrology, The Kidney Centre Postgraduate Training Institute, Karachi, Pakistan.
Correspondence: Murtaza Dhrolia. Email: mfdhrolia@hotmail.com
ORCID ID. 0000-0003-4025-5086

Antigen-inexperienced or naïve T-cells of the recipient in secondary lymphoid organs are activated through the innate immune-recognition system by antigen-presenting cells (APCs), chiefly the dendritic cells (DCs) of the donor.[12-14] Activation of B-cells occur when antigen attaches its receptors, and thus produce anti-donor human leukocyte antigen (HLA) alloantibodies.[16]

The activation of the T-cell requires three events. Signal-1-Presentation of donor antigen to DCs through the T-cell receptor (TCR) is transduced through the cluster of differentiation-3 (CD3) complex.[17,18] Signal-2-DCs cause additional stimulation, which occurs when DCs B7.1 (CD80) and B7.2 (to T-cells CD28.[19] Signal 3 is activated by Signals 1 and 2 and it initiates cell proliferation via three CD86) attach pathways: the calcium-calcineurin, the nuclear factor –κBand mitogen-activated protein kinase (MAPK) pathways.[20] These pathways activate interleukin-2 (IL2), CD154 and CD25 which then activate the mammalian target of rapamycin (mTOR) pathway.[21] This leads to a formation of effector T-cells which along with alloantibodies mediate allograft rejection.

Step 3: Identifying alternative solutions

Evolution of immunosuppressive agents for renal allograft rejection: Over the last six decades, major advances in immune suppression to prevent rejection have been achieved. It began with total lymphoid irradiation to what is now available which has dramatically decreased episodes of acute rejection and significantly increased graft survival in the short term. Nevertheless, long-term graft outcome is still a substantial problem caused by antibody-mediated rejection and chronic allograft dysfunction.

Total lymphoid irradiation: Successful skin homograft with high dosage X-radiation and homologous bone marrow was recommended in 1955 by Joan Main et al.[24], and in 1958 by Joseph Murray et al.[25] to use total lymphoid irradiation (TLI) as the initial approach of immunosuppression. Later, , from 1960 to 1962, four success stories were reported which started with total body irradiation.[26,27] As bone marrow inoculation was not done, chimerism may not be essential. As newer alternatives became available, [28] TLI went obsolete.

Corticosteroids: Early in 1930, human adrenal insufficiency was treated with extracts from animal adrenal cortices[29] and was first used clinically in 1949 by Hench et al. for rheumatoid arthritis (RA).[30] Goodwin et al. in early 1960[31] showed that corticosteroids could undo acute rejection in a live related RT. Starzl et al.[32] in 1963 confirmed the effectiveness of corticosteroids and they became conventional therapy for renal transplantation.

Azathioprine (AZA): Schwartz et al. initiated immunosuppression by pharmacological means in 1959 by showing that the antiproliferative drug, 6-mercaptopurine (6-MP) reduced the formation of antibodies, thereby extending rabbit skin allograft survival.[33] Sir Roy Calne et al. in 1960 for the first time used the imidazole derivative of 6-MP, AZA, and showed that renal graft survival in dogs could be significantly improved from 7.5 to 23.7 days.[34] Till 1978, AZA and high-dose prednisolone remained the conventional therapy for RT.[35]

Calcineurin inhibitors (CNIs): In 1969, cyclosporine (CsA) was derived from tolypocladiuminflatuma fungus in the soila and showed an immunosuppressive effect in transplantation by Jean F. Borel.[36] Successful trials were done in 1978[37,38] and protocols with CsA regimen for immune suppression were used worldwide in 1982.[39]

In 1987 tacrolimus developed from streptomyces tsukubaensis (soil fungus) was observed to be more potent than CsA[40]. Non-adherence, a major cause of renal allograft rejection,[41] is addressed by prolonged-release tacrolimus approved in several countries since 2007.[42]

Mycophenolate mofetil (MMF): Following promising preclinical and phase-I clinical trials[43], MMF, an anti-metabolite, was considered an effective and safe immunosuppressant[44] and in 1995 it replaced AZA as the immunosuppressive agent of choice in kidney transplantation.[45]

mTOR inhibitors: In1989, it was shown that rapamycin (RPM), an mTOR inhibitor and a secondary metabolite of streptomyces hygroscopicus, reduced rejection in solid organ transplants in experimental animals[46,47], but the mTOR inhibitor was first used in human RT in 1999.[48] The introduction of mTOR inhibitors sirolimus and everolimus allowed early and significant CNI reduction/withdrawal without compromising safety or efficacy in the early post-transplant period.[49]

Antibodies: In the mid-1960s came polyclonal antibodies, like antilymphocyte aerum (ALS), antilymphocyte globulin (ALG) and rabbit antithymocyte globulin (rATG). From the 1970s, these were used to defer the start of acute rejection.[50] Polyclonal antibody use has a higher risk of infection and malignancy, and, with the development of CsA, their use was reduced drastically. ATG is now being used again with confidence as better prophylaxis for viral infections as our understanding of viral aetiology of post-transplant lymphoproliferative disorder (PTLD) has become better.[51]

Monoclonal antibodies (mAbs) were developed in 1975

and had monoclonal specificity unlike the polyclonal preparations.[52]

In the early 1980s, Anti-CD3 mAb muromonab (OKT3) was the first mAb used in sensitised patients for induction, for the treatment of rejections that were steroid-resistant, and in patients whose transplant function was delayed. This helped postpone CNI initiation.[53] It is no longer in use because of its serious side-effects and the availability of new agents with less side effects.

In the late 1990s, several mAbs were developed, and anti-CD25 antibodies that block interleukin-2 (IL-2) receptors, daclizumab and basiliximab, came into clinical use as they decreased the frequency of acute cellular rejection.[54, 55]

Alemtuzumab: An anti-CD52, T-cell and B-cell-depleting mAb, initially used for induction in renal transplantation in the late 1990s[56], was used in the early 20th century with excellent results,[57,58] but some studies showed that alemtuzumab may have increased rates of acute or antibody-mediated rejection.[59,60]

In 1997, rituximab, an anti CD20 mAb, was first approved for the treatment of B-cell non-Hodgkin's lymphoma.[61] Rituximab was first used for treating resistantRT rejection in 2000[62]. Rituximab is effectively used for many antibody-mediated events, including desensitisation in transplants that have incompatibility with blood group ABO, transplant with a positive crossmatch after removal of antibodies, and in treating antibody-mediated rejection (AMR).[63,64] Where renal function has been preserved, rituximab is also used in combination with chemotherapy in the treatment of PTLD.[65]

Co-stimulatory blocker: Since 2011, fusion protein balatacept, blocker of co-stimulatory signals, has been in use as a biological non-nephrotoxic maintenance immunosuppressant.[66]

Co-stimulatory blockers, bleselumab (ASKP1240),[67] a fully humanised anti-CD40 mAb, and CFZ533,[68] a fully humanised, anti-CD40 mAb, are under investigation in clinical trials for preventing rejection without the use of CNIs along with their inherent nephrotoxicity.

Blocking co-stimulatory signals at multiple levels is found to be useful in transplantation. Molecules that target other co-stimulation sites, like anti-CD28 antibodies, FR104, a non-agonistic, pegylated monovalent humanized Fab antibody,[66] will likely be developed. Use of two co-stimulatory blockers, e.g. against CD40-CD154 and against CD28-CD80 pathway, were found to be effective in animal research and may be used in humans in the future.[66]

Bortezomib: Bortezomib is a proteasome inhibitor that depletes plasma cells and thereby inhibits antibody production. It was first synthesised in 1995, and was approved in 2002 by the Food and Drug Administration (FDA) as a treatment for multiple myeloma.[69] It is also used for pre-transplant desensitisation and treatment of AMR. Since 2005, it is also being used off-label to decrease DSAs in patients who are highly sensitised was described in 2008 as an additional treatment for AMR.[70,71]

Eculizumab: Eculizumab is a monoclonal immunoglobulin G (IgG) antibody against protein C5 that can diminish the propagation of complement cascade after antibody-antigen binding. It was approved for the treatment of paroxysmal nocturnal haemoglobinuria (PNH)[72] in 2007, and for atypical haemolytic uraemic syndrome (aHUS) in 2011. It was evaluated in several clinical trials in transplant patients to reduce the end results of IRI, to prevent, treat relapsing or de novo aHUS, and in high immunological risk to prevent and cure humoral rejection.[73-75]

Protein C1 inhibitor: Protein C1 inhibitor (C1-INH) inhibits complement activation, both classical and lectin pathways, and prevent leukocyte-endothelial cell adhesion[76]. C1-INH is used safely with some success in hereditary angioedema[77]. C1-INH is currently under evaluation in renal transplantation to see a reduction in IRI and delayed graft function. It is also being evaluated for its potential to decrease sensitisation and reduction in donor-specific antibody production. This is likely to help in AMR, and conditions that may be refractory to other treatments.[78,79]

Sutimlimab, a humanised mAb against complement factor C1s that inhibits the classical complement pathway is also under investigation.[80, 81]

Tocilizumab: Tocilizumab, an IL-6 receptor antagonist, is being tested for chronic active AMR with positive DSAs and transplant glomerulopathy which is unaffected by intravenous immunoglobin (IVIG) and rituximab with and without plasmaperesis (PP).[82, 83]

Cell-based therapy for immune tolerance induction: Cell-based treatments helps chimerism and causes tolerance in major histocompatibility in different recipients. These are recently under evaluation in several trials to replace or at least spare conventional immunosuppressive therapies.[84-87] Recently, a case was reported of a living kidney transplant that achieved immune tolerance by mesenchymal stromal cells (MSC) derived from bone marrow.[88]

Use of IgG-degrading enzyme from Streptococcus pyogenes (IdeS): IdeS, derived from streptococcus (S.) pyogenes, inhibits both complement-dependent and antibody-dependent cellular cytotoxicity by cutting human IgG into fragments and preventing IgG memory B-cell responses by slicing the B-cell receptor from the circulating B-cells, thereby reducing, or eliminating DSAs and helping in desensitisation.[89]

Step 4: Selecting the best solution

Evolution of major clinical trials evaluating the effectiveness of immunosuppressive agents for renal allograft rejection: A delicate balance must be achieved between over-immunosuppression and under-immunosuppression. The former increases the risk of infection, and the latter increases the risk of rejection. A discussion of some of the clinical trials may lead to the selection of the best possible solution to combat the problem of allograft rejection.

TLI vs CsA: A prospective randomised trial, consisting of 20 kidney transplant patients who developed end-stage renal disease (ESRD) secondary to diabetic nephropathy, compared TLI given before the surgery with CsA therapy given after the surgery. Significantly more frequent rejection episodes occurred in the TLI-treated recipients, but the 3-year patient and transplant survival and infectious complications were comparable in both groups.[90]

Result: TLI has fallen out of favour.

Low-dose vs. high-dose steroids vs complete avoidance of steroids: It was found that low-dose (3mg/kg IV bolus) steroids given IV was as effective as high-dose (15-30 mg/kg IV bolus) steroid in reversing acute rejection, and it did not increase the incidence of further rejection episodes.[91]

A randomised trial in which rATG or Interleukin-2 receptor alpha (IL-2RA) was used for induction and maintenance regimen was tacrolimus/CsAe and MMF found that early removal of steroids did not raise the rate of acute rejection or graft failure.[92, 93]

Result: Lower dose or steroid-sparing strategies are now being considered inRT because of the availability of potent maintenance and induction agents.

AZA vs. MMF: Three major studies showed substantial reduction in acute rejection episodes with MMF compared to AZA at six months. However, graft and patient survivals were similar at one year.[94-96]

Comparison of MMF with azathioprine in about 50,000 kidney transplants in the United States renal database system showed that MMF had a protective effect on deteriorating graft function at one year.[97]

Result: MMF has replaced AZA in most immunosuppressive protocols.

CsA-steroid vs. AZA-steroid: The survival rate of cadaveric RTs at one year, treated with CsA and steroids were better compared to recipients treated with Az=ZA and steroids in a 1981 study of 96 patients.[98]

Result: CsA became the cornerstone of immunosuppression regimens all over the world.

CsA vs. tacrolimus: A study showed that individuals on CsA had more hyperuricaemia, and higher systolic and diastolic blood pressure at one year compared to tacrolimus and sirolimus.[99]

A meta-analysis of 30 trials which compared tacrolimus and CsA revealed substantial decrease in graft loss, lower acute rejections and less steroid-resistant rejection in tacrolimus-treated recipients, but it showed a higher incidence of diabetes needing insulin, tremor, headache and gastro-intestinal (GI) symptoms, like nausea, vomiting and diarrhoea. Those treated with CsA had more constipation and hirsutism. There were no disparities in the infection or malignancy rates.[100]

A 5-year study done on 169 patients in Pittsburgh in which patients were shifted to tacrolimus from CsA because of intractable rejection showed 74% success rate in combating rejection with steroid withdrawal in 22% cases.[101]

In a large European study, CsA-induced toxicities, like gingival hyperplasia, hypertrichosis, hyperlipidaemia and hypertension, became better after conversion to tacrolimus.[102]

Result: Tacrolimus progressively replaced CsA because of better results and fewer side effects.

Tacrolimus-MMF vs. Tacrolimus-AZA vs. CsA-MMF: In a trail that compared tacrolimus-AZA, CsA-MM, and tacrolimus-MMF found that the rate of acute rejection was not different between these groups, but they differed in the need for ATG (4.2% in tacrolimus-MMF arm, 10.7% in the CsA-MMF group, and 11.8% in the tacrolimus-AZA group). Patient and graft survival at 1, 2 or 3 years were, however, similar.[103]

A meta-analysis of 9 randomised controlled trials (RCTs) with 1820 participants looked at the effect of steroid withdrawal at 3-6 months of RT showed higher rates of

acute rejection with CsA-MMF compared to tacrolimus-MMF.[104]

Result: Maintenance regimen for kidney transplant recipients comprised mainly tacrolimus-MMF.[105]

Importance of CNIs in regimen: Studies used MMF-steroids with sirolimus,[106] basiliximab with sirolimus,[107] or belatacept with basiliximab without CNIs, but showed higher acute rejection rates.[108]

A Spanish study showed that out of patients treated with MMF, although 65% remained CNI-free at 12 months, the number came down to only 36% at 5years.[109]

Sirolimus-Everolimus vs CNIs: Combining sirolimus with MMF showed reduction in acute rejection, more delayed graft function and reduction in graft survival in RT recipients compared to a combination of tacrolimus-MMF or CsA-MMF regimens.[110] However, studies two large radomised trials[99,111] showed that combining sirolimus and MMF had inferior results than a combination of low-dose tacrolimus-MMF-based triple therapy.

Webster et al.[112] revealed that when sirolimus or everolimus replaced CNI, episodes of acute rejection remained comparable, with a lower serum creatinine, but bone marrow was more suppressed.

Many trials examined the impact of everolimus on withdrawal of CNI in RT recipients. Studies of an early switch to everolimus or halving of CNI dose followed by complete withdrawal at 2 months resulted in high percentage of biopsy-proven acute rejection (BPAR) at 1 year[113,114.] Studies of late conversion (mean >5-7 years) did not show increased numbers of acute rejection.[115, 116]

Result: CNI remains the mainstay of maintenance regimen. Limited use of mTORs can be beneficial in patients with deteriorating kidney function using CNIs, and in those with malignant neoplasms, or non-melanoma skin cancers.

Everolimus-CNIs vs. MMF-CNIs: Maintenance therapy with tacrolimus-MMF appears to be better than either tacrolimus-sirolimus or CsA-sirolimus.[117]

Studies and trials[118-121] looked at the efficacy of everolimus with reduced CNI and compared it with conventional MMF, and standard CNI. Everolimus helped in decreasing CNI dose, thereby reducing the risk of nephrotoxicity with mild-to-moderate immunologic risk. Everolimus was non-inferior to MMF for its immunosuppressive effectiveness and preservation of graft function.

Result: Reduced doses of CNIs combined with everolimus may have better graft survival and stable renal function.

Belatacept vs CsA: In two trials[122,123] the group that received belatacept showed similar percentage of graft and patient survival along with better renal function over a 7-yr post-transplant follow-up [124] and less frequent de novo DSA development with better cardiovascular and metabolic risk profiles[125] compared to the CsA group. However, at 12 months post-transplant, treatment with belatacept showed increase in acute cellular rejection, and PTLD, particularly in seronegative Epstein Barr virus-negative patients.[122,123]

Result: Caution is required for the use of belatacept as part of immunosuppressive regimens.

rATG vs. IL-2RA antagonists: A meta-analysis looked at the role of IL-2RA compared to rATG on the rate of acute rejection, infections, graft and patient survival in RT patients getting tacrolimus with no major difference in the rate of acute rejection or patient and graft survival between the groups, but cytomegalovirus (CMV) infection were less in IL-2RA group. In subgroup analysis in high-risk transplants, acute rejections were more in then IL-2RA group than in the rATG group.[126]

Brennan et al.[127] compared rATG and IL-2RA in 278 patients who had increased probability of delayed transplant function and/or acute rejection. It showed rejection incidence to be almost half in the rATG arm at 1 and 5 years along with decreased severity. All patients received maintenance with cyclosporin, MMF and prednisolone.

In a meta-analysis of 6 studies with a total of 853 patients, Liu et al. compared rATG and basiliximab, showing lower infection risk in the basiliximab group, but the rate of acute rejection, delayed transplant function, and the loss of the transplanted kidney of the patient were not different.[128]

Brokhof et al. assessed the effect of rATG and basiliximab on DSA in 114 cadaveric kidney recipients with positive DSA but negative flow crossmatch, and followed up for 36 months. The ATG group had much lower level of DSAs and decreased incidence of AMR.[129]

Result: ATG is preferable in patients at high risk of rejection.

Ritaximab in acute AMR(AAMR) and chronic AMR (CAMR): A trial[130-131] recruited 38 patients with AMR within one year of kidney transplant and compared the effect of rituximab or placebo infusion, given on the 5th day of the transplant. All patients received comparable

anti-human leukocyte antigens (HLA) sensitisation with plasma exchanges, IVIG and steroids. Both groups showed similar one-year transplant survival and kidney function,[130] and there was no difference at 7 year on death-censored transplanted kidney's survival and its function. Infection rates were also similar, but there were seven cancers in the rituximab group.[131]

A systematic review of seven studies evaluated the application of rituximab in CAMR treatment. Only one study showed improved graft outcomes; three reported poorer outcomes and three showed no difference. In one study, rituximab was associated with an increase in adverse events.[132]

Result: Rituximab may have some benefit in AAMR though high-quality evidence is lacking. Rituximab does not appear to have any benefit in CAMR.

Bortezomib in late AMR: A trial[133] revealed that bortezomib and placebo groups were comparable when compared for glomerular filtration rate (GFR) (median measured) at 2-years, 24-month graft survival, DSA levels, urinary protein concentration or follow-up biopsy samplings, while the bortezomib group showed more GI and haematological side effects.

Result: Treatment with bortezomib for late AMR is still unsettled.

Step 5: List of instruction to solve the problem

The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline related to kidney transplant recipients (KTRs): Only KDIGO clinical practice guidelines[134] on the monitoring, management and treatment of KTRs dating back to 2009 based upon the best information available as of March 2009 is the on guideline available for transplant-care providers (Table).

Step 6: Evaluating the solution

Key challenges and the possible ways forward in renal allograft rejection: Acute rejection has decreased, but the long-term outcome of kidney transplantation has not much changed. The main reason for graft-loss remains chronic rejection. Infections, diabetes, drug-related toxicity, and chronic kidney disease (CKD) still occur, mainly due to the immunosuppression therapy. Therefore, strategies are needed to safely minimise immunosuppression, thereby reducing long-term poor outcomes and cost of kidney transplantation.

Several important studies with some new recommendations have been done after the publishing of the 2009 KDIGO guideline for KTRs. New guidelines are needed to help nephrologists in deciding if induction is needed, which medications to use for induction, and what is the ideal maintenance treatment.

In the era of tacrolimus, mycophenolic acid and steroids, questions are raised about the requirement for IL-2RA in kidney transplantation,[135] as it is not useful in standard-risk transplantation, and in high-risk transplants it may be inferior to rATG.[127]

In search of regimen with CNI avoidance, belatacept promises a better long-term kidney function, graft function and a better patient survival rate,[124] but because of its prohibitively high cost, routine use is not possible. Based on studies on everolimus[118-121], minimal doses of CsA with everolimus are non-inferior for graft survival and stable renal function to MMF, and may replace MMF in conventional regimen suggested by KDIGO 2009.[134]

The newer innovations to improve renal transplant outcomes are likely to come from defining biomarkers of allo-reactivity and strategies to improve clinical tolerance. Personalised immunosuppression may offer the best treatment to individual patient after transplantation. In the field of clinical tolerance, much work is needed before it can replace conventional transplant therapy.

Xenotransplantation is not merely a dream as in 2016, the International Society for Organ Donation and Procurement (ISODP) Congress in Seoul predicted that th world might see a xenotransplant by 2030. Genetically modified pigs are already a reality[136], and on October 19, 2021, for the first time, a human was transplanted with a kidney from a pig without an immediate immune rejection for 54-hours.[137] However, concerns related to thrombogenicity and transmission of unknown infections would remain even if the problems of immunotolerance and immunosuppression are solved.

Similarly, using patient's own cells that are cultured naturally, or printed by a three-dimensional (3D) printer, is already being done and some models (urine bladder) are in clinical trials for more than 10 years, with very promising results.[138]

Unfortunately, the future with xenotransplantation and personalized medicine is still far away, and many challenges still abound in transplantation today that needs to be resolved.

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Table: Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline.

The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the monitoring, management, and treatment of kidney transplant recipients (KTRs)[134]

Induction therapy

- Recommend starting a combination of immunosuppressive medications before, or at the time of, kidney transplantation. (1A)
- Recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. (1A)
  - o Recommend that an nterleukin-2 receptor alpha (IL2-RA) be the first-line induction therapy. (1B)
  - o Suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk. (2B)

Initial maintenance immunosuppressive medications

- Recommend using a combination of immunosuppressive medications as maintenance therapy including a calcineurin inhibitor (CNI) and an antiproliferative agent, with or without corticosteroids. (1B)
- Suggest that tacrolimus be the first-line CNI used. (2A)
  - o Suggest that tacrolimus or cyclosporine (CsA) be started before or at the time of transplantation, rather than delayed until the onset of graft function. (2D tacrolimus; 2B CsA)
- Suggest that mycophenolate be the first-line antiproliferative agent. (2B)
- Suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation. (2B)
- Recommend that if mammalian target of rapamycin inhibitors (mTORi) are used, they should not be started until graft function is established and surgical wounds are healed. (1B)

Long-term maintenance immunosuppressant medications

- Suggest using the lowest planned doses of maintenance immunosuppressive medications by 2–4 months after transplantation, if there has been no acute rejection. (2C)
- Suggest that CNIs be continued rather than withdrawn. (2B)
- If prednisone is being used beyond the first week after transplantation, suggest prednisone be continued rather than withdrawn. (2C)

Treatment of acute rejection

- Recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. (1C)
- Suggest treating subclinical and borderline acute rejection. (2D)
- Recommend corticosteroids for the initial treatment of acute cellular rejection. (1D)
  - o Suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. (2D)
  - o Suggest using lymphocyte-depleting antibodies or muromonab-cluster of differentiation-3 (CD3) (OKT3) for acute cellular rejections that do not respond to corticosteroids, and for recurrent acute cellular rejections. (2C)
- Suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids (2C):
  - o plasma exchange;
  - o intravenous immunoglobulin;
  - o anti-CD20 antibody;
  - o lymphocyte-depleting antibody.
- For patients who have a rejection episode, we suggest adding mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate. (2D)

Treatment of chronic allograft injury

- Recommend kidney allograft biopsy for all patients with declining kidney function of unclear cause, to detect potentially reversible causes. (1C)
- For patients with CAI and histological evidence of CNI toxicity, suggest reducing, withdrawing, or replacing the CNI. (2C)
- For patients with chronic ankle instability (CAI), estimated glomerular filtration rate, (eGFR) 440 ml/min/1.73m2, and urine total protein excretion of 500 mg per gram creatinine (or equivalent proteinuria by other measures), suggest replacing the CNI with a mTORi. (2D)

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