1. TRATAMIENTO DE INDUCCIÓN

1. Renal transplantation with expanded criteria donors: Which is the optimal immunosuppression?

Fioliopoulos V, Boletis JN.
World J Transplant 2016 March 24; 6(1): 103-114.

ABSTRACT
The growing gap between demand and supply for kidney transplants has led to renewed interest in the use of expanded criteria donor (ECD) kidneys in an effort to increase the donor pool. Although most studies of ECD kidney transplantation confirm lower allograft survival rates and, generally, worse outcomes than standard criteria donor kidneys, recipients of ECD kidneys generally have improved survival compared with wait-listed dialysis patients, thus encouraging the pursuit of this type of kidney transplantation. The relative benefits of transplantation using kidneys from ECDs are dependent on patient characteristics and the waiting time on dialysis. Because of the increased risk of poor graft function, calcineurin inhibitor (CNI)- induced nephrotoxicity, increased incidence of infections, cardiovascular risk, and malignancies, elderly recipients of an ECD kidney transplant are a special population that requires a tailored immunosuppressive regimen. Recipients of ECD kidneys often are excluded from transplant trials and, therefore, the optimal induction and maintenance immunosuppressive regimen for them is not known. Approaches are largely center specific and based upon expert opinion. Some data suggest that antithymocyte globulin might be the preferred induction agent for elderly recipients of ECD kidneys. Maintenance regimens that spare CNIs have been advocated, especially for older recipients of ECD kidneys. CNI-free regimens are not universally accepted due to occasionally high rejection rates. However, reduced CNI exposure and CNI-free regimens based on mammalian target of rapamycin inhibitors have shown acceptable outcomes in appropriately selected ECD transplant recipients.

2. Induction Treatment With Low-Dose Thymoglobulin or Basiliximab in Renal Transplants From Older Donors

Gavela Martínez E, Sancho Calabuig A, Escudero Quesada V et al.
Transplantation Proceedings, 40, 2900–2902 (2008).

ABSTRACT
Transplantation of kidneys from older donors is followed by an increase in delayed graft function (DGF) and acute rejection episodes (ARE). In these circumstances, induction treatment, whether with antithymocyte globulin or with interleukin-2 receptor blockers, may delay the introduction of calcineurin inhibitors (CNI) with effective prevention of ARE. We examined the efficacy and safety of induction treatment with 2 low doses of thymoglobulin compared with 2 doses of basiliximab. A group of 27 patients were treated with thymoglobulin and another 36 with basiliximab. CNI introduction was delayed until day 3 posttransplantation. The thymoglobulin group received 2 doses of 1.25 mg/kg on alternate days and the basiliximab group 2 doses of 20 mg. A trend to a lower incidence of DGF was observed in the thymoglobulin group (33% vs 55.6%; P = .08), with lower levels of serum creatinine on days 7 (P = .02) and 14 (P = .02) posttransplantation. No patient in the thymoglobulin group experienced ARE, but 11 patients (30.6%) in the basiliximab group did (P < .001), and 5 needed rescue treatment with thymoglobulin. We found no differences

in the incidence of cytomegalovirus (CMV) disease (P = .945), admission due to infections (P = .274), or neoplasia (P = .340), or differences in graft (P = .69) and patient (P = .21) survivals at 1 and 3 years. Low-dose thymoglobulin was more effective at preventing DGF and ARE in renal transplant recipients of organs from older donors, with no differences in infectious complications or graft and patient survivals.

3. Elderly Kidney Transplant Recipients: Single-Center Experience in the Middle East
Gheith O, Halim MA, Al-Otaibi T et al.
Experimental and Clinical Transplantation (2019) 1: 135-141.

ABSTRACT
OBJECTIVES: The number of renal transplants in elderly patients is increasing as age per se does not constitute a contraindication to transplant. We compared renal transplant outcomes in elderly recipients versus a group of middle-aged patients.
MATERIALS AND METHODS: Our retrospective case controlled study compared elderly transplant recipients (n = 252; > 60 y old) with a matched cohort of younger adult recipients (n = 710; between 40 and 60 years old) who underwent renal transplant at the Hamed Al-Essa Organ Transplant Center of Kuwait between 2000 and 2014. Demographic characteristics, comorbidities, complications after transplant, and graft and patient outcomes were compared between groups.
RESULTS: There were 252 elderly kidney transplant recipients (mean age of 65.5 ± 4.8 y; 59.52% males) and 710 younger adult patients (mean age of 49.3 ± 5.5 years; 61.4% males). Most donors were males in their thirties. Deceased donors predominated in the younger adult group, whereas living unrelated donors predominated in the elderly group (P < .05). Diabetes represented the most common cause of endstage kidney disease. Younger patients tended to receive heavier induction therapy but comparable maint enance immunosuppression. Posttransplant diabetes was higher in younger patients; however, there were more elderly patients with micro- and macroangiopathies (P < .05). No significant differences were shown between groups with regard to patient or graft survival (P > .05). This could be attributed to a significantly higher number of patients with cardiovascular risks, less rejection episodes, and higher number of malignancies in the elderly group (P < .05).
CONCLUSIONS: Due to relatively less potent immunosuppression, elderly patients experienced lower rejection rates and better graft survival; however, patient survival was lower due to higher cardiovascular risk factors. Older patients should not be discouraged from living-donor renal transplant. Targeted research studies on protocols for the elderly are needed.

4. Induction Immunosuppression in Kidney Transplant Recipients Older than 60 Years of Age Safety and Efficacy of ATGAM®, OKT3® and Simulect®
Heifets M, Saeed MI, Parikh MH et al.
Drugs Aging 2004; 21 (11): 747-756.

ABSTRACT
BACKGROUND: The choice of induction immunosuppression for kidney transplantation in elderly recipients is dictated by the consideration of the risk of infection as well as efficacy in the prevention of acute rejection, thus allowing a reduction in subsequent maintenance immunosuppression and its attendant long-term adverse effects.

OBJECTIVE: To compare the efficacy and safety of the antibody induction immunosuppression strategies in elderly recipients of kidney transplants.
PATIENTS AND METHODS: We present retrospective data analysis on 183 kidney transplant recipients ≥60 years of age at Hahnemann University Hospital (Philadelphia, PA, USA) over a 12-year period. We compared four consecutive cohorts of kidney transplant recipients receiving lymphocyte immune globulin, equine antithymocyte globulin (ATGAM®) [n = 29]; muromonab CD3 (OKT3®) [n = 45]; basiliximab (Simulect®) with corticosteroid maintenance [n = 40]; and Simulect® without corticosteroid maintenance (n = 69).
RESULTS: Delayed graft function (DGF) was observed in 48% of patients receiving ATGAM®, 35.6% in the OKT3® group and 35% in the Simulect® group with corticosteroid maintenance and 36.2% in the Simulect® group without corticosteroid maintenance. The rejection rate within the first 3 months was 31% in the ATGAM® and OKT3® groups, 17.5% in the Simulect® group with corticosteroid maintenance and 14.5% in the Simulect® group without corticosteroid maintenance.
These differences for DGF and acute rejection were statistically significant between patients receiving ATGAM® and OKT3®, ATGAM® or OKT3® and both groups of Simulect® (all $p < 0.05$). Patients receiving Simulect® were free of adverse effects typically encountered by patients receiving polyclonal and monoclonal antibodies for induction. Patients receiving Simulect® had much shorter hospital stays and benefited from significant reduction of costs compared with other groups.
CONCLUSION: Our data indicate that kidney transplant recipients ≥60 years of age benefit from induction therapy with Simulect® followed by corticosteroid-free maintenance immunosuppression.

5. Immunosuppression in Elderly Renal Transplant Recipients Are Current Regimens Too Aggressive?
Meier-Kriesche H, Kaplan B
Drugs & Aging 2001; 18 (10): 751-759.

ABSTRACT
Renal transplantation is an accepted and successful treatment modality in elderly patients with end-stage renal disease. In comparison with maintenance dialysis, transplantation has been shown to confer a mortality benefit as well as improvements in quality of life in older individuals with end-stage renal disease. Despite this, overall outcomes of renal transplantation in elderly individuals have, in general, been less successful than those of younger renal transplant recipients. Largely, this has been due to the particular vulnerability of elderly patients to the immunosuppressive medications used in renal transplantation. This review article covers these issues in some detail and briefly discusses some of the pharmacokinetic, pharmacodynamic, physiological and immunological differences between younger and older transplant recipients. Elderly renal transplant recipients have both a higher rate of patient death and allograft loss censored for death. Upon multivariate analysis, age of the recipient is strongly associated with allograft loss independent of other known factors. Acute rejections are less frequent in older individuals; however the consequence of a rejection if it occurs is negative for long-term graft survival. On the other hand, death by infection is vastly increased in older versus younger renal transplant recipients. In general, the pharmacokinetics of the immunosuppressive agents are little affected by age, but the tolerance to these agents seems to decrease with increasing age.

Elderly renal transplant recipients present a very difficult clinical challenge. As the elderly become an ever-increasing segment of the renal transplant population, new and innovative immunosuppressive strategies will have to be considered and applied.

6. Comparison of Sequential Protocol using Basiliximab versus Antithymocyte Globulin with High-Dose Mycophenolate Mofetil in Recipients of a Kidney Graft from an Expanded-Criteria Donor

Pallet N, Angliecheau D, Martinez F et al.
Transplantation 2006;81: 949–952.

ABSTRACT
This retrospective pilot study investigated use of high-dose mycophenolate mofetil with biological induction and sequential introduction of low-dose cyclosporine in recipients of expanded criteria donor (ECD) kidneys. Fifty-four patients received mycophenolate mofetil 3 g/day for 45 days, cyclosporine 4 mg/kg/day, prednisolone, and rabbit antithymocyte globulin (rATG, n=14) or basiliximab (n=40). Acute rejection incidence was 11.3% (7.1% with rATG, 12.6% with basiliximab). Delayed graft function was observed in 31 patients (54%). At one year, measured glomerular filtration rate was 54±4 ml/min, with no significant differences between induction therapies. Thirty patients (55%) required≥1 MMF dose reduction within month 1 due to adverse events (gastrointestinal symptoms, 67%; leucopenia 33%). Leucopenia was more frequent with rATG, while gastrointestinal symptoms were more frequent with basiliximab. Cytomegalovirus replication occurred in three patients (23%) with rATG and 3 (8%) with basiliximab. In conclusion, high-dose MMF, corticosteroids, delayed low-dose cyclosporine and induction therapy offers an excellent risk-to-benefit ratio in patients receiving an ECD allograft.

7. Rabbit antithymocyte induction and dosing in deceased donor renal transplant recipients over 60 yr of age

Patel SJ, Knight RJ, Suki WN et al.
Clin Transplant 2011: 25: E250–E256.

ABSTRACT
BACKGROUND: Antithymocyte globulin (rATG) is a commonly used induction agent in renal transplantation; however, data in older kidney recipients are limited.
METHODS: We reviewed charts of 301 deceased donor renal transplants who received a protocol consisting of 3–7 doses of rATG and triple maintenance therapy. Outcomes of patients >60 yr of age (n = 45) were compared to those aged 18–59 yr (n = 256).
RESULTS: Older recipients had more diabetics, were more likely to receive expanded criteria donor kidneys ($p < 0.01$), and over 30% were sensitized. Recipients >60 received less cumulative rATG (4.6 vs. 5.1 mg/kg; $p < 0.01$). Three-yr acute rejection was lower in the >60 group (2% vs. 16%, $p < 0.01$) although glomerular filtration rates were similar between groups. Actuarial graft survival was similar; however, patient survival in the >60 group at three yr was lower (80% vs. 95%; $p = 0.02$). Specifically, patients >60 with delayed graft function and rATG cumulative dosing >6 mg/kg had a survival of <50% by two yr.

CONCLUSION: Recipients over 60 yr receiving rATG induction have acceptable renal function and a low risk of rejection; however, reduced survival was noted among those receiving >6 mg/kg. These data suggest that when used, lower cumulative dosages of rATG are preferable in the older recipient.

8. Personalized immunosuppression in elderly renal transplant recipients

Peeters LEJ, Andrews LM, Hesselink DA et al.
Pharmacological Research 130 (2018) 303–307.

ABSTRACT

The number of elderly people has increased considerably over the last decades, due to a rising life expectancy and ageing populations. As a result, an increased number of elderly with end-stage-renal-disease are diagnosed, for which the preferred treatment is renal transplantation. Over the past years the awareness of the elderly as a specific patient population has grown, which increases the importance of research in this group.

Elderly patients often receive kidneys from elderly donors while younger donor kidneys are preferentially reserved for younger recipients. Although the rate of acute rejection after transplantation is lower in the elderly, these rejections may lead to graft loss more frequently, as kidneys from elderly donors have marginal reserve capacity. To prevent acute rejection, immunosuppressive therapy is needed. On the other hand, elderly patients have a higher risk to die from infectious complications, and thus less immunosuppression would be preferable. Immunosuppressive treatment in the elderly is complicated further by changes in the pharmacokinetics and pharmacodynamics, with increasing age. Adjustments in standard immunosuppressive regimes are therefore suggested for this population.

An unmet need in transplantation medicine is a tool to guide a personalized approach to immunosuppression. Recently several promising biomarkers that identify injury to the graft at an early stage or predict acute rejection have been identified. Unfortunately, none of these biomarkers were tested specifically in the elderly. We believe there is an urgent need to perform clinical trials investigating novel immunosuppressive regimens in conjunction with biomarker studies in this specific population.

9. Safety and Efficacy of Induction Treatment with Low Thymoglobulin Doses in Kidney Transplantation from Expanded-Criteria Donors

Sancho Calabuig A, Gavela Martínez E, Kanter Berga J et al.
Transplantation Proceedings, 47, 50-53 (2015).

ABSTRACT

BACKGROUND: Induction treatment has been recommended as part of the initial immunosuppressive regimen in kidney transplantation, and antithymocyte globulin is one of the drugs used for it, but at usual dosage it has been related to an increase of infectious and neoplastic complications. Our aim was to analyze the safety and efficacy of induction treatment with low doses of antithymocyte globulin, compared to basiliximab.

METHODS: In this retrospective cohort study of 321 kidney transplant patients with a minimum follow-up of 2 years, 162 were treated with low doses of antithymocyte globulin (1.25 mg/kg,

every other day) and 159 with basiliximab. Mean follow-up was 76.6 ± 37.51 months (range, 24-187 mo) and was similar for the 2 groups.
RESULTS: Mean number of antithymocyte globulin doses was 1.89 ± 0.32 mg/kg (range, 1-3). The globulin group received a higher proportion of kidneys from donors >70 years old (25.3% vs 13.8%; P = .010) and donors with higher creatinine levels (1.01 ± 0.62 vs 0.86 ± 0.28 mg/dL; P = .006). The basiliximab group presented a higher incidence of acute rejection (22.1% vs 9.1%; P = .010). Cytomegalovirus disease was more frequent in the globulin group (18.6% vs 8.1%; P = .011) without an increase of infectious hospitalizations. Graft (P = .214) and patient (P = .533) survivals were similar.
CONCLUSIONS: Induction with low doses of antithymocyte globulin resulted in a lower incidence of acute rejection with graft and patient survivals similar to that obtained with basiliximab induction, in spite of a worse donor profile. CMV disease was more frequent with antithymocyte globulin, without an increase of infectious hospitalizations or cancer development, in long-term follow-up.

10. Induction Immunosuppressive Therapy in the Elderly Kidney Transplant Recipient in the United States

Gill J, Sampaio M, Gill JS et al.
Clin J Am Soc Nephrol 6: 1168–1178, 2011.

ABSTRACT
BACKGROUND AND OBJECTIVES: The choice of induction agent in the elderly kidney transplant recipient is unclear.
DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: The risks of rejection at 1 year, functional graft loss, and death by induction agent (IL2 receptor antibodies [IL2RA], alemtuzumab, and rabbit antithymocyte globulin [rATG]) were compared among five groups of elderly ≥60 years) deceased-donor kidney transplant recipients on the basis of recipient risk and donor risk using United Network of Organ Sharing data from 2003 to 2008.
RESULTS: In high-risk recipients with high-risk donors there was a higher risk of rejection and functional graft loss with IL2RA versus rATG. Among low-risk recipients with low-risk donors there was no difference in outcomes between IL2RA and rATG. In the two groups in which donor or recipient was high risk, there was a higher risk of rejection but not functional graft loss with IL2RA. Among low-risk recipients with high-risk donors, there was a trend toward a higher risk of death with IL2RA.
CONCLUSIONS: rATG may be preferable in high-risk recipients with high-risk donors and possibly low-risk recipients with high-risk donors. In the remaining groups, although rATG is associated with a lower risk of acute rejection, long-term outcomes do not appear to differ. Prospective comparison of these agents in an elderly cohort is warranted to compare the efficacy and adverse consequences of these agents to refine the use of induction immunosuppressive therapy in the elderly population.

11. Rabbit Antithymocyte Globulin Is More Beneficial in Standard Kidney Than In Extended Donor Recipients

Hardinger KL, Brennan DC, Schnitzler MA.
Transplantation. 2009 May 15;87(9):1372-6.

ABSTRACT
BACKGROUND: In a randomized, international study comparing rabbit antithymocyte globulin (TMG) and basiliximab (BAS) induction in renal transplant recipients at risk for delayed graft function or acute rejection (n=278), TMG was associated with less acute rejection at 1 year.
METHODS: This study analyzed outcomes stratified by standard criteria donor (SCD), extended criteria donor (ECD), and hypertensive donor. Data-capture limitations necessitated defining ECD as donor age more than 60 years or 50 to 60 years with hypertension and renal insufficiency.
RESULTS: Seventy-five recipients received ECD-kidneys (28.4% TMG vs. 25.6% BAS, P=NS) and 203 recipients received SCD-kidneys (72.6% TMG vs. 74.4% BAS, P=NS). Recipients of an ECD or hypertensive donor-kidney had similar outcomes between treatment groups. Recipients of an SCD-kidney treated with TMG had less rejection (odds ratio [OR] 0.48). Recipients of a normotensive donor-kidney treated with TMG had less rejection (OR 0.56). Recipients of a normotensive, SCD-kidney treated with TMG had less rejection (OR 0.47) and death (OR 0.17) than their counterparts treated with BAS.
CONCLUSIONS: Contrary to its perceived niche in recipients of ECD-kidneys, TMG was most beneficial in patients who received a normotensive, deceased SCD kidney.

12. Evaluating Safety and Efficacy of Rabbit Antithymocyte Globulin Induction in Elderly Kidney Transplant Recipients

Khanmoradi K, Knorr JP, Feyssa EL et al.

Exp Clin Transplant. 2013 Jun;11(3):222-8.

ABSTRACT
OBJECTIVES: The optimal immunosuppression regimen for elderly kidney transplant recipients is poorly defined. We sought to evaluate the short-term efficacy and safety of thymoglobulin in geriatric recipients of deceased-donor kidneys.
MATERIALS AND METHODS: A single-center, retrospective analysis was undertaken between elderly (≥ 65 years) (n=137) and nonelderly (n=276) kidney transplant recipients who received rabbit antithymocyte globulin induction and calcineurin inhibitor, mycophenolic acid, and prednisone maintenance.
RESULTS: The mean age was 70 versus 52 years. Fewer elderly patients had an earlier transplant or panel reactive antibodies > 20%, but had more machine perfused, older, and extended criteria donor kidneys. Elderly patients received lower rabbit antithymocyte globulin (5.4 vs 5.6 mg/kg; P = .04) and initial mycophenolic acid doses (1620 vs 1774 mg; P = .002), and experienced less delayed graft function (31.1% vs 50.0%; P < .001). Death-censored graft survival and graft function at 3 years and biopsy-proven acute rejection at 1 year were comparable; however, there was lower 3-year patient survival in elderly patients. Donor age was the only factor associated with reduced patient survival. Rates of malignancy, infection, or thrombocytopenia were similar; however, leukopenia occurred less frequently in elderly patients (11.7% vs 19.9%; P = .038).
CONCLUSIONS: Elderly kidney transplant recipients receiving rabbit antithymocyte globulin did not experience different short-term graft survival, graft function or rates of infection, malignancy or hematologic adverse reactions than did nonelderly patients; they experienced fewer episodes of delayed graft function, but had lower 3-year patient survival.

2. TRATAMIENTO DE MANTENIMIENTO

MANTEINANCE IS ON THE ELDERLY

13. What immunosuppression should be used for old-to-old recipients?
Le Meur Y.
Transplant Rev (Orlando). 2015 Oct;29(4):231-6.

ABSTRACT
Elderly patients receiving a kidney from old donors (old-to-old) are a growing population of transplant recipients. This population cumulates risks of complications due to the co-morbidities and the immunodeficiency state and the frailty of the recipients together with the kidney senescence of the donors. In this context, the choice of immunosuppression is complicated and must take into account some contradictory principles explaining why no consensus exists today.

14. Immunological characteristics of the elderly allograft recipient
Klinger M, Banasik M.
Transplant Rev (Orlando). 2015 Oct;29(4):219-23.

ABSTRACT
The increasing number of elderly people with a demand for organ transplantation poses an important medical challenge. The effect of aging on the immune system concerns wide modifications with a considerable influence on transplant outcomes. Aging causes significant changes in immune cells repertoire. Thymic involution impairs the production of new naïve cells. Immune remodeling induces important alterations in the activity of immunological molecules. Therefore, clinical implications in elderly transplant recipients should consider appropriate organ allocation with adequate individualization of immunosuppression.

15. Need for optimized immunosuppression in elderly kidney transplant recipients
Lehner LJ, Staeck O, Halleck F, et al.
Transplant Rev (Orlando). 2015 Oct;29(4):237-9.

ABSTRACT
The proportion of elderly kidney transplant candidates is increasing worldwide due to higher number of patients with end-stage renal disease in aging societies.
ALLOCATION: Accordingly, organ allocation policies in this population were adjusted in several countries. The European Senior Program is the most prominent example, where elderly patients (≥65 years) receive elderly (≥65 years) donor organs with acceptable results.
IMMUNOSENESCENCE: Because of age-dependent changes in the immune response and higher susceptibility to immunosuppressant side effects, outcomes in elderly patients are different compared to younger kidney transplant recipients. However, elderly patients do reject, especially poorly matched elderly donor organs. This warrants tailored immunosuppressive regimes with regard to the age-related changes of the immune system.
SIDE EFFECTS: Rejection therapies may have detrimental side effects in the seniors and are frequently leading to over-immunosuppression (malignancy and infections) in long-term therapy.

It is hypothesized that after initial graft adaptation elderly patients may benefit from less immunosuppression in order to lower cancer risk and reduce infection rates and cardiovascular comorbidities.
LACK OF DATA: Current evidence on recommended standard immunosuppressive therapy was mainly derived from trials, where elderly patients were excluded or only a minority. In order to improve immunosuppressive therapy in elderly transplant recipients, current immunosuppressive regimes have to be re-investigated in this growing population. Up to date, only a few well-designed prospective studies were performed in elderly populations and demonstrate the need for effective immunosuppression in the first months after transplantation.
CONCLUSION: It is evident that novel treatment strategies and adequately powered prospective clinical trials are needed to establish time-adapted immunosuppressive regimens according to the needs of this vulnerable group of kidney transplant recipients.

CNI FREE STRATEGIES

16. Calcineurin inhibitor-free immunosuppressive strategy in elderly recipients of renal allografts from deceased donors: 1-year results from a prospective single center trial
Arbogast HP, Hoffmann JN, Illner WD, et al.
Transplant Proc 2009; 41: 2529-2532.

ABSTRACT
Recently published data from our center have demonstrated the feasibility of a nephrotoxicity- and atherogenicity-free, mycophenolate mofetil (MMF)-based immunosuppressive protocol for elderly recipients of kidneys from elderly cadaveric donors. We investigated a therapeutic regimen of strictly monitored MMF (target mycophenolic acid [MPA] trough levels between 2-6 microg/mL) and steroids combined with a polyclonal-monoclonal induction regimen consisting of a low-dose, single shot of rabbit ATG (ATG-Fresenius) and the interleukin-2 receptor (IL-2R)-antibody basiliximab (d0 and d4). Between 1997 and 2007, we treated 175 elderly patients with an MMF-based, calcinearin inhibitor (CNI)-free immunosuppressive protocol. For the present cohort, 30 elderly recipients (67.8 +/- 3.8 years) of renal transplants from deceased donors (69.4 +/- 13.3 years) were recruited consecutively for this 5-year prospective, open, single center, pilot trial. One-year results of this clinical trial were patient and renal allograft survivals of 87% and 83%, respectively; death-censored 1-year graft survival was 97%. Mostly steroid-sensitive rejection episodes were observed in 46% of patients, with only 3 patients requiring serum antibody therapy. Renal allograft function was satisfactory, as reflected by a mean serum creatinine of 1.78 +/- 0.45 mg/dL and a Nankivell glomerular filtration rate (GFR) of 48.8 +/- 13.9 mg/dL at 6 months. Twenty-three percent of all patients demonstrated cytomegalovirus (CMV) infections; however, only 3.3% developed CMV disease. Application of a combined polyclonal-monoclonal induction regimen using a nephrotoxicity- and atherogenicity-free, MMF-based immunosuppressive maintenance protocol in elderly cadaveric kidney transplant recipients led to acceptable short-term outcomes, albeit at the expense of an increased rejection rate, comparable to that previously published for elderly (>50 years) recipients of allografts from elderly (>50 years) cadaveric donors.

17. Sequential Quadruple Immunosuppression Including Sirolimus in Extended Criteria and Nonheartbeating Donor Kidney Transplantation

Diekmann F, Campistol JM, Saval N, et al.
Transplantation 2007;84: 429–432.

ABSTRACT
The aim was to evaluate feasibility and safety of calcineurin inhibitor–free immunosuppression in high-risk donor kidney transplantation with sequential sirolimus introduction. Kidney transplant patients (n=76) with a donor aged >60 years, donor with acute renal failure, or a nonheartbeating donor were included. Immunosuppression consisted of antithymocyte globulin or basiliximab, mycophenolate mofetil, prednisone, and sequential introduction of sirolimus.
One-year patient survival was 96.2% and 95.8%; graft survival was 94.2% and 91.7%; acute rejection rates were 21.2% and 12.4%; delayed graft function was 21.2% and 66.7%; and creatinine clearance was 58±20 mL/min and 56±21 mL/min for the brain-dead donor group and the nonheartbeating donor group, respectively. Most adverse events were infections, but also three lymphoceles, three urinary fistulas, three wound seromas. Sequential sirolimus introduction in high-risk donor kidney transplantation was found to lead to good patient and graft survival and incidence of acute rejection and delayed graft function.

18. Calcineurin-inhibitor avoidance in elderly renal allograft recipients using ATG and basiliximab combined with mycophenolate mofetil
Guba M, Rentsch M, Wimmer CD, et al.
Transpl Int 2008;21:637-45.

ABSTRACT
In old recipients of renal allografts from old donors, benefits of calcineurininhibitors (CNI) are curtailed by nephrotoxicity. Intending to improve the outcome of these recipients, we analyzed a CNI-free immunosuppressive regimen consisting of anti-thymocyte globulin (ATG), basiliximab, mycophenolate mofetil (MMF) and steroids. Kidney allograft recipients with low immunological risk (panel reactive antibodies <30%) were eligible for this study. Immunosuppression induction included ATG (4 mg/kg, day 0), basiliximab (20 mg, day 0 + 4) and steroids, followed by MMF (TL 2–6 µg/ml) and steroid maintenance treatment. Patient and graft survival rates respectively were 89.3% and 85.4% (12 months), and 86.6% and 76.8% (24 months). Delayed graft function occurred in 44.6%. S-creatinine at 12 months was 1.85 ± 0.94 mg/dl. Thirty patients (53.6%) showed biopsy-proven rejections (6x Banff 3, 13x Banff 4I and 16x Banff 4II), 77% of which were steroid-sensitive, 23% required antibody treatment. After 12 months, 83% of the patients had an MMF-based immunosuppression, 43% were CNI-free. Cytomegalovirus (CMV) infections occurred in 28, tissue-invasive disease in three patients. Despite acceptable renal graft survival and function in some of patients with marginal organs, high incidences of rejections and CMV infections suggest the feasibility of CNIavoidance using an MMF-based protocol only in carefully selected patients.

19. Results of a Calcineurin-Inhibitor-Free Immunosuppressive Protocol in Renal Transplant Recipients of Expanded Criteria Deceased Donors
Re LS, Rial MC, Guardia OE, et al.
Transplant Proc 2006; 38: 3468-3469.

ABSTRACT

The increasing number of patients on waiting lists and the relatively stable organ procurement rate provide the groundwork for the use of expanded criteria deceased donors. While calcineurin-inhibitors (CNI) are excellent immunosuppressive drugs, their nephrotoxicity is largely responsible for the lack of improvement in long-term graft survival.
The objective of this study was to analyze the results obtained with the use of a calcineurin inhibitor-free immunosuppressive protocol (polyclonal antibody induction, plus sirolimus, mycophenolate mofetil, and low doses of steroids) in terms of graft and patient survival as well as posttransplant clinical complications over 2 years.
Under this immunosuppressive protocol, 78.04% of the patients completed the followup. A protocol biopsy was performed on 17 patients (53.1%) within 2 years posttransplant of which 82.31% were diagnosed as chronic allograph nephropathy grade I. The incidence of clinical complications was low and not significantly different from that reported with other immunosuppressive schemes. Death-censored graft survival was 95.12%.
In conclusion, the use of a calcineurin inhibitor-free protocol in renal-transplant recipients of expanded criteria deceased donors was associated with excellent graft and patient survival rates and a low incidence of adverse events.

20. Immunosuppression without calcineurin inhibition: optimization of renal function in expanded criteria donor renal transplantation
Luke PP, Nguan CY, Horovitz D, et al.
Clin Transplant 2007; 23: 9-1.

ABSTRACT
INTRODUCTION: To assess the efficacy of calcineurin inhibitor (CNI)-free immunosuppression vs. calcineurin-based immunosuppression in patients receiving expanded criteria donor (ECD) kidneys.
PATIENT AND METHODS: Thirteen recipients of ECD kidneys were enrolled in this pilot study and treated with induction therapy and maintained on sirolimus, mycophenolate mofetil (MMF) and prednisone. A contemporaneous control group was randomly selected comprised of 13 recipients of ECD kidneys who had been maintained on CNI plus MMF and prednisone.
RESULTS: For the study group vs. the control group, two-yr graft survival was 92.3% vs. 84.6% (p = NS), two-yr patient survival was 100% vs. 92.3% (p = NS) and the acute rejection rates were 23% vs. 31% (p = NS), respectively. Renal function was significantly better in the study group compared with control up to the six-month mark, after which, it remained numerically but not statistically significant. Complications were more common in the study group, but serious adverse events requiring discontinuation were rare.
CONCLUSION: This pilot study demonstrates that CNI-free regimens can be safely implemented in patients receiving ECD kidneys with excellent two-yr patient and graft survival and good renal allograft function. Longer follow-up in larger randomized controlled trials are necessary to establish these findings.

REDUCED CNI EXPOSURE, MTOR INHIBITOR

21. Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation
Ekberg H, Tedesco-Silva H, Demirbas A, et al.
N Engl J Med 2007; 357: 2562-2575.

ABSTRACT
BACKGROUND: Immunosuppressive regimens with the fewest possible toxic effects are desirable for transplant recipients. This study evaluated the efficacy and relative toxic effects of four immunosuppressive regimens.
METHODS: We randomly assigned 1645 renal-transplant recipients to receive standard-dose cyclosporine, mycophenolate mofetil, and corticosteroids, or daclizumab induction, mycophenolate mofetil, and corticosteroids in combination with low-dose cyclosporine, low-dose tacrolimus, or low-dose sirolimus. The primary end point was the estimated glomerular filtration rate (GFR), as calculated by the Cockcroft–Gault formula, 12 months after transplantation. Secondary end points included acute rejection and allograft survival.
RESULTS: The mean calculated GFR was higher in patients receiving low-dose tacrolimus (65.4 ml per minute) than in the other three groups (range, 56.7 to 59.4 ml per minute). The rate of biopsy-proven acute rejection was lower in patients receiving low-dose tacrolimus (12.3%) than in those receiving standard-dose cyclosporine (25.8%), low dose cyclosporine (24.0%), or low-dose sirolimus (37.2%). Allograft survival differed significantly among the four groups (P = 0.02) and was highest in the low-dose tacrolimus group (94.2%), followed by the low-dose cyclosporine group (93.1%), the standard dose cyclosporine group (89.3%), and the low-dose sirolimus group (89.3%). Serious adverse events were more common in the low-dose sirolimus group than in the other groups (53.2% vs. a range of 43.4 to 44.3%), although a similar proportion of patients in each group had at least one adverse event during treatment (86.3 to 90.5%).
CONCLUSIONS: A regimen of daclizumab, mycophenolate mofetil, and corticosteroids in combination with low-dose tacrolimus may be advantageous for renal function, allograft survival, and acute rejection rates, as compared with regimens containing daclizumab induction plus either low-dose cyclosporine or low-dose sirolimus or with standard-dose cyclosporine without induction.

22. Everolimus with Reduced Calcineurin Inhibitor Exposure in Renal Transplantation
Pascual J, Berger SP, Witzke O, et al.
J Am Soc Nephrol. 2018 Jul;29(7):1979-1991.

ABSTRACT
BACKGROUND: Everolimus permits reduced calcineurin inhibitor (CNI) exposure, but the efficacy and safety outcomes of this treatment after kidney transplant require confirmation.
METHODS: In a multicenter noninferiority trial, we randomized 2037 de novo kidney transplant recipients to receive, in combination with induction therapy and corticosteroids, everolimus with reduced-exposure CNI (everolimus arm) or mycophenolic acid (MPA) with standard-exposure CNI (MPA arm). The primary end point was treated biopsy-proven acute rejection or eGFR<50 ml/min per 1.73 m^2 at post-transplant month 12 using a 10% noninferiority margin.
RESULTS: In the intent-to-treat population (everolimus n=1022, MPA n=1015), the primary end point incidence was 48.2% (493) with everolimus and 45.1% (457) with MPA (difference 3.2%; 95% confidence interval, -1.3% to 7.6%). Similar between-treatment differences in incidence were observed in the subgroups of patients who received tacrolimus or cyclosporine. Treated biopsy-proven acute rejection, graft loss, or death at post-transplant month 12 occurred in 14.9% and 12.5% of patients treated with everolimus and MPA, respectively (difference 2.3%; 95% confidence interval, -1.7% to 6.4%). De novo donor specific antibody incidence at 12 months and

antibody-mediated rejection rate did not differ between arms. Cytomegalovirus (3.6% versus 13.3%) and BK virus infections (4.3% versus 8.0%) were less frequent in the everolimus arm than in the MPA arm. Overall, 23.0% and 11.9% of patients treated with everolimus and MPA, respectively, discontinued the study drug because of adverse events.
Conclusions In kidney transplant recipients at mild-to-moderate immunologic risk, everolimus was noninferior to MPA for a binary composite end point assessing immunosuppressive efficacy and preservation of graft function.

23. An open-label, randomized trial indicates that everolimus with tacrolimus or cyclosporine is comparable to standard immunosuppression in *de novo* kidney transplant patients
Sommerer C, Suwelack B, Dragun D, et al.
Kidney Int. 2019 Jul;96(1):231-244.

ABSTRACT
This is a randomized trial (ATHENA study) in *de novo* kidney transplant patients to compare everolimus versus mycophenolic acid (MPA) with similar tacrolimus exposure in both groups, or everolimus with concomitant tacrolimus or cyclosporine (CsA), in an unselected population. In this 12-month, multicenter, open-label study, de novo kidney transplant recipients were randomized to everolimus with tacrolimus (EVR/TAC), everolimus with CsA (EVR/CsA) or MPA with tacrolimus (MPA/TAC), with similar tacrolimus exposure in both groups. Non-inferiority of the primary end point (estimated glomerular filtration rate [eGFR] at month 12), assessed in the per-protocol population of 338 patients, was not shown for EVR/TAC or EVR/CsA versus MPA/TAC. In 123 patients with TAC levels within the protocol-specified range, eGFR outcomes were comparable between groups. The mean increase in eGFR during months 1 to 12 post-transplant, analyzed post hoc, was similar with EVR/TAC or EVR/CsA versus MPA/TAC. The incidence of treatment failure (biopsy proven acute rejection, graft loss or death) was not significant for EVR/TAC but significant for EVR/CsA versus MPA/TAC. Most biopsy-proven acute rejection events in this study were graded mild (BANFF IA). There were no differences in proteinuria between groups. Cytomegalovirus and BK virus infection were significantly more frequent with MPA/TAC. Thus, everolimus with TAC or CsA showed comparable efficacy to MPA/TAC in de novo kidney transplant patients. Non-inferiority of renal function, when pre-specified, was not shown, but the mean increase in eGFR from month 1 to 12 was comparable to MPA/TAC.

24. Efficacy and Safety of Everolimus Plus Low-Dose Tacrolimus Versus Mycophenolate Mofetil Plus Standard-Dose Tacrolimus in *De Novo* Renal Transplant Recipients: 12-Month Data
Qazi Y, Shaffer D, Kaplan B, et al.
Am J Transplant. 2017 May;17(5):1358-1369.

ABSTRACT
In this 12-month, multicenter, randomized, openlabel, noninferiority study, de novo renal transplant recipients (RTxRs) were randomized (1:1) to receive everolimus plus low-dose tacrolimus (EVR+LTac) or mycophenolate mofetil plus standard-dose Tac (MMF+STac) with induction therapy (basiliximab or rabbit anti-thymocyte globulin). Noninferiority of composite efficacy failure rate (treated biopsy-proven acute rejection [tBPAR]/graft loss/death/loss to

follow-up) in EVR+LTac versus MMF+STac was missed by 1.4%, considering the noninferiority margin of 10% (24.6% vs. 20.4%; 4.2% [-3.0, 11.4]). Incidence of tBPAR (19.1% vs. 11.2%; $p < 0.05$) was significantly higher, while graft loss (1.3% vs. 3.9%; $p < 0.05$) and composite of graft loss/death/lost to follow-up (6.1% vs. 10.5%, $p = 0.05$) were significantly lower in EVR+LTac versus MMF+STac groups, respectively. Mean estimated glomerular filtration rate was similar between EVR+LTac and MMF+STac groups (63.1 [22.0] vs. 63.1 [19.5] mL/min/1.73 m^2) and safety was comparable. In conclusion, EVR+LTac missed noninferiority versus MMF+STac based on the 10% noninferiority margin. Further studies evaluating optimal immunosuppression for improved efficacy will guide appropriate dosing and target levels of EVR and LTac in RTxRs.

25. Prospective Comparison of the Use of Sirolimus and Cyclosporine in Recipients of a Kidney From an Expanded Criteria Donor

Durrbach A, Rostaing L, Tricot L, et al.
Transplantation. 2008;85: 486-490.

ABSTRACT

A 6-month, open-label, multicenter prospective pilot study was conducted to evaluate the effects of sirolimus (SRL) versus cyclosporine (CsA) in recipients of kidneys from expanded criteria donors. All patients also received antithymocyte globulins induction, mycophenolate mofetil, and steroids. Sixty-nine patients (33 SRL, 36 CsA) were randomized. More patient were withdrawn in the SRL group (16 vs. 6, P<0.01), because of delayed graft function and surgical complications. Delayed graft function tended to be more frequent with SRL than with CsA (45.4% vs. 30.6%, P=0.22). Graft survival was numerically lower in the SRL group (87.5% vs. 97%, P=0.19). At 6 months, there were no significant differences in biopsy-proven acute rejection or calculated creatinine clearance (SRL 12.1% vs. CsA 8.3%; P=0.7 and 44.7±16.6 vs. 41.9±15.2 mL/min; P0.54 respectively). These results do not support the use of SRL immediately after transplantation in expanded criteria donor recipients.

iMTOR and ECD

26. Sirolimus in Kidney Transplantation From Marginal Donors

Pisani F, Buonomo O, Iaria G, et al.
Transplant Proc 2004; 36: 495-496.

ABSTRACT

Nephrotoxicity caused by calcineurin inhibitors can lead to either delayed graft function or long-term decline of renal function after kidney transplantation. Therefore, recipients of renal transplants from marginal donors require non-nephrotoxic immunosuppression.
Eighteen patients received kidney transplants from marginal donors, with a calcineurin inhibitor–free immunosuppressive regimen, based on basiliximab, mycophenolate mofetil, steroids, and sirolimus. Renal graft biopsy was performed in all cases before surgery. Mean follow-up was 11.8 months. We report immediate renal function in 9 patients, delayed graft function in 5 and acute tubular necrosis in 4 patients. One patient was successfully treated for biopsy-proven acute rejection. Hypercholesterolemia and hypertriglyceridemia were the most common adverse effects (n = 13) associated with arthralgia (n = 2) and thrombocytopenia (n = 2). Five patients underwent a

switch to tacrolimus, due to sirolimus-induced side effects. Immunosuppression without the use of calcineurin inhibitors is a safe and effective regimen in kidney transplantation, although sirolimus-related side effects still represent a morbidity factor in these patients.

27. Influence of sirolimus on proteinuria in de novo kidney transplantation with expanded criteria donors: comparison of two CNI-free protocols

Diekmann F, Gutiérrez-Dalmau A, López S, et al.
Nephrol Dial Transplant 2007; 22: 2316-2321.

ABSTRACT

BACKGROUND: The contribution of mammalian target of rapamycin (mTOR) inhibitors to proteinuria is controversial. The aim was to analyse proteinuria in suboptimal kidney calcineurin inhibitor-(CNI) free de novo immunosuppression.

METHODS: All patients from our centre with donors >60 years and CNI-free treatment were included (n=108). Patients were divided into two groups: (i) SRL group: sirolimus (SRL)+ prednisone+ mycophenolate mofetil (MMF)+antiCD25; (ii) MMF group: prednisone+MMF w/ or w/o antiCD25 (n=75). Follow-up was 12 months.

RESULTS: Donors were slightly younger in the SRL group (68 vs 71 years; P<0.05), receptor age (67 vs 65 years) was not significantly different. Patient survival in the MMF group was 88 vs 94% in the SRL group, however, these differences did not reach statistical significance. One-year graft survival censored for death was 83% in the MMF group and 94% in the SRL group. Acute rejection rate was 45% in the MMF and 15% in the SRL group (P<0.01). The incidence of CNI introduction was higher in the MMF-group (35 vs 5; P<0.05). The intention-to-treat analysis revealed significant differences of proteinuria [SRL vs MMF at 12 months: 461 (163–6988) vs 270 (53–3029) mg/day], which did not exist in the on-therapy (OT) analysis [SRL vs MMF at 12 months: 357 (199–1428) vs 279 (53–3029) mg/day]. New onset nephrotic range proteinuria seemed to occur slightly more frequently in SRL patients (3/33 vs 1/75; P=0.049), however, all four cases occurred in a context of recurrent disease, or previous drug-independent damage or non-adherence. All of these patients were converted to CNI.

CONCLUSION: SRL-based compared with MMF-based treatment in kidney transplantation with advanced age donors is associated with an acceptable outcome, however, with increased proteinuria in the intentiontotreat analysis. A large subgroup of the patients in the MMF group experienced acute rejection and required conversion to CNI.

28. Immunosuppression for Dual Kidney Transplantation with Marginal Organs: The Old Is Better Yet

Cruzado JM, Bestard O, Riera L, et al.
Am J Transplant 2007; 7: 639-644.

ABSTRACT

Immunosuppressive protocols in dual kidney transplantation (DKT) are based on calcinerurin inhibitors (CNI).We wonder whether a CNI-free immunosuppression can improve outcome in older patients receiving a DKT with marginal donor organs. Thirty-six were treated with CsA, MMF and prednisone (CsA group) and 42 with rATG, SRL, MMF and prednisone (SRL group). Incidence of

delayed graft function and acute rejection was 44% and 11% in the CsA group, and 40% and 8% in the SRL group. CMV infection incidence was low in both protocols. Three-year patient survival was 89% in the CsA and 76% in the SRL group. One- and 3-year graft survival after censoring for dead with a functioning allograft was 94.2% and 94% in CsA and 95% and 90% in SRL, respectively. Renal function was similar in both groups whereas proteinuria was higher in the SRL group. Uninephrectomy due to graft thrombosis or urinary-related complications was numerically higher in the SRL (21%) than in the CsA group (8%) (p= 0.13) and it was associated with renal failure and proteinuria. In DKT, a new induction immunosuppressive protocol based on rATG, SRL, MMF and prednisone does not offer any advantage in comparison to the old CsA, MMF and prednisone.

29. Clinical Experience with Everolimus (Certican) in Elderly Recipients: The "Old-for-Old" Concept

Pascual J, Marcén R, Ortuño J.
Transplantation 2005; 79: S85-S88.

ABSTRACT
BACKGROUND: With an increasing number of elderly patients now waiting for a kidney transplant, and the percentage of kidney donors over 55 years also rising, harvesting older kidneys specifically for use in older recipients is a way of extending the donor pool for renal transplantation.
METHODS: Two case studies from an everolimus (Certican) Phase III trial (A2306) are presented. They illustrate clinical experience of achieving stable graft function in the "old-for-old" kidney transplant program at the Ramón y Cajal Hospital in Madrid, Spain.
RESULTS: The first case study demonstrates that stable graft function can be achieved in an "old-for-old" kidney transplant patient, who receives everolimus in combination with reduced-exposure cyclosporine (CsA). To optimize graft function in the long-term, CsA C2 blood levels should be400 ng/ml. The second case study highlights how "old-forold" renal transplant recipients can be at risk of calcineurin-inhibitor (CNI)-induced nephrotoxicity. Here, graft function did not improve following CsA dose reduction; thus, CsA was withdrawn 1 year posttransplant. Stable graft function that is acceptable for an "old-for-old" kidney transplant was then achieved with everolimus trough blood levels of 10–15 ng/ml and low-dose prednisone.
CONCLUSIONS: In these cases, everolimus was used safely and effectively in the "old-for-old" kidney transplant setting. Its combination with reduced-exposure CsA, or its facilitation of CsA withdrawal, minimized the risk of nephrotoxicity in the older renal graft. These findings need to be confirmed in larger studies specific to this population.

Switch to iMTOR standard

30. Early Conversion From Calcineurin Inhibitor- to Everolimus-Based Therapy Following Kidney Transplantation: Results of the Randomized ELEVATE Trial

Fijter JW, Holdaas H, Oyen O, et al.
Am J Transplant. 2017 Jul;17(7):1853-1867.

ABSTRACT
In a 24-month, multicenter, open-label, randomized trial, 715 de novo kidney transplant recipients were randomized at 10–14 weeks to convert to everolimus (n = 359) or remain on standard

calcineurin inhibitor (CNI) therapy (n = 356; 231 tacrolimus; 125 cyclosporine), all with mycophenolic acid and steroids. The primary endpoint, change in estimated glomerular filtration rate (eGFR) from randomization to month 12, was similar for everolimus versus CNI: mean (standard error) 0.3(1.5) mL/min/1.73^2 versus -1.5(1.5) mL/min/ 1.73^2 (p = 0.116). Biopsy-proven acute rejection (BPAR) at month 12 was more frequent under everolimus versus CNI overall (9.7% vs. 4.8%, p = 0.014) and versus tacrolimus-treated patients (2.6%, p < 0.001) but similar to cyclosporine-treated patients (8.8%, p = 0.755). Reporting on de novo donor-specific antibodies (DSA) was limited but suggested more frequent anti-HLA Class I DSA under everolimus. Change in left ventricular mass index was similar. Discontinuation due to adverse events was more frequent with everolimus (23.6%) versus CNI (8.4%). In conclusion, conversion to everolimus at 10–14 weeks posttransplant was associated with renal function similar to that with standard therapy overall. Rates of BPAR were low in all groups, but lower with tacrolimus than everolimus.

3. MANTENIMIENTO VS. RETIRADA DE ESTEROIDES

31. Outcomes of Late Corticosteroid Withdrawal after Renal Transplantation in Patients Exposed to Tacrolimus and/or Mycophenolate Mofetil: Meta-Analysis of Randomized Controlled Trials

Ali AK, Guo J, Ahn H et al.
Int J Organ Transplant Med. 2011;2(4):149-59.

ABSTRACT

BACKGROUND: Corticosteroids are increasingly used in renal transplant patients to minimize organ rejection after transplantation. In attempts to reduce corticosteroids adverse effects, transplant professionals are customary attempted to taper off, and permanently stop corticosteroids after few months of administration with other immunosuppressants.
OBJECTIVE: To evaluate clinical benefits and risks of late corticosteroid withdrawal in renal transplant patients treated with tacrolimus (TAC) or mycophenolate mofetil (MMF), or both.
METHODS: A meta-analysis was performed of published randomized controlled trials that reported outcomes in kidney transplant patients who were randomized to corticosteroids maintenance or late withdrawal under concomitant immunosuppression by TAC, MMF or both. Outcomes included acute graft rejection; graft failure rate; all-cause mortality; incidence of post-transplant diabetes; change in serum creatinine and total cholesterol; and change in pediatric standardized height z-score. PubMed and Google Scholar were used in literature search between 1999 and April 1, 2010. Data were combined using unweighted random effects model.
RESULTS: Nine studies randomized 1907 patients met the inclusion criteria: TAC (n=1); MMF (n=6); both (n=2). Compared to maintenance therapy, late corticosteroid withdrawal was associated with 34% increase in the risk of acute graft rejection (95% CI for OR: 0.47–3.82); 35% and 5% reductions in the risk of graft failure and patient's all-cause mortality (95% CI for OR: 0.26–1.60; 0.23–3.93, respectively); and 4% increase in post-transplant diabetes risk (95% CI for OR: 0.45–2.41). Late corticosteroid withdrawal was associated with substantial reduction in total cholesterol levels (mean difference: 18.1 mg/dL; 95% CI: 7.1–29.0 mg/dL), but did not reduce serum creatinine levels (-0.00 mg/dL; 95% CI: -0.17 to 0.17). Stopping corticosteroids was associated with better pediatric growth outcomes.
CONCLUSION: Late corticosteroid withdrawal under TAC and/or MMF-lead immunosuppression after kidney transplantation could provide benefits in terms of total cholesterol, patient and graft survival, and pediatric growth. This strategy, however did not reduce the risk of acute graft rejection, post-transplant diabetes mellitus, and deterioration in serum creatinine levels.

32. Post-Renal Transplantation Outcomes in Elderly Patients Compared to Younger Patients in the Setting of Early Steroid Withdrawal

Alsheikh R, Gabardi S
Prog Transplant. 2018 Dec;28(4):322-329

ABSTRACT
BACKGROUND: Previous studies reported improved outcomes for renal recipients undergoing early steroid withdrawal (ESW), with significantly lower rates of new-onset diabetes, cytomegalovirus (CMV), and malignancy. As renal transplants in older adults has increased, studies have shown similar outcomes between elderly and younger patients. We aim to evaluate post-

renal transplantation outcomes in elderly patients compared to yo unger patients who have undergone ESW.
METHODS: A retrospective analysis of adults who received transplants between January 2004 and December 2014 and received either basiliximab or antithymocyte globulin for induction, underwent ESW, and received tacrolimus and mycophenolate for maintenance. Patients were stratified based on age (≥60 vs <60). The 1-year primary end point was a composite of patient survival, graft survival, biopsy-proven acute rejection, and serum creatinine. The secondary outcomes included renal function, the incidence of opportunistic infections, malignancies, diabetes, and cardiovascular complications. Cox regression was used to evaluate variables that may affect rejection.
RESULTS: The sample included 292 patients; 72 were elderly individuals and 220 were younger adults. No significant differences were found in the primary end point or incidence of CMV, BK virus, or malignancy (P = 1.0, .82, and .06, respectively). The use of blood pressure medications and the need for lipid-lowering agents were significantly higher in elderly patients at last follow-up. Diabetes was more common in elderly patients (15.2% vs 8.41%, P = .11). The induction agent used did not show any significant effect on rejection risk.
CONCLUSION: We report similar outcomes in elderly patients compared to younger patients in the setting of ESW.

33. No Occurrence of De Novo HLA Antibodies in Patients With Early Corticosteroid Withdrawal in a 5-year Prospective Randomized Study
Delgado JC, Fuller A, Ozawa M et al.
Transplantation 2009;87: 546–548

ABSTRACT
The purpose of this study was to determine the effect of early corticosteroid cessation on the occurrence of de novo human leukocyte antigen (HLA) antibody posttransplant. Renal transplant recipients (n=37) were randomized to early corticosteroid withdrawal at day 7 posttransplant (n=21 patients), or to chronic steroids (n=16), all in combination with thymoglobulin as induction agent, tacrolimus and mycophenolic acid as maintenance therapy. To establish the time course of HLA antibody appearance, sera collected pretransplant and for up to 5 years posttransplant were screened for the appearance of HLA antibodies. In this 5-year longitudinal study, only one patient in the control group developed a de novo donor-specific HLA antibody. We conclude that renal transplant recipients on steroid withdrawal by the end of week 1 are not at higher risk for developing HLA antibodies compared with a standard steroid regimen up to 5 years posttransplant.

34. Glucocorticoids use in kidney transplant setting
De Lucena DD, Rangel ÉB .
Expert Opin Drug Metab Toxicol. 2018 Oct;14(10):1023-1041

ABSTRACT
INTRODUCTION: Despite major advances in kidney transplant, glucocorticoids (GCs) or steroids remain one of the mainstay treatments. They possess adverse events (AEs) that are related to cumulative dosage, as documented in experimental and clinical studies. Therefore, it is important

to comprehend and interpret experimental data and equally important to critically review clinical studies.
AREAS COVERED: This article provides a broad overview of the structure, pharmacokinetics, and pharmacodynamics of systemically administered GCs in transplant setting. It further discusses at length the results of in vitro and pre-clinical studies, as well as steroid avoidance (SA) or withdrawal (SW)-based clinical studies. We summarized the main AEs and discussed the alternatives to minimize these events. Some clinically relevant drug-drug interactions are also highlighted.
EXPERT OPINION: Although SA/SW in kidney transplant is a desirable strategy due to its AEs, there is no evidence to support that strategy based on the available data, despite some encouraging reports. Furthermore, early diagnosis and treatment of GC-induced AEs seem to be the most efficacious strategies. Likewise, some risks factors predate transplant and could be used to risk-stratify patients to determine appropriate risk-reduction strategies. Additional randomized-controlled studies are required to assess the impact of SA/SW during short and long follow-ups.

35. Steroid avoidance or withdrawal for kidney transplant recipients

Haller MC, Royuela A, Nagler EV et al.
Cochrane Database Syst Rev. 2016 Aug 22;(8):CD005632.

ABSTRACT
BACKGROUND: Steroid-sparing strategies have been attempted in recent decades to avoid morbidity from long-term steroid intake among kidney transplant recipients. Previous systematic reviews of steroid withdrawal after kidney transplantation have shown a significant increase in acute rejection. There are various protocols to withdraw steroids after kidney transplantation and their possible benefits or harms are subject to systematic review. This is an update of a review first published in 2009.
OBJECTIVES: To evaluate the benefits and harms of steroid withdrawal or avoidance for kidney transplant recipients.
SEARCH METHODS: We searched the Cochrane Kidney and Transplant Specialised Register to 15 February 2016 through contact with the Information Specialist using search terms relevant to this review.
SELECTION CRITERIA: All randomised and quasi-randomised controlled trials (RCTs) in which steroids were avoided or withdrawn at any time point after kidney transplantation were included.
DATA COLLECTION AND ANALYSIS: Assessment of risk of bias and data extraction was performed by two authors independently and disagreement resolved by discussion. Statistical analyses were performed using the random-effects model and dichotomous outcomes were reported as relative risk (RR) and continuous outcomes as mean difference (MD) with 95% confidence intervals.
MAIN RESULTS: We included 48 studies (224 reports) that involved 7803 randomised participants. Of these, three studies were conducted in children (346 participants). The 2009 review included 30 studies (94 reports, 5949 participants). Risk of bias was assessed as low for sequence generation in 19 studies and allocation concealment in 14 studies. Incomplete outcome data were adequately addressed in 22 studies and 37 were free of selective reporting. The 48 included studies evaluated three different comparisons: steroid avoidance or withdrawal compared with steroid maintenance, and steroid avoidance compared with steroid withdrawal. For the adult studies there was no significant difference in patient mortality either in studies comparing steroid withdrawal versus steroid maintenance (10 studies, 1913 participants, death at one year post

transplantation: RR 0.68, 95% CI 0.36 to 1.30) or in studies comparing steroid avoidance versus steroid maintenance (10 studies, 1462 participants, death at one year after transplantation: RR 0.96, 95% CI 0.52 to 1.80). Similarly no significant difference in graft loss was found comparing steroid withdrawal versus steroid maintenance (8 studies, 1817 participants, graft loss excluding death with functioning graft at one year after transplantation: RR 1.17, 95% CI 0.72 to 1.92) and comparing steroid avoidance versus steroid maintenance (7 studies, 1211 participants, graft loss excluding death with functioning graft at one year after transplantation: RR 1.09, 95% CI 0.64 to 1.86). The risk of acute rejection significantly increased in patients treated with steroids for less than 14 days after transplantation (7 studies, 835 participants: RR 1.58, 95% CI 1.08 to 2.30) and in patients who were withdrawn from steroids at a later time point after transplantation (10 studies, 1913 participants, RR 1.77, 95% CI 1.20 to 2.61). There was no evidence to suggest a difference in harmful events, such as infection and malignancy, in adult kidney transplant recipients. The effect of steroid withdrawal in children is unclear.
AUTHORS' CONCLUSIONS: This updated review increases the evidence that steroid avoidance and withdrawal after kidney transplantation significantly increase the risk of acute rejection. There was no evidence to suggest a difference in patient mortality or graft loss up to five year after transplantation, but long-term consequences of steroid avoidance and withdrawal remain unclear until today, because prospective long-term studies have not been conducted.

36. Steroid Avoidance or Withdrawal After Renal Transplantation Increases the Risk of Acute Rejection but Decreases Cardiovascular Risk. A Meta-Analysis
Knight SR1, Morris PJ.
Transplantation. 2010 Jan 15;89(1):1-14.

ABSTRACT
INTRODUCTION: The morbidity related to long-term steroid therapy has led to continued interest in withdrawal of steroids from immunosuppressant regimens after renal transplantation. A number of recent trials have provided long-term information regarding the risks and benefits of steroid avoidance or withdrawal (SAW).
METHODS: A literature search was performed using Ovid Medline, Embase, the Cochrane Library, and the Transplant Library. Randomized controlled trials comparing a maintenance steroid group with complete avoidance or withdrawal of steroids were selected. All studies were assessed for methodological quality. Trials were pooled by meta-analysis to provide summary effects (relative risk [RR] or weighted mean difference) with 95% confidence intervals (CI).
RESULTS: Thirty-four studies including 5,637 patients met the inclusion criteria. SAW regimens significantly increased the risk of acute rejection (AR) over maintenance steroids (RR 1.56, CI 1.31-1.87, P<0.0001). No significant differences in corticosteroid resistant AR, patient survival, or graft survival were observed. Serum creatinine was increased and creatinine clearance was reduced with SAW. Cardiovascular risk factors including incidence of hypertension (RR 0.90, CI 0.85-0.94, P<0.0001), new onset diabetes (RR 0.64, CI 0.50-0.83, P=0.0006), and hypercholesterolemia (RR 0.76, CI 0.67-0.87, P<0.0001) were reduced significantly by SAW.
CONCLUSION: Despite an increase in the risk of AR with SAW protocols, there is only a small effect on graft function with no measurable effect on graft or patient survival. There are significant benefits in cardiovascular risk profiles after SAW. SAW protocols would seem justified with current immunosuppressive protocols in low-risk recipients.

37. Early steroid withdrawal results in improved patient and graft survival and lower risk of post-transplant cardiovascular risk profiles: A single-center 10-year experience

Lopez-Soler RI, Chan R, Martinolich J et al.

Clinical Transplantation 2017;31:e12878.

ABSTRACT

Long-term use of steroids results in predictable secondary effects that can lead to increased morbidity and mortality. In this study, we present 10 years worth of data of early steroid withdrawal (ESW) immunosuppression consisting of mycophenolate, sirolimus, and tacrolimus. From 2003 to 2013, 563 kidney transplant recipients were weaned off steroids prior to discharge. We compared outcomes with that of our 65 historical controls maintained on steroids. We analyzed graft and patient survival and determined the incidence of steroid-related comorbidities such as hypertension, hypercholesterolemia, diabetes, coronary artery disease, and weight gain. Patients on ESW maintenance immunosuppression had improved patient and graft survival compared to controls. (HR: 0.23; P≤.011, 0.57; P=.026). Rates of biopsy-proven acute rejection were not different among both groups (HR: 1.24; P=.610). Incidence of post-transplant diabetes were reduced but not statistically significant (OR: 0.67; P=.138).

Additionally, the development of hypertension (OR: 0.86, P≤.01), hypercholesterolemia (RR: 0.82; P=.027), CAD (RR: 0.43; P=.002), and >20 lbs. weight gain (RR: 0.29; P≤.01) was significantly improved over 10 years following initiation of ESW protocols. Early steroid withdrawal in renal transplant recipients results in improved patient and graft survival as well as better rates of post-transplant comorbid conditions.

38. Short-term adverse effects of early subclinical allograft inflammation in kidney transplant recipients with a rapid steroid withdrawal protocol

Mehta R, Bhusal S, Randhawa et al.

Am J Transplant. 2018;18:1710–1717.

ABSTRACT

The impact of subclinical inflammation (SCI) noted on early kidney allograft biopsies remains unclear. This study evaluated the outcome of SCI noted on 3-month biopsy. A total of 273/363 (75%) kidney transplant recipients with a functioning kidney underwent allograft biopsies 3-months posttransplant. Among those with stable allograft function at 3 months, 200 biopsies that did not meet the Banff criteria for acute rejection were identified. These were Group I: No Inflammation (NI, n = 71) and Group II: Subclinical Inflammation (SCI, n = 129). We evaluated differences in kidney function at 24-months and allograft histology score at 12-month biopsy. SCI patients had a higher serum creatinine (1.6 ± 0.7 vs 1.38 ± 0.45; P = .02) at 24-months posttransplant, and at last follow-up at a mean of 42.5 months (1.69 ± 0.9 vs 1.46 ± 0.5 mg/dL; P = .027). The allograft chronicity score (ci + ct + cg + cv) at 12-months posttransplant was higher in the SCI group (2.4 ± 1.35 vs 1.9 ± 1.2; P = .02). The incidence of subsequent rejections within the first year in SCI and NI groups was 24% vs 10%, respectively (P = .015). De novo donor-specific antibody within 12 months was more prevalent in the SCI group (12/129 vs 1/71, P = .03). SCI is likely not a benign finding and may have long-term implications for kidney allograft function.

39. Association Between Steroid Dosage and Death With a Functioning Graft After Kidney Transplantation

Opelz G, Döhler B.

American Journal of Transplantation 2013; 13: 2096–2105

ABSTRACT

Death with a functioning graft remains a major challenge following kidney transplantation. Steroid dosing may be a modifiable risk factor. Collaborative Transplant Study (CTS) data were analyzed to assess the relationship between long-term steroid dose and deathwith function during years 2–5 posttransplant in 41 953 adult recipients of a deceased-donor kidney transplant during 1995–2010. Steroid dose at year 1 correlated significantly with death with function overall, and with death due to cardiovascular disease or infection (all $p < 0.001$). In patients with optimal graft function (serum creatinine <130 mmol/L) and no anti-rejection treatment during (a) year 1 (b) years 1 and 2, these significant associations remained (all $p < 0.001$). The center-specific incidence of steroid withdrawal during year 2 showed a significant inverse association with death due to cardiovascular disease ($p < 0.001$) or infection ($p < 0.001$) overall, and within the subpopulation with good graft function and no rejection during year 1 ($p = 0.002$ and $p < 0.001$, respectively). Maintenance steroid dose shows a highly significant association with death with a functioning graft caused by cardiovascular disease or infection during years 2–5 after kidney transplantation, even in patients with good graft outcomes in whom steroid treatment would appear to be unnecessary.

40. A Systematic Review on Steroid Withdrawal Between 3 and 6 Months After Kidney Transplantation

Pascual J, Galeano C, Royuela A et al.

Transplantation 2010;90: 343–349

ABSTRACT

BACKGROUND. Steroid withdrawal (SW) after the first posttransplant months in patients receiving a kidney transplant has been recently discouraged in clinical guidelines.

METHODS. Asystematic review and meta-analysis of randomized controlled trials assessing SW(beyond the second week after kidney transplantation) was performed. Only trials using a calcineurin inhibitor plus mycophenolic acid were included.

RESULTS. The nine trials (1820 participants) randomly withdrew steroids between 3 and 6 months after transplantation.

Death and graft loss were similar in SW and control patients. Including all trials, acute rejection was not more frequent after SW, but stratifying by the drug used, cyclosporine A (CsA) was associated with an increased incidence of overall acute rejection (risk ratio 1.42, 95% confidence interval 1.08 –1.87) or biopsy-proven acute rejection (risk ratio 1.61 95% confidence interval 1.20 –2.17). Contrarily, tacrolimus allowed SW without increased biopsy-proven acute rejection (P interaction=0.005). Serum cholesterol level was lower after SW than in controls using CsA or tacrolimus. Serum creatinine, blood pressure, serum triglycerides, new-onset diabetes mellitus, infections, or malignancies were similar in SW and control patients.

CONCLUSIONS. SW after 3 to 6 months of kidney transplantation is associated with increased rates of acute rejection only if CsA is used but not with tacrolimus. Graft function and survival

remain stable up to 3 years after transplantation, the longest follow-up reported. The interest for late SW has decreased during the past years in the literature. More trials with carefully designed outcome measures are needed in patients treated with low-exposure tacrolimus and mycophenolic acid derivatives.

41. Very early steroid withdrawal or complete avoidance for kidney transplant recipients: a systematic review

Pascual J, Royuela A, Galeano C et al.
Nephrol Dial Transplant (2012) 27: 825–832

ABSTRACT
BACKGROUND: The safety and efficacy of early steroid withdrawal or avoidance in patients receiving a kidney transplant (KT) are controversial.
METHODS: We performed a systematic review and a metaanalysis of the randomized controlled studies about steroid avoidance or withdrawal after a few days in patients receiving a KT and treated with antibody induction and cyclosporine (CsA) or tacrolimus (Tac) plus mycophenolate mofetil (MMF) (nine available studies and 1934 participants).
RESULTS: Death and graft loss (including or excluding death with function) were similar in steroid avoidance and control patients, with no differences between CsA and Tac studies. After steroid avoidance, acute rejection was more frequent than conventional steroid use in CsA trials [risk ratios (RR) 1.59, 95% confidence intervals (95% CI) 1.01–2.49] but not when Tac was used (RR 1.06, 95% CI 0.79–1.42). Steroid avoidance was associated with less frequent new-onset diabetes mellitus, but this decrease was only evident with CsA (RR 0.54, 95% CI 0.30–0.98), whereas this difference was not significant analysing Tac studies (RR 0.75, 95% CI 0.32–1.77). Despite this trend, the corresponding interaction tests were not statistically significant (P = 0.140 and P = 0.535, for acute rejection and new-onset diabetes mellitus, respectively). Serum creatinine, creatinine clearance, mean blood pressure, serum cholesterol and serum triglycerides were similar in both groups.
CONCLUSIONS: Steroid avoidance or early withdrawal within the first 2 weeks is safe in KT recipients receiving induction with anti-interleukin-2 receptor antibodies or thymoglobulin and a drug regimen based on calcineurin inhibitor and MMF. However, the real benefits remain unclear.

42. Early Steroid Withdrawal Compared With Standard Immunosuppression in Kidney Transplantation - Interim Analysis of the Amsterdam-Leiden-Groningen Randomized Controlled Trial

van Sandwijk MS, de Vries APJ, Bakker SJL et al.
Transplant Direct. 2018 May 15;4(6):e354.

ABSTRACT
BACKGROUND: The optimal immunosuppressive regimen in kidney transplant recipients, delivering maximum efficacy with minimal toxicity, is unknown.
METHODS: The Amsterdam, LEiden, GROningen trial is a randomized, multicenter, investigator-driven, noninferiority, open-label trial in 305 kidney transplant recipients, in which 2 immunosuppression minimization strategies-one consisting of early steroid withdrawal, the other of tacrolimus minimization 6 months after transplantation-were compared with standard

immunosuppression with basiliximab, corticosteroids, tacrolimus, and mycophenolic acid. The primary endpoint was kidney function. Secondary endpoints included death, primary nonfunction, graft failure, rejection, discontinuation of study medication, and a combined endpoint of treatment failure. An interim analysis was scheduled at 6 months, that is, just before tacrolimus minimization.

RESULTS: This interim analysis revealed no significant differences in Modification of Diet in Renal Disease between the early steroid withdrawal group and the standard immunosuppression groups (43.2 mL/min per 1.73 m^2 vs 45.0 mL/min per 1.73 m^2, $P = 0.408$). There were also no significant differences in the secondary endpoints of death (1.0% vs 1.5%; $P = 0.737$), primary nonfunction (4.1% vs 1.5%, $P = 0.159$), graft failure (3.1% vs 1.5%, $P = 0.370$), rejection (18.6% vs 13.6%, $P = 0.289$), and discontinuation of study medication (19.6% vs 12.6%, $P = 0.348$). Treatment failure, defined as a composite endpoint of these individual secondary endpoints, was more common in the early steroid withdrawal group ($P = 0.027$), but this group had fewer serious adverse events and a more favorable cardiovascular risk profile.

CONCLUSIONS: Based on these interim results, early steroid withdrawal is a safe short-term immunosuppressive strategy. Long-term outcomes, including a comparison with tacrolimus minimization after 6 months, will be reported in the final 2-year analysis.

4. BELATACEPT

43. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study)

Durrbach A, Pestana JM, Pearson T et al.
Am J Transplant. 2010 Mar;10(3):547-57.

ABSTRACT
Recipients of extended criteria donor (ECD) kidneys are at increased risk for graft dysfunction/loss, and may benefit from immunosuppression that avoids calcineurin inhibitor (CNI) nephrotoxicity. Belatacept, a selective costimulation blocker, may preserve renal function and improve long-term outcomes versus CNIs. BENEFIT-EXT (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial-EXTended criteria donors) is a 3-year, Phase III study that assessed a more (MI) or less intensive (LI) regimen of belatacept versus cyclosporine in adult ECD kidney transplant recipients. The co-primary endpoints at 12 months were composite patient/graft survival and a composite renal impairment endpoint. Patient/graft survival with belatacept was similar to cyclosporine (86% MI, 89% LI, 85% cyclosporine) at 12 months. Fewer belatacept patients reached the composite renal impairment endpoint versus cyclosporine (71% MI, 77% LI, 85% cyclosporine; p = 0.002 MI vs. cyclosporine; p = 0.06 LI vs. cyclosporine). The mean measured glomerular filtration rate was 4-7 mL/min higher on belatacept versus cyclosporine (p = 0.008 MI vs. cyclosporine; p = 0.1039 LI vs. cyclosporine), and the overall cardiovascular/metabolic profile was better on belatacept versus cyclosporine. The incidence of acute rejection was similar across groups (18% MI; 18% LI; 14% cyclosporine). Overall rates of infection and malignancy were similar between groups; however, more cases of posttransplant lymphoproliferative disorder (PTLD) occurred in the CNS on belatacept. ECD kidney transplant recipients treated with belatacept-based immunosuppression achieved similar patient/graft survival, better renal function, had an increased incidence of PTLD, and exhibited improvement in the cardiovascular/metabolic risk profile versus cyclosporine-treated patients.

44. Three-year outcomes from BENEFIT-EXT: a phase III study of belatacept versus cyclosporine in recipients of extended criteria donor kidneys

Pestana JO, Grinyo JM, Vanrenterghem Y et al.
Am J Transplant. 2012 Mar;12(3):630-9.

ABSTRACT
Recipients of extended-criteria donor (ECD) kidneys have poorer long-term outcomes compared to standard-criteria donor kidney recipients. We report 3-year outcomes from a randomized, phase III study in recipients of de novo ECD kidneys (n = 543) assigned (1:1:1) to either a more intensive (MI) or less intensive (LI) belatacept regimen, or cyclosporine. Three hundred twenty-three patients completed treatment by year 3. Patient survival with a functioning graft was comparable between groups (80% in MI, 82% in LI, 80% in cyclosporine). Mean calculated GFR (cGFR) was 11 mL/min higher in belatacept-treated versus cyclosporine-treated patients (42.7 in MI, 42.2 in LI, 31.5 mL/min in cyclosporine). More cyclosporine-treated patients (44%) progressed to GFR <30 mL/min (chronic kidney disease [CKD] stage 4/5) than belatacept-treated patients (27-30%). Acute rejection rates were similar between groups. Posttransplant lymphoproliferative disorder (PTLD) occurrence was higher in belatacept-treated patients (two in MI, three in LI), most of which

occurred during the first 18 months; four additional cases (3 in LI, 1 in cyclosporine) occurred after 3 years. Tuberculosis was reported in two MI, four LI and no cyclosporine patients. In conclusion, at 3 years after transplantation, immunosuppression with belatacept resulted in similar patient survival, graft survival and acute rejection, with better renal function compared with cyclosporine. As previously reported, PTLD and tuberculosis were the principal safety findings associated with belatacept in this study population.

45. Long-term exposure to belatacept in recipients of extended criteria donor kidneys
Charpentier B, Medina Pestana JO, Del C Rial M, et al.
Am J Transplant2013;13:2884-2891.

ABSTRACT
Patients in the BENEFIT-EXT study received extended criteria donor kidneys and a more intensive (MI) or less intensive (LI) belatacept immunosuppression regimen, or cyclosporine A (CsA). Patients who remained on assigned therapy through year 3 were eligible to enter a long-term extension (LTE) study. Three hundred four patients entered the LTE (n = 104 MI; n = 113 LI; n = 87 CsA), and 260 continued treatment through year 5 (n = 91 MI; n = 100 LI; n = 69 CsA). Twenty patients died during the LTE (n = 5 MI; n = 9 LI; n = 6 CsA), and eight experienced graft loss (n = 2 MI; n = 1 LI; n = 5 CsA). Three patients experienced an acute rejection episode (n = 2 MI; n = 1 LI). The incidence rate of serious adverse events, viral infections and fungal infections was similar across groups during the LTE. There were four cases of posttransplant lymphoproliferative disorder (PTLD) from the beginning of the LTE to year 5 (n = 3 LI; n = 1 CsA); two of three PTLD cases in the LI group were in patients who were seronegative for Epstein-Barr virus (EBV(-)) at transplantation. Mean ± SD calculated GFR at year 5 was 55.9 ± 17.5 (MI), 59.0 ± 29.1 (LI) and 44.6 ± 16.4 (CsA) mL/min/1.73 m(2) . Continued treatment with belatacept was associated with a consistent safety profile and sustained improvement in renal function versus CsA over time.

46. Long-Term Outcomes in Belatacept- Versus Cyclosporine-Treated Recipients of Extended Criteria Donor Kidneys: Final Results From BENEFIT-EXT, a Phase III Randomized Study
Durrbach A, Pestana JM, Florman S, et al.
Am J Transplant. 2016 Nov;16(11):3192-3201.

ABSTRACT
In the Belatacept Evaluation of Nephroprotection and Efficacy as First-Line Immunosuppression Trial-Extended Criteria Donors (BENEFIT-EXT), extended criteria donor kidney recipients were randomized to receive belatacept-based (more intense [MI] or less intense [LI]) or cyclosporine-based immunosuppression. In prior analyses, belatacept was associated with significantly better renal function compared with cyclosporine. In this prospective analysis of the intent-to-treat population, efficacy and safety were compared across regimens at 7 years after transplant. Overall, 128 of 184 belatacept MI-treated, 138 of 175 belatacept LI-treated and 108 of 184 cyclosporine-treated patients contributed data to these analyses. Hazard ratios (HRs) comparing time to death or graft loss were 0.915 (95% confidence interval [CI] 0.625-1.339; p = 0.65) for belatacept MI versus cyclosporine and 0.927 (95% CI 0.634-1.356; p = 0.70) for belatacept LI versus cyclosporine. Mean estimated GFR (eGFR) plus or minus standard error at 7 years was 53.9 ± 1.9, 54.2 ± 1.9, and 35.3 ± 2.0 mL/min per 1.73 m2 for belatacept MI, belatacept LI and

cyclosporine, respectively (p < 0.001 for overall treatment effect). HRs comparing freedom from death, graft loss or eGFR <20 mL/min per 1.73 m2 were 0.754 (95% CI 0.536-1.061; p = 0.10) for belatacept MI versus cyclosporine and 0.706 (95% CI 0.499-0.998; p = 0.05) for belatacept LI versus cyclosporine. Acute rejection rates and safety profiles of belatacept- and cyclosporine-based treatment were similar. De novo donor-specific antibody incidence was lower for belatacept (p ≤ 0.0001). Relative to cyclosporine, belatacept was associated with similar death and graft loss and improved renal function at 7 years after transplant and had a safety profile consistent with previous reports.

47. Belatacept and Long-Term Outcomes in Kidney Transplantation

Vincenti F, Rostaing L, Grinyo J, et al.
N Engl J Med. 2016 Jan 28;374(4):333-43.

ABSTRACT

BACKGROUND: In previous analyses of BENEFIT, a phase 3 study, belatacept-based immunosuppression, as compared with cyclosporine-based immunosuppression, was associated with similar patient and graft survival and significantly improved renal function in kidney-transplant recipients. Here we present the final results from this study.

METHODS: We randomly assigned kidney-transplant recipients to a more-intensive belatacept regimen, a less-intensive belatacept regimen, or a cyclosporine regimen. Efficacy and safety outcomes for all patients who underwent randomization and transplantation were analyzed at year 7 (month 84).

RESULTS: A total of 666 participants were randomly assigned to a study group and underwent transplantation. Of the 660 patients who were treated, 153 of the 219 patients treated with the more-intensive belatacept regimen, 163 of the 226 treated with the less-intensive belatacept regimen, and 131 of the 215 treated with the cyclosporine regimen were followed for the full 84-month period; all available data were used in the analysis. A 43% reduction in the risk of death or graft loss was observed for both the more-intensive and the less-intensive belatacept regimens as compared with the cyclosporine regimen (hazard ratio with the more-intensive regimen, 0.57; 95% confidence interval [CI], 0.35 to 0.95; P=0.02; hazard ratio with the less-intensive regimen, 0.57; 95% CI, 0.35 to 0.94; P=0.02), with equal contributions from the lower rates of death and graft loss. The mean estimated glomerular filtration rate (eGFR) increased over the 7-year period with both belatacept regimens but declined with the cyclosporine regimen. The cumulative frequencies of serious adverse events at month 84 were similar across treatment groups.

CONCLUSIONS: Seven years after transplantation, patient and graft survival and the mean eGFR were significantly higher with belatacept (both the more-intensive regimen and the less-intensive regimen) than with cyclosporine. (Funded by Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00256750.).

48. Effect of an early switch to belatacept among CNI-intolerant graft recipients of kidneys from extended criteria donors.

Le Meur Y, Aulagnon F, Bertrand D, et al.
Am J Transplant. 2016 Jul;16(7):2181-6.

ABSTRACT

Transplant recipients receiving a kidney from an extended-criteria donor (ECD) are exposed to calcineurin inhibitor (CNI) nephrotoxicity, as demonstrated by severe delayed graft function and/or a low GFR. Belatacept is a nonnephrotoxic drug that is indicated as an alternative to CNIs. We reported 25 cases of conversion from a CNI to belatacept due to CNI intolerance within the first 6 mo after transplantation. The mean age of the recipients was 59 years, and 24 of 25 patients received ECD kidneys. At the date of the medication switch, 12 of 25 patients displayed a calculated GFR (cGFR) <15 mL/min, six patients remained on dialysis, and the biopsies showed evidence of acute tubular damage associated with severe vascular or tubulointerstitial chronic lesions. Three patients did not recover renal function, and three patients died during the follow-up period. Among the remaining patients, renal function improved: The cGFR was 18.28 ± 12.3 mL/min before the medication switch compared with 34.9 ± 14.5 mL/min at 1 year after conversion to belatacept (p = 0.002). Tolerance of and compliance with belatacept were good, and only one patient experienced acute rejection. Belatacept is an effective therapy that preserves renal function in kidney transplant patients who are intolerant of CNIs.

49. Early post-transplant conversion from tacrolimus to belatacept for prolonged delayed graft function improves renal function in kidney transplant recipients

Wojciechowski D, Chandran S, Vincenti F.

Clin Transplant. 2017 May;31(5).

ABSTRACT

Prolonged delayed graft function (DGF) in kidney transplant recipients imparts a risk of poor allograft function; tacrolimus may be detrimental in this setting. We conducted a retrospective single center analysis of the first 20 patients converted to belatacept for prolonged DGF as part of a clinical protocol as a novel treatment strategy to treat prolonged DGF. Prior to conversion, patients underwent an allograft biopsy to rule out rejection and confirm tubular injury. The primary outcome was the estimated glomerular filtration rate (eGFR) at 12 months post-transplant; secondary outcome was the change in eGFR 30 days post-belatacept conversion. At 1 year post-transplant, the mean eGFR was 54.2 (SD 19.2) mL/min/1.73 m2 . The mean eGFR on the day of belatacept conversion was 16 (SD 12.7) mL/min/1.73 m2 and rose to 43.1 (SD 15.8) mL/min/1.73 m2 30 days post-conversion (P<.0001). The acute rejection rate was 20% with 100% patient survival at 12 months post-transplant. There was one graft loss in the setting of an invasive Aspergillus infection that resulted in withdrawal of immunosuppression and transplant nephrectomy. Belatacept conversion for prolonged DGF is a novel treatment strategy that resulted in an improvement in eGFR. Additional follow-up is warranted to confirm the long-term benefits of this strategy.

50. Belatacept rescue for delayed kidney allograft function in a patient with previous combined heart-liver transplant

Kumar D, Yakubu I, Cooke RH et al.

Am J Transplant. 2018 Oct;18(10):2613-2614.

Abstract not available

51. Safe conversion from tacrolimus to belatacept in high immunologic risk kidney transplant recipients with allograft dysfunction

Gupta G, Regmi A, Kumar D et al.

Am J Transplant. 2015 Oct;15(10):2726-31.

ABSTRACT

There is no literature on the use of belatacept for sensitized patients or regrafts in kidney transplantation. We present our initial experience in high immunologic risk kidney transplant recipients who were converted from tacrolimus to belatacept for presumed acute calcineurin inhibitor (CNI) toxicity and/or interstitial fibrosis/tubular atrophy. Six (mean age = 40 years) patients were switched from tacrolimus to belatacept at a median of 4 months posttransplant. Renal function improved significantly from a peak mean estimated glomerular filtration rate (eGFR) of 23.8 ± 12.9 mL/min/1.73 m(2) prior to the switch to an eGFR of 42 ± 12.5 mL/min/1.73 m(2) (p = 0.03) at a mean follow-up of 16.5 months postconversion. No new rejection episodes were diagnosed despite a prior history of rejection in 2/6 (33%) patients. Surveillance biopsies performed in 5/6 patients did not show subclinical rejection. No development of donor-specific antibodies (DSA) was noted. In this preliminary investigation, we report improved kidney function without a concurrent increase in risk of rejection and DSA in six sensitized patients converted from tacrolimus to belatacept. Improvement in renal function was noted even in patients with chronic allograft fibrosis without evidence of acute CNI toxicity. Further studies with protocol biopsies are needed to ensure safety and wider applicability of this approach.

52. Experience with belatacept rescue therapy in kidney transplant recipients

Brakemeier S, Kannenkeril D, Dürr M et al.

Transpl Int. 2016 Nov;29(11):1184-1195.

ABSTRACT

In kidney transplant recipients with chronic graft dysfunction, long-term immunosuppression with calcineurin inhibitors (CNIs) or mTOR inhibitors (mTORi) can be challenging due to adverse effects, such as nephrotoxicity and proteinuria. Seventy-nine kidney transplant recipients treated with CNI-based or mTORi-based maintenance immunosuppression who had CNI-induced nephrotoxicity or severe adverse events were switched to belatacept. Mean time from transplantation to belatacept conversion was 69.0 months. Mean estimated glomerular filtration rate (eGFR) ± standard deviation at baseline was 26.1 ± 15.0 ml/min/1.73 m2 , increasing to 34.0 ± 15.2 ml/min/1.73 m2 at 12 months postconversion (P < 0.0005). Renal function improvements were also seen in patients with low eGFR (<25 ml/min/1.73 m2) or high proteinuria (>500 mg/l) at conversion. The Kaplan-Meier estimates for patient and graft survival at 12 months were 95.0% and 85.6%, respectively. The discontinuation rate due to adverse events was 7.9%. One case of post-transplant lymphoproliferative disorder occurred at 17 months postconversion. For comparison, a historical control group of 41 patients converted to mTORi-based immunosuppression because of biopsy-confirmed CNI-induced toxicity was examined; eGFR increased from 27.6 ± 7.2 ml/min/1.73 m2 at baseline to 31.1 ± 11.9 ml/min/1.73 m2 at 12 months (P = 0.018). Belatacept-based immunosuppression may be an alternative regimen for kidney transplant recipients with CNI- or mTORi-induced toxicity.

53. Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study

Rostaing L, Massari P, Garcia VD et al.

Clin J Am Soc Nephrol. 2011 Feb;6(2):430-9.

ABSTRACT

BACKGROUND AND OBJECTIVES: Prolonged use of calcineurin inhibitors (CNIs) in kidney transplant recipients is associated with renal and nonrenal toxicity and an increase in cardiovascular risk factors. Belatacept-based regimens may provide a treatment option for patients who switch from CNI-based maintenance immunosuppression.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: This is a randomized, open-label Phase II trial in renal transplant patients with stable graft function and receiving a CNI-based regimen. Patients who were ≥6 months but ≤36 months after transplantation were randomized to either switch to belatacept or continue CNI treatment. All patients received background maintenance immunosuppression. The primary end point was the change in calculated GFR (cGFR) from baseline to month 12.

RESULTS: Patients were randomized either to switch to belatacept (n=84) or to remain on a CNI-based regimen (n=89). At month 12, the mean (SD) change from baseline in cGFR was higher in the belatacept group versus the CNI group. Six patients in the belatacept group had acute rejection episodes, all within the first 6 months; all resolved with no allograft loss. By month 12, one patient in the CNI group died with a functioning graft, whereas no patients in the belatacept group had graft loss. The overall safety profile was similar between groups.

CONCLUSIONS: The study identifies a potentially safe and feasible method for switching stable renal transplant patients from a cyclosporine- or tacrolimus-based regimen to a belatacept-based regimen, which may allow improved renal function in patients currently treated with CNIs.

54. Improvement in renal function in kidney transplant recipients switched from cyclosporine or tacrolimus to belatacept: 2-year results from the long-term extension of a phase II study

Grinyo J, Alberu J, Contieri FL et al.

Transpl Int. 2012 Oct;25(10):1059-64.

ABSTRACT

Kidney transplant recipients who switched from a calcineurin inhibitor (CNI) to belatacept demonstrated higher calculated glomerular filtration rates (cGFRs) at 1 year in a Phase II study. This report addresses whether improvement was sustained at 2 years in the long-term extension (LTE). Patients receiving cyclosporine or tacrolimus were randomized to switch to belatacept or continue CNI. Of 173 randomized patients, 162 completed the 12-month main study and entered the LTE. Two patients (n = 1 each group) had graft loss between Years 1-2. At Year 2, mean cGFR was 62.0 ml/min (belatacept) vs. 55.4 ml/min (CNI). The mean change in cGFR from baseline was +8.8 ml/min (belatacept) and +0.3 ml/min (CNI). Higher cGFR was observed in patients switched from either cyclosporine (+7.8 ml/min) or tacrolimus (+8.9 ml/min). The frequency of acute rejection in the LTE cohort was comparable between the belatacept and CNI groups by Year 2. All acute rejection episodes occurred during Year 1 in the belatacept patients and during Year 2 in the CNI group. There were more non-serious mucocutaneous fungal infections in the belatacept group. Switching to a belatacept-based regimen from a CNI-based regimen resulted in a continued trend toward improved renal function at 2 years after switching.

55. Safety and efficacy outcomes 3 years after switching to belatacept from a calcineurin inhibitor in kidney transplant recipients: results from a phase 2 randomized trial

Grinyó JM, Del Carmen Rial M, Alberu J et al.

Am J Kidney Dis. 2017 May;69(5):587-594.

ABSTRACT

BACKGROUND: In a phase 2 study, kidney transplant recipients of low immunologic risk who switched from a calcineurin inhibitor (CNI) to belatacept had improved kidney function at 12 months postconversion versus those continuing CNI therapy, with a low rate of acute rejection and no transplant loss.

STUDY DESIGN: 36-month follow-up of the intention-to-treat population.

SETTING & PARTICIPANTS: CNI-treated adult kidney transplant recipients with stable transplant function (estimated glomerular filtration rate [eGFR], 35-75mL/min/1.73m2).

INTERVENTIONS: At 6 to 36 months posttransplantation, patients were randomly assigned to switch to belatacept-based immunosuppression (n=84) or continue CNI-based therapy (n=89).

OUTCOMES: Safety was the primary outcome. eGFR, acute rejection, transplant loss, and death were also assessed.

MEASUREMENTS: Treatment exposure-adjusted incidence rates for safety, repeated-measures modeling for eGFR, Kaplan-Meier analyses for efficacy.

RESULTS: Serious adverse events occurred in 33 (39%) belatacept-treated patients and 36 (40%) patients in the CNI group. Treatment exposure-adjusted incidence rates for serious infections (belatacept vs CNI, 10.21 vs 9.31 per 100 person-years) and malignancies (3.01 vs 3.41 per 100 person-years) were similar. More patients in the belatacept versus CNI group had any-grade viral infections (14.60 vs 11.00 per 100 person-years). No posttransplantation lymphoproliferative disorder was reported. Belatacept-treated patients had a significantly greater estimated gain in mean eGFR (1.90 vs 0.07mL/min/1.73m2 per year; P for time-by-treatment interaction effect = 0.01). The probability of acute rejection was not significantly different for belatacept (8.38% vs 3.60%; HR, 2.50 [95% CI, 0.65-9.65; P=0.2). HR for the comparison of belatacept to the CNI group for time to death or transplant loss was 1.00 (95% CI, 0.14-7.07; P=0.9).

LIMITATIONS: Exploratory post hoc analysis with a small sample size.

CONCLUSIONS: Switching patients from a CNI to belatacept may represent a safe approach to immunosuppression and is being further explored in an ongoing phase 3b trial.

56. Use of belatacept as alternative immunosuppression in three renal transplant patients with de novo drug-induced thrombotic microangiopathy

Cicora F, Paz M, Mos F et al.

Case Rep Med. 2013;2013:260254.

ABSTRACT

Thrombotic microangiopathy (TMA), a severe complication of renal transplantation, is a pathological process involving microvascular occlusion, thrombocytopenia, and microangiopathic hemolytic anemia. It generally appears within the first weeks after transplantation, when immunosuppressive drugs are used at high doses. De novo TMA may also be drug-induced when calcineurin inhibitors or proliferation signal inhibitors are used. We report three cases of de novo drug-induced TMA in renal transplant patients who were managed by replacing calcineurin inhibitors or proliferation signal inhibitors with belatacept, a primary maintenance

immunosuppressive drug, which blocks the CD28 costimulation pathway, preventing the activation of T lymphocytes. To identify the cause of TMA, we ruled out HUS, hepatitis C serology, HIV serology, parvovirus B19, cytomegalovirus, anti-HLA antibodies, and prolonged activated partial thromboplastin time. We suspect that the TMA was caused by the calcineurin inhibitors or proliferation signal inhibitors. Belatacept treatment was initiated at a dose of 10 mg/kg on days 1, 5, 14, 28, 60, and 90; maintenance treatment was 5 mg/kg once a month for 1 year. Belatacept, in combination with other agents, prevented graft rejection in three patients.

57. Belatacept as maintenance immunosuppression for postrenal transplant de novo drug-induced thrombotic microangiopathy

Ashman N, Chapagain A, Dobbie H et al.

Am J Transplant. 2009 Feb;9(2):424-7.

ABSTRACT

De novo posttransplant thrombotic microangiopathy (TMA) is a complication of solid organ transplantation, which remains difficult to treat. In many cases, immunosuppressants and particularly calcineurin inhibitors, trigger TMA. Although withdrawing the offending drug may lead to resolution of TMA, graft and patient outcomes are poor. Specific treatments, including plasma exchange, have not gained widespread acceptance in those with fulminant disease and new approaches to the condition are urgently needed. We report a case of posttransplant de novo TMA presenting serially in association with ciclosporin, tacrolimus and sirolimus in a young recipient of a living donor kidney transplant. We describe a patient treated with belatacept, a novel CTLA4 Ig fusion protein, as ongoing maintenance immunosuppression to allow avoidance of conventional agents once associated with TMA. We report excellent early graft outcome, with no adverse events using this strategy. We suggest that belatacept may have a role in this traditionally difficult-to-treat group of patients.

58. Belatacept as Immunosuppression in Patient With Recurrence of Hemolytic Uremic Syndrome After Renal Transplantation

Midtvedt K, Bitter J, Dørje C et al.

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ABSTRACT

Recurrence of hemolytic uremic syndrome (HUS) after renal transplantation is relatively common and remains a threat to long-term graft outcome. HUS is described as de novo if the disorder arises after renal transplantation in a patient with no previous history of HUS. Calcineurin inhibitors (CNIs; tacrolimus and cyclosporine) are considered to be major offenders in de novo posttransplant HUS (1–4). Finally, the mammalian target of rapamycin (mTOR) sirolimus also has been associated with development of posttransplant HUS (5, 6). We report a patient with recurrence of HUS after renal transplantation in two subsequent grafts, the first recurrence leading to graft loss. Retransplantation was performed but once again with recurrence of HUS. This time the patient was successfully treated with withdrawal of tacrolimus, intensive plasma exchange PE, and introduction of belatacept as part of maintenance immunosuppressive therapy.