review

memo (2019) 12:216–221
https://doi.org/10.1007/s12254-019-0507-4

memo
magazine of european medical oncology

Immunosuppression after renal transplantation

Hannes Neuwirt · Michael Rudnicki · Peter Schratzberger · Markus Pirklbauer · Andreas Kronbichler · Gert Mayer

Received: 26 February 2019 / Accepted: 20 June 2019 / Published online: 10 July 2019

Summary Immunosuppression (IS) is administered to kidney transplant recipients to prevent rejection episodes and loss of the renal allograft. Most centers rely on a triple IS after induction with either interleukin-2 receptor antibodies or antithymocyte globulin. The most frequently used substances for maintenance IS are glucocorticoids, antimetabolites, mTOR inhibitors (mTORi), calcineurin inhibitors (CNI) and the costimulation blocker belatacept. Guidelines recommend a triple combination consisting of CNIs, antimetabolites and corticosteroids for the majority of patients. The long-term risk for malignancy in general is increased in solid organ recipients compared to the general population. Modification of IS may result in reduced risk for nonmelanoma skin cancers but results in higher graft rejection rates and in the case of mTORi, deaths. In the case of posttransplantation lymphoproliferative disorders (PTLD) treatment options are reduction of IS, rituximab, chemotherapy, radiation therapy or a combination of these. The optimal protocol has not yet been established and depends on patient age and status, tumor load, laboratory findings, organ functions (heart, kidney, liver) and PTLD subtype. Posttransplantation diabetes mellitus is a frequent complication after kidney transplantation. Tacrolimus more than cyclosporine A, sirolimus and corticosteroids are considered to be diabetogenic; however, tacrolimus remains the first choice as the mainstay of IS. In general, the IS regimen should be tailored for optimal kidney allograft survival rather than better diabetic control. Concerning infections, cytomegalovirus and *Pneumocystis jerovecii* are best managed by prophylaxis. In the case of virus reactivation or opportunistic infections, targeted therapy is applied and the net state of IS is most often reduced.

Keywords Induction therapy · Maintenance therapy · Complications · Malignancy · Diabetes · Cytomegalovirus · Polyoma virus

H. Neuwirt (✉) · M. Rudnicki · P. Schratzberger · M. Pirklbauer · A. Kronbichler · G. Mayer
Department of Internal Medicine IV—Nephrology and Hypertension, Medical University Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria
Hannes.Neuwirt@i-med.ac.at

Introduction

Immunosuppression (IS) is administered to kidney transplant recipients to prevent rejection episodes and loss of the renal allograft. The optimal regimen of both induction and maintenance therapy has not been established. However, most centers rely on a triple IS after induction with either interleukin-2 receptor antibodies (IL2-RA) or anti-thymocyte globulin (ATG). This minireview focuses on clinical standards concerning IS in general and management of complications such as malignancies, diabetes, infections and other special situations.

Induction

Induction therapy is administered before, during or after renal transplantation. Two drugs are mainly used: the IL2-RA basiliximab and ATG. A number of clinical studies highlighted that the use of induction therapy in combination with standard maintenance IS is superior in reducing renal allograft rejection and graft failure compared to maintenance therapy alone [1–4]. The only exceptions are Caucasian recipients of full-house-identical organs and potential patients already receiving maintenance IS after solid organ transplantation other than kidney [5], while in the latter setting some nephrologists also administer IL2-RA.

IL-2-RA and ATG had similar efficacy concerning graft loss and clinically diagnosed acute rejection. Biopsy-proven acute rejection rates were slightly higher with IL2-RA (hazard ratio [HR] 1.3, 95% confidence interval [CI] 1.01–1.67). However, less side effects, particularly cytomegalovirus (CMV) disease and malignancies, made IL-2-RA the first choice in induction therapy [6, 7].

ATG was superior over IL2-RA in the setting of high immunologic risk, which includes among other factors a higher number of human leukocyte antigen (HLA) mismatches, young donor age, high recipient age, panel reactive antibody status >0%, preformed donor specific antibodies, ABO-incompatible renal transplantation, delayed graft function and cold ischemia time >24 h [3, 7].

Alemtuzumab, a humanized anti-CD52 antibody, is an infrequently and not routinely used induction therapy in kidney transplantation, while it is approved for the treatment of relapsing–remitting multiple sclerosis in Europe and chronic lymphocytic leukemia in the US. Furthermore, alemtuzumab-treated patients had similar transplant failure rates compared to basiliximab [8], but worse graft survival rates and more chronic allograft nephropathy compared to ATG, under a maintenance IS without steroids [9]. Additionally, several groups have described occurrence of autoimmune diseases after alemtuzumab, e.g. anti-glomerular basement membrane disease [10].

Maintenance

The most frequently used substances for maintenance IS are glucocorticoids, antimetabolites such as azathioprine, mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS), calcineurin inhibitors (CNI) such as cyclosporine A (CsA) or tacrolimus (Tac), mTOR inhibitors (mTORi) such as everolimus and sirolimus or the co-stimulation blocker belatacept. Kidney Disease-Improving Global Outcomes (KDIGO) suggests a triple combination consisting of CNIs, antimetabolites and corticosteroids for the majority of patients. In particular, the first-line recommended triple regimen is Tac, mycophenolate and corticosteroids. Patients with low immunological risk and induction therapy may be treated with a dual combination of Tac and MMF after rapid corticosteroid discontinuation within the first week [7]. Patients with Tac-related side effects, e.g. tremor, headache, diarrhea, dyspepsia, vomiting or alopecia may be switched to CsA, which—on the other hand—more frequently induces hirsutism, gingival hyperplasia and hypertension [11]. Target C0 levels of Tac and CsA are 7–10 and 150–300 ng/ml in the first 1–3 months and 5–7 and 50–150 ng/ml in subsequent months, respectively [7, 12].

Mycophenolate is the first-line antimetabolic agent as it was shown to be superior to azathioprine in preventing acute rejections with fewer side effects [13]. Most centers switch from MMF to EC-MPS in case of gastrointestinal side effects or generally prefer EC-MPS rather than MMF, which are similar in efficacy and safety [14, 15]. Mycophenolate is generally avoided in female recipients of childbearing age without sufficient contraceptive measures, whereas a dose reduction is mostly sufficient in other complications such as viral infections (as discussed below).

Glucocorticoids may be withdrawn within the first week after renal transplantation in low immunological risk patients after induction therapy only [7]. The long-term maintenance dose usually is 5 mg prednisone equivalent. Withdrawal of glucocorticoids is not associated with improvement of insulin sensitivity [16] and is associated with recurrence of glomerulonephritis [17] and higher myelosuppressive effects of azathioprine, MMF and EC-MPS. Furthermore, late withdrawal increases the risk of acute rejection [18, 19].

Some patients do not tolerate CNIs due to nephrotoxic or other adverse effects. Alternative immunosuppressive regimens are mainly based on either belatacept or mTORi. In patients with CNI nephrotoxicity without contraindication for belatacept (e.g. seronegativity for Epstein-Barr virus [EBV]) we switch to belatacept as various studies have shown superior renal allograft function compared to CsA without significant safety concerns [20–22]. Of note, belatacept is approved for IS in renal transplant recipients after induction with IL2-RA in combination with mycophenolate and corticosteroids. Compared to CNIs, mTORI had no significant difference in allograft and patient survival with higher rates of bone marrow suppression or dyslipidemia [23]. Similar results were published in patients converted from CNIs to mTORi plus a higher risk of acute rejection (relative risk [RR] 1.72, 95% CI 1.34–2.22) [24]. Hence, only in EBV-negative patients with an estimated glomerular filtration rate (eGFR) > 45 ml/min/1.73 m^2, a urinary protein-creatinine ratio (PCR) < 0.4 g/g AND a rationale for mTOR inhibitors is a switch to either everolimus or sirolimus performed, although the eGFR and PCR threshold might slightly vary between institutions [24–27].

Take home message: The standard IS regimen consists of induction with either IL2-RA or ATG followed by a triple maintenance therapy consisting of Tac (or belatacept in case of CNI nephrotoxicity), mycophenolate and steroids.

Complications

Malignancy—non-melanoma skin cancer

The long-term risk for malignancy in general is increased (standardized incidence ratio [SIR] 2.1, 95% CI 2.06–2.14) in solid organ recipients compared to the general population [28]. The risks for Kaposi sarcoma (SIR 61), non-melanoma skin cancer (NMSC; SIR 13.9), non-Hodgkin lymphoma (NHL; SIR 7.5) and

liver cancer (SIR 11.6) are most significantly increased. Reduction of IS may result in tumor regression in some cases; however, the optimal regimen has not been established. Treatment with low doses of CsA and azathioprine resulted in an approximately 35% reduction of cases with squamous or basal cell skin cancers compared to normal doses. However, acute graft rejection was increased by 8.7-fold, but graft survival rates were similar [29]. In general, reduction of IS increases the risk for rejection episodes, which commonly are treated at least by high doses of steroids plus an increase of IS. Hence, the potential risks or benefits of modifying IS must be carefully assessed on an individual basis. In 2006, Otley et al. published a consensus statement for reduction of IS in transplant-associated skin cancer [30]. In brief, a mild reduction of IS is proposed in patients with up to 25 NMSCs per year or stage 1A/B melanoma. Moderate reduction of IS is suggested in patients with a 3-year skin cancer mortality of 10–25% or stage II A/B melanoma and a severe reduction is proposed only in patients with metastatic skin cancer or stage >IIC melanoma.

Another modification of IS is to switch from CNI to mTORi. In a meta-analysis of 21 randomized trials of 5879 kidney and kidney–pancreas allograft recipients switch to sirolimus resulted in a significant reduction of NMSC risk (HR 0.44, 95% CI 0.30–0.63). Interestingly, patients on de novo sirolimus had the same risk compared to CNI-treated patients, suggesting that switching from CNI to mTORi is superior over prophylactic administration of mTORi-based IS in patients at risk for NMSC. However, the same study revealed a 43% higher risk of death (predominantly cardiovascular and infection-related) in patients on sirolimus [31]. A 47 and 37% increase of deaths was found also in an observational trial of 9353 kidney transplant patients on sirolimus and everolimus, respectively [32]. In a small study the decrease of new squamous cell cancer was not statistically significant [33].

Take home message: Modification of IS may result in reduced risk for NMSC but results in higher graft rejection rates and—in case of mTORi—deaths.

Post-transplant lymphoproliferative disorders

Post-transplant lymphoproliferative disorders (PTLDs) appear mostly related to the presence of EBV but EBV-negative disease may also occur. In general, EBV surveillance is performed in many centers and most nephrologists would reduce IS in case of EBV reactivation. In this context, it is interesting that the multivariate-adjusted relative risk for PTLDs was shown to be reduced by 38% for every 30 days of ganciclovir use after renal transplantation in 100 PTLD cases matched to 375 controls [34].

Treatment options are reduction of IS, rituximab, chemotherapy, radiation therapy or a combination of these. While polyclonal B cell proliferations (early lesions) are usually treated by reduction of IS, rituximab is added in patients with CD20+ polymorphic PTLDs, who do not meet all criteria for B- or T-cell lymphomas. In monomorphic PTLDs a combination of the two mentioned measures with chemotherapy is usually administered. The definitive protocol depends on patients' age and status, tumor load, laboratory findings, organ functions (heart, kidney, liver), PTLD subtype and may vary from institution to institution.

Reduction of IS is usually performed in almost all patients with PTLDs. Most early lesions improve significantly within 5 weeks [35, 36]. The optimal regimen of reduced IS is not known. Guidelines from the BTS and Mayo Clinic suggest a reduction to 25–50% from baseline for kidney allograft recipients [37, 38]. However, complete withdrawal of CNIs was associated with reduced graft (HR 3.07, 95% CI 1.04–9.09) and patients' survival (HR 4.00, 95% CI 1.77–9.04) in a multivariate analysis of a retrospective multicenter study [39].

Diabetes

Post-transplant diabetes mellitus (PTDM) is a frequent complication after kidney transplantation. PTDM patients have higher blood glucose values in the afternoon compared to non-transplanted diabetic patients. Despite that fact, diagnostic criteria of PTDM are the same as in otherwise healthy individuals [40]. Concerning IS, CNIs (Tac more than CsA), sirolimus and corticosteroids are considered to be diabetogenic. Steroids are usually not tapered off in the setting of PTDM, since the benefit of patients after renal transplantation mainly relies on preserved kidney function. Tac remains the first choice as mainstay of IS as 70% of Caucasian patients with early PTDM were able to discontinue insulin on Tac plus glucocorticoids [41] with the exception of specific indications for CsA or mTORi. Tac resulted in similar patient and graft survival rates despite higher PTDM incidence when compared to CsA [42]. Sirolimus is generally not recommended [43] in patients at risk for PTDM. Of note, in patients with pre-existing diabetes the immunosuppressive regimen should not be tailored to better diabetic control but to optimal kidney allograft survival (as stated above: Tac, mycophenolate, corticosteroids) [7, 44]. A consensus statement nicely summarizes important issues on PTDM prevention, diagnosis and therapy [44]. Of note, patients with PTDM without a history of preformed diabetes mellitus might benefit from early administration of basal insulin and should not be treated primarily using sulfonylureas [44, 45].

Take home message: The immunosuppressive regimen should be tailored for optimal kidney allograft survival rather than better diabetic control.

Infections

Cytomegalovirus

Cytomegalovirus (CMV) frequently reactivates after kidney transplantation. CMV infection and disease are associated with increased risk of graft failure and death. CMV infections are diagnosed by PCR in blood of asymptomatic patients. CMV syndrome is defined as attributable symptoms in CMV-PCR positive patients, whereas those with tissue-invasive CMV disease additionally suffer from organ dysfunction (e.g. enteritis, colitis, nephritis, hepatitis, pneumonitis). The cornerstone of CMV management is prophylaxis using the antiviral drug valganciclovir. In case of infection, timely diagnosis and reduction/withdrawal of antimetabolites and—if not already started—administration of valganciclovir or ganciclovir are the relevant measures. The exact regimen depends mainly on each center's practice: while some would stop antimetabolites and introduce antiviral therapy later, others reduce antimetabolites and start antiviral therapy immediately. In CMV syndrome or disease, antimetabolites are commonly withdrawn, antiviral therapy is started and additional therapies (i.e. CMV immune globulin) are administered. In ganciclovir-resistant CMV disease, foscarnet and cidofovir are alternative antiviral options, which however bear high nephrotoxic potential.

Polyomavirus

BK and JC viruses are the only two polyomaviruses associated with nephropathy after transplantation, i.e. tubulointerstitial nephritis and ureteral stenosis. Typically, at the first stage of BKV reactivation, BKV particles are only found in urine. If untreated over weeks to months, BKV progresses to detectable viral particles in plasma and finally BKV nephropathy (BKVN), which is associated with graft failure in 15–50%. Screening and preemptive reduction or withdrawal of the antimetabolite at onset of viremia prevents progression to BKVN in 95% of cases [46, 47] without increased risk of allograft rejection or loss. In case of BKV viremia and kidney allograft dysfunction, a kidney biopsy is performed in order to distinguish BKVN from rejection. In case of BKVN the pivotal role of decreased IS has been highlighted above and is recommended by the American Society of Transplantation [48, 49]. In addition to reduction of antimetabolites, CNI doses may be decreased or Tac may be switched to CsA, which also lowers mycophenolate concentrations [50], or sirolimus [51, 52] in cases with progressive BKV diseases. Additional therapies that may be administered are immunoglobulin preparations, which contain anti-BKV antibodies, leflunomide [53] or cidofovir [54]. Levofloxacin has no relevant antiviral effects in patients with BKV viremia [55, 56].

Take home message: CMV is best managed by prophylaxis. In case of reactivation of CMV or BKV the net-state of IS is reduced.

Pneumocystis jirovecii

Pneumocystis jirovecii pneumonia (PJP) was a well-known disease in solid organ recipient, which, however, has been almost completely eliminated since the introduction of prophylactic use of trimethoprim-sulfamethoxazole [57]. PJP prophylaxis is recommended for 3–6 months after kidney transplantation. Additional prophylactic administration for at least 6 weeks has been proposed for patients having received treatment for acute allograft rejection episodes [7].

Other infections

Although there are no randomized controlled trials, most centers have similar standards of care in this context. In patients with community-acquired infections who are otherwise stable, the immunosuppressive regimens remain unmodified. In patients, who are admitted to inpatient care or who require intravenous antibiotics most centers decrease or withhold the antimetabolite. In case of life-threatening infections low-dose glucocorticoids are continued while CNIs and antimetabolites are withheld.

Special situations

In general, IS is usually not changed for elective surgery. The important exception are patients treated with mTORi, which has to be withdrawn due to wound healing problems. The optimal alternative regimen is not known and obviously the presumed time for wound healing also influences the choice of regimen. While some centers prefer to continue the antimetabolite and slightly increase corticosteroids, others switch to a CNI-based regimen until wound healing is completed.

Women of childbearing age without sufficient contraceptive measures should not be treated with mycophenolate. Pregnant women are switched from mTORi and/or mycophenolate to a CNI, azathioprine and corticosteroids.

Funding Open access funding provided by University of Innsbruck and Medical University of Innsbruck.

Conflict of interest H. Neuwirt, M. Rudnicki, P. Schratzberger, M. Pirklbauer, A. Kronbichler, and G. Mayer declare that they have no competing interests.

References

1. Webster AC, Playford EG, Higgins G, Chapman JR, Craig JC. Interleukin 2 receptor antagonists for renal transplant recipients: A meta-analysis of randomized trials. Transplantation. 2004;77(2):166–76.
2. Szczech LA, Berlin JA, Aradhye S, Grossman RA, Feldman HI. Effect of anti-lymphocyte induction therapy on renal allograft survival: A meta-analysis. J Am Soc Nephrol. 1997;8(11):1771–7.
3. Szczech LA, Berlin JA, Feldman HI. The effect of antilymphocyte induction therapy on renal allograft survival. A meta-analysis of individual patient-level data. Anti-Lymphocyte Antibody Induction Therapy Study Group. Ann Intern Med. 1998;128(10):817–26.
4. Cai J, Terasaki PI. Induction immunosuppression improves long-term graft and patient outcome in organ transplantation: An analysis of United Network for Organ Sharing registry data. Transplantation. 2010;90(12):1511–5.
5. Vincenti F, Kirkman R, Light S, Bumgardner G, Pescovitz M, Halloran P, et al. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. N Engl J Med. 1998;338(3):161–5.
6. Webster AC, Ruster LP, McGee R, Matheson SL, Higgins GY, Willis NS, et al. Interleukin 2 receptor antagonists for kidney transplant recipients. Cochrane Database Syst Rev. 2010;1:CD3897.
7. Kidney Disease: Improving Global Outcomes Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9(Suppl3):1–155.
8. 3C Study Collaborative Group, Haynes R, Harden P, Judge P, Blackwell L, Emberson J, et al. Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): A randomised trial. Lancet. 2014;384(9955):1684–90.
9. Ciancio G, Burke GW, Gaynor JJ, Roth D, Kupin W, Rosen A, et al. A randomized trial of thymoglobulin vs. alemtuzumab (with lower dose maintenance immunosuppression) vs. daclizumab in renal transplantation at 24 months of follow-up. Clin Transplant. 2008;22(2):200–10.
10. Clatworthy MR, Wallin EF, Jayne DR. Anti-glomerular basement membrane disease after alemtuzumab. N Engl J Med. 2008;359(7):768–9.
11. Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: Meta-analysis and meta-regression of randomised trial data. BMJ. 2005;331(7520):810.
12. Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, Gurkan A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007;357(25):2562–75.
13. Wagner M, Earley AK, Webster AC, Schmid CH, Balk EM, Uhlig K. Mycophenolic acid versus azathioprine as primary immunosuppression for kidney transplant recipients. Cochrane Database Syst Rev. 2015;12:CD7746.
14. Budde K, Curtis J, Knoll G, Chan L, Neumayer HH, Seifu Y, et al. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: Results of a 1-year study. Am J Transplant. 2004;4(2):237–43.
15. Salvadori M, Holzer H, de Mattos A, Sollinger H, Arns W, Oppenheimer F, et al. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. Am J Transplant. 2004;4(2):231–6.
16. Midtvedt K, Hjelmesaeth J, Hartmann A, Lund K, Paulsen D, Egeland T, et al. Insulin resistance after renal transplantation: The effect of steroid dose reduction and withdrawal. J Am Soc Nephrol. 2004;15(12):3233–9.
17. Kukla A, Chen E, Spong R, Weber M, El-Shahawi Y, Gillingham K, et al. Recurrent glomerulonephritis under rapid discontinuation of steroids. Transplantation. 2011;91(12):1386–91.
18. Kasiske BL, Chakkera HA, Louis TA, Ma JZ. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. J Am Soc Nephrol. 2000;11(10):1910–7.
19. Pascual J, Quereda C, Zamora J, Hernández D, Spanish Group for Evidence-Based Medicine in Renal Transplantation. Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolate mofetil: A meta-analysis of randomized, controlled trials. Transplantation. 2004;78(10):1548–56.
20. Vincenti F, Larsen CP, Alberu J, Bresnahan B, Garcia VD, Kothari J, et al. Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. Am J Transplant. 2012;12(1):210–7.
21. Vincenti F, Rostaing L, Grinyo J, Rice K, Steinberg S, Gaite L, et al. Belatacept and long-term outcomes in kidney transplantation. N Engl J Med. 2016;374(4):333–43.
22. Rostaing L, Massari P, Garcia VD, Mancilla-Urrea E, Nainan G, del Carmen Rial M, et al. Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: A randomized phase II study. Clin J Am Soc Nephrol. 2011;6(2):430–9.
23. Webster AC, Lee VW, Chapman JR, Craig JC. Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients. Cochrane Database Syst Rev. 2006;2:CD4290.
24. Lim WH, Eris J, Kanellis J, Pussell B, Wiid Z, Witcombe D, et al. A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. Am J Transplant. 2014;14(9):2106–19.
25. Gatault P, Lebranchu Y. Conversion to mTOR-inhibitor-based immunosuppression: Which patients and when? Transplant Res. 2013;2(Suppl 1):S3.
26. Holdaas H, Rostaing L, Seron D, Cole E, Chapman J, Fellstrom B, et al. Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: A randomized, multicenter, 24-month study. Transplantation. 2011;92(4):410–8.
27. Schena FP, Pascoe MD, Alberu J, del Carmen Rial M, Oberbauer R, Brennan DC, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation. 2009;87(2):233–42.
28. Engels EA, Pfeiffer RM, Fraumeni JF Jr., Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306(17):1891–901.
29. Dantal J, Hourmant M, Cantarovich D, Giral M, Blancho G, Dreno B, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: Randomised comparison of two cyclosporin regimens. Lancet. 1998;351(9103):623–8.
30. Otley CC, Berg D, Ulrich C, Stasko T, Murphy GM, Salasche SJ, et al. Reduction of immunosuppression for transplant-associated skin cancer: Expert consensus survey. Br J Dermatol. 2006;154(3):395–400.
31. Knoll GA, Kokolo MB, Mallick R, Beck A, Buenaventura CD, Ducharme R, et al. Effect of sirolimus on malignancy and survival after kidney transplantation: Systematic re-

view and meta-analysis of individual patient data. BMJ. 2014;349:g6679. Erratum in BMJ 2014;349:g7543.
32. Badve SV, Pascoe EM, Burke M, Clayton PA, Campbell SB, Hawley CM, et al. Mammalian target of rapamycin inhibitors and clinical outcomes in adult kidney transplant recipients. Clin J Am Soc Nephrol. 2016;11(10):1845–55.
33. Hoogendijk-van den Akker JM, Harden PN, Hoitsma AJ, Proby CM, Wolterbeek R, Bouwes Bavinck JN, et al. Two-year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus. J Clin Oncol. 2013;31(10):1317–23.
34. Funch DP, Walker AM, Schneider G, Ziyadeh NJ, Pescovitz MD. Ganciclovir and acyclovir reduce the risk of post-transplant lymphoproliferative disorder in renal transplant recipients. Am J Transplant. 2005;5(12):2894–900.
35. Armitage JM, Kormos RL, Stuart RS, Fricker FJ, Griffith BP, Nalesnik M, et al. Posttransplant lymphoproliferative disease in thoracic organ transplant patients: Ten years of cyclosporine-based immunosuppression. J Heart Lung Transplant. 1991;10(6):877–86. discussion 886–887.
36. Tsai DE, Hardy CL, Tomaszewski JE, Kotloff RM, Oltoff KM, Somer BG, et al. Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: Analysis of prognostic variables and long-term follow-up of 42 adult patients. Transplantation. 2001;71(8):1076–88.
37. Parker A, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G, et al. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients—BCSH and BTS Guidelines. Br J Haematol. 2010;149(5):693–705.
38. Paya CV, Fung JJ, Nalesnik MA, Kieff E, Green M, Gores G, et al. Epstein-Barr virus-induced posttransplant lymphoproliferative disorders. ASTS/ASTP EBV-PTLD Task Force and The Mayo Clinic Organized International Consensus Development Meeting. Transplantation. 1999;68(10):1517–25.
39. Rabot N, Büchler M, Foucher Y, Moreau A, Debiais C, Machet MC, et al. CNI withdrawal for post-transplant lymphoproliferative disorders in kidney transplant is an independent risk factor for graft failure and mortality. Transpl Int. 2014;27(9):956–65.
40. American Diabetes Association. Standards of medical care in diabetes—2011. Diabetes Care. 2011;34(Suppl 1):11–61.
41. Neylan JF. Racial differences in renal transplantation after immunosuppression with tacrolimus versus cyclosporine. FK506 Kidney Transplant Study Group. Transplantation. 1998;65(4):515–23.
42. Woodward RS, Flore MC, Machnicki G, Brennan DC. The long-term outcomes and costs of diabetes mellitus among renal transplant recipients: Tacrolimus versus cyclosporine. Value Health. 2011;14(4):443–9.
43. Schold JD, Kaplan B, Chumbler NR, Howard RJ, Srinivas TR, Ma L, et al. Access to quality: Evaluation of the allocation of deceased donor kidneys for transplantation. J Am Soc Nephrol. 2005;16(10):3121–7.
44. Sharif A, Hecking M, de Vries AP, Porrini E, Hornum M, Rasoul-Rockenschaub S, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: Recommendations and future directions. Am J Transplant. 2014;14(9):1992–2000.
45. Hecking M, Haidinger M, Doller D, Werzowa J, Tura A, Zhang J, et al. Early basal insulin therapy decreases new-onset diabetes after renal transplantation. J Am Soc Nephrol. 2012;23(4):739–49.
46. Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. Am J Transplant. 2005;5(3):582–94. Erratum in Am J Transplant 200; 5(4 Pt 1):839.
47. Vasudev B, Hariharan S, Hussain SA, Zhu YR, Bresnahan BA, Cohen EP. BK virus nephritis: Risk factors, timing, and outcome in renal transplant recipients. Kidney Int. 2005;68(4):1834–9.
48. Hirsch HH, Randhawa P, AST Infectious Diseases Community of Practice. BK virus in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S136–S46.
49. Hirsch HH, Randhawa P, AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):179–88.
50. Gerbase MW, Fathi M, Spiliopoulos A, Rochat T, Nicod LP. Pharmacokinetics of mycophenolic acid associated with calcineurin inhibitors: Long-term monitoring in stable lung recipients with and without cystic fibrosis. J Heart Lung Transplant. 2003;22(5):587–90.
51. Ramos E, Drachenberg CB, Papadimitriou JC, Hamze O, Fink JC, Klassen DK, et al. Clinical course of polyoma virus nephropathy in 67 renal transplant patients. J Am Soc Nephrol. 2002;13(8):2145–51.
52. Wali RK, Drachenberg C, Hirsch HH, Papadimitriou J, Nahar A, Mohanlal V, et al. BK virus-associated nephropathy in renal allograft recipients: Rescue therapy by sirolimus-based immunosuppression. Transplantation. 2004;78(7):1069–73.
53. Josephson MA, Gillen D, Javaid B, Kadambi P, Meehan S, Foster P, et al. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplantation. 2006;81(5):704–10.
54. Kuypers DR, Vandooren AK, Lerut E, Evenepoel P, Claes K, Snoeck R, et al. Adjuvant low-dose cidofovir therapy for BK polyomavirus interstitial nephritis in renal transplant recipients. Am J Transplant. 2005;5(8):1997–2004.
55. Lee BT, Gabardi S, Grafals M, Hofmann RM, Akalin E, Aljanabi A, et al. Efficacy of levofloxacin in the treatment of BK viremia: A multicenter, double-blinded, randomized, placebo-controlled trial. Clin J Am Soc Nephrol. 2014;9(3):583–9.
56. Knoll GA, Humar A, Fergusson D, Johnston O, House AA, Kim SJ, et al. Levofloxacin for BK virus prophylaxis following kidney transplantation: A randomized clinical trial. JAMA. 2014;312(20):2106–14.
57. Fishman JA. Prevention of infection caused by pneumocystis carinii in transplant recipients. Clin Infect Dis. 2001;33(8):1397–405.