1. Kidney Transplantation

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1.1 Induction therapy

Vu, V. A., Bhayana, S., Sweiss, H., Castro, N., Hall, R., & Nelson, J. (2024). Impact of Cumulative 6 mg/kg Antithymocyte Globulin on Early Posttransplant Outcomes in Kidney Transplant Recipients with Delayed Graft Function. Progress in transplantation (Aliso Viejo, Calif.), 15269248241237816. Advance online publication. https://doi.org/10.1177/15269248241237816

- Single center, retrospective study aiming to assess the effectiveness and tolerability of an increased net state of immunosuppression in adult recipients with DGF, using cumulative 6 mg/kg rATG induction and fixed-dose mycophenolate mofetil.
- Patients were divided into 2 cohorts: those who received 4.5 mg/kg rATG induction and weight-based MMF and those who received 6 mg/kg rATG induction, fixed-dose MMF (1000 mg bid)
- Found a significant reduction of biopsy-proven acute rejection incidence occurred in those who got the 6 mg/kg rATG induction (30.3% 4.5 mg/kg rATG vs 10.9% 6 mg/kg rATG; P = .04)
- Of those with rejection, significantly less patients who got 6 mg /kg rATG induction were classified as acute cellular rejection (90.0% 4.5 mg/kg rATG vs 33.3% 6 mg/kg rATG; P = .04)
- No death-censored graft loss was observed in either group
- Rates of cytopenia and infection were similar pre- versus post-protocol implementation

Lee, J. H., Lee, H. R., Lee, S. W., Song, J. H., & Hwang, S. D. (2024). Effect of Induction Therapy Dose on Survival in Abo-Incompatible Kidney Transplantation: A Network Meta-Analysis Using Recent Data. *Transplantation proceedings*, S0041-1345(24)00025-3. Advance online publication. https://doi.org/10.1016/j.transproceed.2024.01.026

- Network meta analysis aiming to identify the most appropriate dose of rituximab for induction in ABO incompatible kidney transplants (four dose groups: 1) placebo, 2) rituximab 200 mg, 3) rituximab 200−500 mg, and 4) rituximab 500 mg)

- Included 25 trials (n= 5,378 subjects)
- Compared with the ABO-compatible group (control group), the placebo group, rituximab 200 mg-500 mg and rituximab 500 mg groups all had a significantly higher mortality rate. The rituximab 200 mg group had a lower inclination toward increased mortality
- When comparing each rituximab dosing strategy to placebo, the rituximab 200-500 mg and rituximab 500 mg groups did not show any statistically significant difference in mortality. The rituximab 200 mg group had an 86% reduction in mortality compared with the placebo group.
- No difference among the groups regarding incidence of heart failure, stroke, hospitalization, peripheral artery disease, myocardial infarction, anemia, leukopenia, herpes zoster, or adverse events

Viklicky, O., Zahradka, I., Bold, G., Bestard, O., Hruba, P., Otto, N. M., Stein, M., Sefrin, A., Modos, I., Meneghini, M., Crespo, E., Grinyo, J., Volk, H. D., Christakoudi, S., & Reinke, P. (2024). Tacrolimus After rATG and Infliximab Induction Immunosuppression-RIMINI Trial. *Transplantation*, *108*(1), 242–251. https://doi.org/10.1097/TP.0000000000004736

- phase II international multicenter open-label single-arm clinical trial aimed at assessing the efficacy and safety of rabbit antithymocyte globulin and infliximab induction in kidney transplantation
- The primary endpoint of efficacy failure was a composite of BPAR, graft loss occurring up to 12 months after transplantation, or poor graft function defined as eGFR <40mL/min. Overall, 32.8% experienced the composite efficacy failure endpoint at 12-months post-transplant.
- There was no statistical difference in the frequency of the primary composite efficacy endpoint (32.8% versus 32.8%) or in any of its components when compared to a historical matched control cohort.
- The overall eGFR from month 3 onward steadily increased (P=0.005). Immediate graft function occurred in 70.1% of patients, whereas delayed graft function occurred in 26.9% of patients and primary nonfunction occurred in 3% of patients
- there was no difference in graft function at the end of the 12 month follow-up compared to a historical matched control cohort.
- Compared to the compared to a historical matched control cohort, the study cohort had lower rates of BK replication (6% versus 22.4%; P = 0.013) but higher rates of de novo DSAs (11.9% versus 1.5%; P = 0.039).

Ali, et al. (2023). Outcomes of thymoglobulin versus basiliximab induction therapies in living donor kidney transplant recipients with mild to moderate immunological risk - a retrospective analysis of UNOS database. *Annals of medicine*, *55*(1), 2215536. https://pubmed.ncbi.nlm.nih.gov/37232582/

- Retrospective cohort study examining living donor kidney recipients with mild to moderate immunological risk (defined as first transplant, PRA <20%, but with two HLA-DR mismatches). Study compared incidence of acute rejection episodes at one-year post-transplant, serum creatinine levels at one-year post-transplant, and death-censored graft survival between patients receiving induction with basiliximab (n=788) vs. thymoglobulin (n=1727).
- Dose of thymoglobulin was retrospectively estimated at 1.5 mg/kg/day and number of days of induction therapy received. The majority of patients receiving thymoglobulin (n=918) received 3 days (estimated to be 4.5 mg/kg total for induction).
- All patients were discharged on tacrolimus and mycophenolate mofetil for maintenance. Glucocorticoid maintenance therapy was more frequent in the basiliximab group (p<0.1).
- No difference was observed in acute rejection episodes at one-year post-transplant (p=0.106), serum creatinine levels at one-year post-transplant (p=0.128), or death-censored graft survival (p=0.201). The authors concluded that basiliximab is safe to use for induction immunosuppression in this specific class of recipients.

Montero, et al. (2023). The use of lymphocyte-depleting antibodies in specific populations of kidney transplant recipients: A systematic review and meta-analysis. *Transplantation reviews (Orlando, Fla.)*, *37*(4), 100795. https://pubmed.ncbi.nlm.nih.gov/37774445/

- A meta-analysis of 37 randomized, controlled trials and 99 observational studies comparing effects of interleukin-2-receptor antibodies (IL2RA), anti-thymocyte globulin (ATG), and alemtuzumab in specific kidney transplant recipient (KTR) subgroups
- ATG reduced risk of acute rejection at two years compared to IL2RA in standard KTR (RR 0.74, 95% CI 0.61-0.89) and high risk of rejection KTR (RR 0.55, 95% CI 0.43-0.72), but without decreasing risk of graft loss
    - For rejection, the definition for “high-risk” or “highly sensitized” varied widely between studies
    - For high-risk of DGF, the most commonly used definition was kidney transplants using a donor after brain death with a cold ischemia time ≥18 hours or donors after circulatory death
- No significant differences were found comparing ATG vs. alemtuzumab or different ATG dosages in any KTR group
- Compared with IL2RA, ATG reduced rejection in standard-risk, highly sensitized and living donor graft recipients, but not in high DGF risk or elderly recipients

Jarmi, et al. (2023). Basiliximab is associated with a lower incidence of De novo donor-specific HLA antibodies in kidney transplant recipients: A single-center experience. *Transplant immunology*, *77*, 101778. https://pubmed.ncbi.nlm.nih.gov/36584928/

- Retrospective, single center trial including 390 patients comparing association of induction therapies (basiliximab vs. alemtuzumab vs. rabbit antithymocyte globulin) with development of de novo donor-specific HLA antibodies (DSA) in the first 12 months post-renal transplant
- De novo HLA DSA were detected in 12/104 (11.5%), 43/186 (23.11%), and 26/100 (26%) of recipients who received basiliximab, alemtuzumab, and rATG respectively (p=0.006). Patients receiving basiliximab were significantly older and had significantly lower last follow-up creatinine clearance at 42 mL/min compared to those who received alemtuzumab or rATG (p=0.006).
- Induction immunosuppression with basiliximab is associated with significant reduction in development of de novo DSA within the first 12 months post-kidney transplant but had lower creatinine clearance with long-term follow up.

Abou-Jaoudé, et al. (2023). The impact of induction therapy in low-immunological risk kidney transplant recipients regardless of HLA matching. *Transplant immunology*, *76*, 101773. https://pubmed.ncbi.nlm.nih.gov/36526105/

- Retrospective, multicenter study assessing 218 patients undergoing living donor kidney transplantation. 82 patients received no induction therapy (Group I) and 136 patients received induction with either anti-IL2 antibodies or anti-thymocyte globulin (Group II). All patients had PRA <20% and were absent of DSA.
- Patients in group II either received basiliximab on days 0 and 4 (n=67) or 6 mg/kg of rabbit ATG given intraoperatively (n=69)
- Donor-to-recipient HLA matching was significantly higher in group I (p<0.001), but between the two groups HLA class II matching was not significantly different.
- Duration of hospital stay, rate and severity of acute rejection, occurrence of DGF, rate and type of surgical complications at one year, and graft function and survival at one and three years were similar between both groups.

- Group II had significantly greater incidence of CMV disease than group I (9.6% vs. 2.4%, p=0.044) despite receiving CMV prophylaxis more frequently (78.6% vs. 47.5%, p=0.002). Group II also had significantly greater incidence of bacterial infection (p=0.032).
- A much lower financial burden was associated with group I, suggesting (along with other results) that induction therapy in low-immunological risk kidney transplant patients is not a must regardless of donor-to-recipient HLA matching. Induction therapy did not yield significant health results but had negative financial consequences

Evans, R., et al (2022). Use and Outcomes of Induction Therapy in Well-Matched Kidney Transplant Recipients. *Clinical Journal of the American Society of Nephrology*, 17(2)271-279. https://cjasn.asnjournals.org/content/17/2/271

- Retrospective, single center trial comparing induction treatments in low-immune risk kidney transplant recipients
- There was no difference found between patients treated with IL2 receptor antagonists and no induction therapy. Suggests no form of induction therapy is necessary for zero HLA mismatch transplant recipients with relatively no other immunologic risks
- Use of induction therapy with T cell–depleting therapy or IL-2 receptor antagonists in first kidney transplant recipients who are well matched with their donor at the HLA-A, -B, -DR, -DQB1 gene loci is not associated with improved post-transplant outcomes

Martinez-Mier, et al (2021). Low-dose thymoglobulin vs basiliximab induction therapy in low-risk living related kidney transplant recipients: a prospective randomized trial. *Transplant Proc*. 2021; 53(3): 1005-1009. https://pubmed.ncbi.nlm.nih.gov/32178925/

- A single-center, randomized study comparing safety and efficacy of low-dose thymoglobulin (3 mg/kg total) to basiliximab (20 mg on D0 and D4) induction with tacrolimus (target trough first 6 months 8-10 ng/mL), MMF 2g/day, steroid taper for maintenance immunosuppression
- No difference between groups (thymoglobulin vs. basiliximab) in patient survival (100% vs. 98.1%) and graft survival (93.6% vs. 92.5%)
- No difference between groups (thymoglobulin vs. basiliximab) in biopsy proven acute rejection (6.4% vs. 3.8%), delayed graft function (4.3% vs. 3.8%), slow graft function (3.4% vs. 5.7%) and 12-month leukopenia (21.3% vs. 11.3%)

Ali, et al. (2021) Outcomes of interleukin-2 receptor antagonist induction therapy in standard-risk renal transplant recipients maintained on tacrolimus: a systematic review and meta-analysis. *Am J Nephrol*. 2021; 52(4): 279-291. https://pubmed.ncbi.nlm.nih.gov/33887727/

- A meta-analysis of 11 studies, n=2886, split into two groups; group A included studies that used the same dose of tacrolimus in both arms and group B included studies that used induction and low-dose tacrolimus vs. no induction and high-dose tacrolimus
- IL2-RA induction is not associated with better outcomes in patients on tacrolimus-based immunotherapy (with or without corticosteroids); no difference in acute rejection rates or graft survival within both groups as well as within each group

Ali, et al (2020) Effect of Interleukin-2 receptor antibody induction therapy on survival in renal transplant patients receiving tacrolimus. *Am J Nephrol*. 2020; 51(50); 366-372. https://pubmed.ncbi.nlm.nih.gov/32268334/

- Assessment of outcomes from the British Renal Transplant Registry
- Compared patients who received IL-2RA induction vs no induction. There was no difference in eGFR at 1 year post-transplant, graft survival at 1 year and 5 years post-transplant, and patient survival at 1 year and 5 years post-transplant

- Subgroup analysis comparing IL-2RA induction vs no induction in steroid-free vs triple immunosuppression also found no difference in outcomes

Hwang, et al (2020). Effect of rituximab used as induction in patients with ABO mismatch kidney transplant: a systematic review and meta-analysis. *Transplant Proc.* 2020; 52(10): 3125-3128. https://pubmed.ncbi.nlm.nih.gov/32553506/

- Grouped based off rituximab dose, either 200 mg or 375 mg/m^2
- Outcomes of 5 trials (n=390) did not differ in GFR rates, graft loss, AMR, T-cell mediated rejection, fungal infections, and patient survival rates. Incidence of infection was significantly less in the 200 mg group.

Bae, et al (2020). Antithymocyte globulin versus interleukin-2 receptor antagonist in kidney transplant recipients with hepatitis C virus. *Transplantation*. 2020; 104(6): 1294-1303. https://pubmed.ncbi.nlm.nih.gov/32433232/

- Scientific Registry of Transplant Recipients and Medicare claims from 1999-2016 for patients who received ATG or IL2RA for induction
- HCV+ recipients were less likely to receive rATG, but those who did receive rATG had lower risk of acute rejection. There was no difference between induction therapies and risk of graft failure, death, liver transplant registration (prior history of liver transplant or on liver transplant waitlist), and cirrhosis

Masset, et al. (2020) Induction therapy in elderly kidney transplant recipients with low immunological risk. Transplantation 2020; 104(3), 613-622. https://journals.lww.com/transplantjournal/Fulltext/2020/03000/Induction_Therapy_in_Elderly_Kidney_Transplant.31.aspx

- This multicenter study compared survival and clinical outcomes in elderly (≥ 65 YO) kidney transplant recipients at low immunological risk who received rATG (1.5 mg/kg/day- maximum 75 to 100 mg/d) vs. basiliximab (20 mg IV POD 0 and 4) induction therapy
- Patient and graft survival at 3 years were not significantly different between the 2 groups (74 vs. 68%)
- There was a significantly higher incidence of post-transplant diabetes in the basiliximab group associated with higher FK trough levels at 3 months

Alloway, et al. (2019) Rabbit anti-thymocyte globulin for the prevention of acute rejection in kidney transplantation. Am J Transplant. 2019: 19(8); 2252-2561. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6767488/

- Results of 2 international randomized trials consisting of 508 total kidney transplant recipients looking at rATG vs. basiliximab with composite end point of BPAR (biopsy-proven acute rejection), death, graft loss or loss to follow up
- Pooled analysis supports non-inferiority between these agents for induction therapy
- Further meta analysis of 7 trials suggests rATG may have a lower BPAR rate at 12 months

Singh, et al. (2018) Tailored Rabbit Antithymocyte Globulin Induction Dosing for Kidney Transplantation. Transplant Direct. 2018: 4(2):e343. https://www.ncbi.nlm.nih.gov/pubmed?term=29464204

- Evaluated cumulative conventional dosing for induction using rabbit ATG (6-10 mg/kg) vs. reduced dosing (4.5 mg/kg) in a five year retrospective cohort consisting of 224 kidney transplant recipients
- Cumulative dosing of 3mg/kg was given to non-sensitized living donor recipients, 4.5 mg/kg was given to non-sensitized deceased donor recipients and 6 mg/kg was given to high immunological risk patients
- No differences in patient or graft survival or infection risk between the 3 groups

Koyawala, et al. (2017) Comparing Outcomes between Antibody Induction Therapies in Kidney Transplantation. J Am Soc Nephrol 2017; 28:2188. https://www.ncbi.nlm.nih.gov/pubmed?term=28320767

- Using OPTN and medicare claims data compared outcomes for rabbit ATG, basiliximab and alemtuzumab in 1:1 pairs. Primary outcome was death and death or allograft failure.
- Compared to rATG, alemtuzumab had a higher rate of death and death or allograft failure, which was consistent even among subgroups
- Compared to rATG, basiliximab had a higher rate of death and death or lymphoma
- rATG may be associated with a lower risk of side effects and mortality

Thomusch, et al. (2016) Rabbit-ATG or basiliximab induction for rapid steroid withdrawal after renal transplantation (Harmony): an open-label, multicentre, randomised controlled trial. Lancet. 2016; 388(10063): 3006-3016. https://www.ncbi.nlm.nih.gov/pubmed?term=27871759

- Open-label multi center trial randomizing low immunological risk kidney transplant patients to receive basiliximab induction with low dose tacrolimus, mycophenolate mofetil and maintenance corticosteroids, rapid corticosteroid withdrawal on day 8, or rapid corticosteroid withdrawal on day 8 after rabbit ATG induction.
- BPAR rates at 1 year did not differ between use of basiliximab or rabbit ATG induction therapy with rapid steroid withdrawal

Haynes, et al. (2014) Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomised trial. Lancet. 2014;384(9955):1684-90. https://www.ncbi.nlm.nih.gov/pubmed/25078310

- Randomly assigned 852 kidney transplant recipients to induction treatment with alemtuzumab (followed by low-dose tacrolimus and mycophenolate without steroids) or basiliximab (followed by standard-dose tacrolimus, mycophenolate, and prednisolone).
- The primary outcome was biopsy-proven acute rejection at 6 months. In the alemtuzumab group 31 (7%) patients vs 68 (16%) patients in the basiliximab group; (HR 0.42, 95% CI 0.28–0.64; log-rank p<0.0001) had biopsy-proven acute rejection.
- No difference in treatment effect on transplant failure, serious infection, or death. Alemtuzumab induction therapy reduced the risk of biopsy-proven acute rejection at 6 months in kidney transplant recipients.

Ejaz, et al. (2013) Randomized controlled pilot study of B cell-targeted induction therapy in HLA sensitized kidney transplant recipients. Am J Transplant. 2013;13(12):3142-54. https://www.ncbi.nlm.nih.gov/pubmed/24266968

- Prospective, randomized study evaluating the addition of B cell/plasma cell–targeting agents to T cell–based induction with rabbit antithymocyte globulin (rATG) in high immunologic risk renal transplant recipients (n=40).
- Patients were randomized to induction with rATG, rATG + rituximab, rATG + bortezomib or rATG + rituximab + bortezomib.
- No difference in patient survival, renal allograft survival, and renal allograft function at one year post-transplant was observed.

Gabardi, et al. (2011) Induction Immunosuppressive Therapies in Renal Transplantation. American Journal of Health-Systems Pharmacist, 2011;68:211-8. http://www.ncbi.nlm.nih.gov/pubmed/21258026.

- A review article discussing the therapeutic agents available for induction therapy.

Hanaway, et al (2011) Alemtuzumab induction in renal transplantation. New England Journal of Medicine, 364(20):1909-19. http://www.ncbi.nlm.nih.gov/pubmed/21591943.

- Superiority trial of alemtuzumab as an induction agent. Rates of acute rejection were less frequent with alemtuzumab in low risk transplant recipients when compared to basiliximab and antithymocyte.

Farney, et al. (2009) A randomized trial of alemtuzumab versus antithymocyte globulin induction in renal and pancreas transplantation. Transplantation. 2009;88(6):810-9. https://www.ncbi.nlm.nih.gov/pubmed/19920781

- Prospective randomized single-center trial comparing alemtuzumab and rATG induction in adult kidney and pancreas transplantation in patients (n=122).
- Biopsy-proven acute rejection (BPAR) episodes occurred in 16 (14%) alemtuzumab patients compared with 28 (26%) rATG patients ($P < 0.02$).
- Infections and malignancy were similar between the two induction arms. Alemtuzumab was associated with less BPAR than rATG induction.

Ciancio, et al. (2008) Alemtuzumab (Campath-1H) in Kidney Transplantation. American Journal of Transplantation, 8:15-20. http://www.ncbi.nlm.nih.gov/pubmed/18093269.

- Mini-review regarding use of alemtuzumab in kidney transplant, including site experiences.

Brennan, et al. (2006) Rabbit Antithymocyte Globulin versus Basiliximab in Renal Transplantation. New England Journal of Medicine, 355: 1967-77. http://www.ncbi.nlm.nih.gov/pubmed/17093248.

- High risk patients receiving a transplant from a deceased donor had reduced incidence and severity of acute rejection when induction was done with antithymocyte globulin when compared to basiliximab.

1.2 Maintenance therapy

Romine, M. M., Leeser, D. B., Kennamer, K., Nguyen, C., Jones, H., McLawhorn, K., Kendrick, S., & Irish, W. (2024). Early outcomes associated with de novo once-daily extended-release versus twice-daily immediate-release tacrolimus in a predominantly African American kidney transplant population: A single-center observational study. *Clinical transplantation*, *38*(3), e15268. https://doi.org/10.1111/ctr.15268

- Single center, retrospective cohort study exploring early post-transplant outcomes associated with the use of de novo once-daily extended-release tacrolimus (LCPT) [starting daily dose of 0.14mg/kg] versus twice-daily immediate-release- tacrolimus (IR TAC) [starting daily 0.1mg/kg administered twice a day] in a predominantly African American kidney transplant population
- n = 271 patients (n=161 patients in the immediate release tacrolimus cohort and n=110 patients in the extended release tacrolimus cohort)
- Patients in the LCPT cohort had a higher peak level at, 14 days post-discharge (LCPT cohort was 0.245 ng/mL per day vs 0.107 ng/mL per day in the IR TAC cohort; $p<0.001$) followed by a more rapid decline up to Day 60 (−0.015 ng/mL per day vs.−0.010 ng/mL per day with IR TAC; $p=0.0894$)
- eGFR was similar between the two cohorts at 12 months post-transplant, the rate of increase was slower in the LCPT cohort (0.1371 mL/min per day vs. 0.1852mL/min per day; $p=0.0314$)
- No significant difference regarding graft survival, DGF, BPAR, CMV, or BK infection

Toniato de Rezende Freschi, J., Cristelli, M. P., Viana, L. A., Ficher, K. N., Nakamura, M. R., Proença, H., Dreige, Y. C., de Marco, R., de Lima, M. G., Foresto, R. D., Aguiar, W. F., Medina-Pestana, J., & Tedesco-Silva, H. (2024). A Head-to-head Comparison of De Novo Sirolimus or Everolimus Plus Reduced-dose Tacrolimus in Kidney Transplant Recipients: A Prospective and Randomized Trial. *Transplantation*, *108*(1), 261. https://doi.org/10.1097/TP.0000000000004749

- Single-center prospective, randomized study of 266KTRs with thymoglobulin induction, tacrolimus (goal 3-5 ng/mL with mTORi or 5-10 with mycophenolate), and prednisone, who were randomized to receive either sirolimus, everolimus, or mycophenolate. Sirolimus and everolimus target troughs were 4-8 ng/mL. Patients did not receive pharmacologic CMV prophylaxis.
- Incidence of first CMV was significantly lower in sirolimus and everolimus groups compared to mycophenolate (10.5% versus 7.8% versus 43.3%, $P < 0.0001$). No difference was observed for incidence of BK viremia and DSA.

- Graft outcomes were similar across groups. Treatment discontinuation was numerically higher in sirolimus or everolimus groups compared to mycophenolate (18.6% vs 15.6% vs 6.7%, P=0.054). Lack of efficacy was the reason for discontinuation in 37.5% of discontinuations in the sirolimus group, 14.3% in the everolimus group, and 0% in the mycophenolate group.

Peddi, V. R., Marder, B., Gaite, L., Oberholzer, J., Goldberg, R., Pearson, T., Yang, H., Allamassey, L., Polinsky, M., & Formica, R. N. (2023). Treatment of De Novo Renal Transplant Recipients With Calcineurin Inhibitor–free, Belatacept Plus Everolimus–based Immunosuppression. *Transplantation Direct*, *9*(2), e1419. https://doi.org/10.1097/TXD.0000000000001419

- Prospective, randomized, multicenter phase 2 trial comparing belatacept+everolimus (n=26) vs tacrolimus+MMF (n=32) in KTRs who received rATG induction and rapid steroid withdrawal.
- Enrollment was terminated early due to belatacept supply constraints. Among the 58 included patients, rejection rates were similar between groups. At 24 months, the mean eGFR was 71.8 versus 68.7 mL/min/1.73 m2 in the BELA+EVL versus TAC+MMF groups.

van den Born JC, et al (2023). Comparison of 2 Immunosuppression Minimization Strategies in Kidney Transplantation: The ALLEGRO Trial. *Transplantation*. Published online August 30, 2023. https://pubmed.ncbi.nlm.nih.gov/37650722/

- Randomized, multicenter noninferiority, open-label trial in 295 de novo KTRs receiving basiliximab for induction that compared two immunosuppression minimization strategies (steroid withdrawal on day 3 vs tacrolimus minimization to goal 3-5 ng/ml at 6 months) to standard immunosuppression
- Noninferiority of the primary outcome was met for both groups with eGFR rate at 24 mo of 45.3 mL/min/1.73m^2 in the early steroid withdrawal group, 49.0 mL/ min/1.73m^2 in the standard immunosuppression group, and 44.7 mL/min/1.73 m2 in the tacrolimus minimization group.
- Early steroid withdrawal led to more episodes of treated rejection (23.5% in early steroid withdrawal, 14.0% in standard immunosuppression, and 11.3% in tacrolimus minimization, P=0.04) but improved metabolic outcomes at 24 months. Tacrolimus minimization was similarly safe and effective as standard immunosuppression. There was no difference in overall survival or graft survival at year 1 or 2.

Santos, E., Spensley, K., Gunby, N., Clarke, C., Anand, A., Roufosse, C., & Willicombe, M. (2023). Steroid Sparing Maintenance Immunosuppression in Highly Sensitised Patients Receiving Alemtuzumab Induction. *Transplant international : official journal of the European Society for Organ Transplantation*, 36, 11056. https://doi.org/10.3389/ti.2023.11056

- Retrospective analysis of sensitized patients (calculated reaction frequency > 85%) who received alemtuzumab induction and steroid withdrawal at 1 week with either tacrolimus monotherapy (n=53) or tacrolimus + mycophenolate (n=67).
- One-year patient and graft survival did not differ between groups, but rejection-free survival was better in the tacrolimus + mycophenolate group (65.4% vs 91.4%, p <0.01). CMV-free survival was better in the tacrolimus monotherapy group (98.1% vs 86.0%, p=0.026). Survival free from diabetes was better in tacrolimus + mycophenolate group (89.6% vs 100%, p=0.027), possibly due to higher rates of steroid treatment for rejection in the monotherapy group.

Johnson et al (2023). Three-year Outcomes After Conversion From Monthly to Every 2-month Belatacept Maintenance Therapy in Kidney Transplant Recipients: Results From a Randomized Controlled Trial. *Transplant Direct*. 2023;9(3):e1449. doi:10.1097/TXD.0000000000001449

- 3 year outcomes of a prospective, randomized, single-center trial in stable low immunologic risk KTRs that compared every 2 month (n=81) belatacept maintenance dosing to standard every 1 month (n=82)
- No difference was detected in baseline-adjusted eGFR (time-averaged mean difference of 0.2 mL/min/1.73 m2; 95% confidence interval: −2.5, 2.9). There was no difference in freedom from death/graft loss (P=0.49). Differences in freedom from rejection at 36 months (98.7% in q1m group vs 92.4% in q2m group, P=0.059) and freedom from DSAs at 36 months (98.7% in q1m group vs 92.4% in q2m group, P=0.06) did not reach statistical significance.

Tawhari, I., Hallak, P., Bin, S., Yamani, F., Safar-Boueri, M., Irshad, A., Leventhal, J., Ansari, M. J., Cravedi, P., & Gallon, L. (2022). Early calcineurin-inhibitor to belatacept conversion in steroid-free kidney transplant recipients. *Frontiers in Immunology*, *13*, 1096881. https://doi.org/10.3389/fimmu.2022.1096881

- Stable kidney transplant recipients who had undergone early steroid withdrawal (methylprednisolone on POD 1 and 2 only) were randomized to either belatacept + mycophenolic acid (bela+MPA, n=9), belatacept + low-dose tacrolimus (goal <5 ng/mL) (bela+tac, n=8), or to continue tacrolimus and mycophenolic acid (tac+MPA, n=10).
- Trial was terminated early due to high rates of biopsy-proven acute rejection (BPAR) in bela+MPA group. Incidence of BPAR at 24 months was 4/9 in bela+MPA, 0/8 in bela+tac, and 2/10 in tac+MPA (P=0.087), with one graft loss in the bela+MPA group. Two patients in the tac+MPA group developed DSAs, while no belatacept-treated patients developed DSAs.

Nelson, J., Alvey, N., Bowman, L., Schulte, J., Segovia, M. C., McDermott, J., Te, H. S., Kapila, N., Levine, D. J., Gottlieb, R. L., Oberholzer, J., & Campara, M. (2022). Consensus recommendations for use of maintenance immunosuppression in solid organ transplantation: Endorsed by the American College of Clinical Pharmacy, American Society of Transplantation, and the International Society for Heart and Lung Transplantation. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *42*(8), 599–633. https://doi.org/10.1002/phar.2716

- Comprehensive guidelines providing recommendations for the use of calcineurin inhibitors, antimetabolites, corticosteroids, mammalian target of rapamycin inhibitors, co-stimulation inhibitors, and interleukin-2 receptor antagonists as maintenance immunosuppression in kidney, liver, pancreas, intestine, heart, and lung transplantation

Breslin, et al (2022). Comparing weight-based dosing of tacrolimus XR in obese and non-obese renal transplant recipients. *Clinical transplantation*. 36(2), e14529. https://pubmed.ncbi.nlm.nih.gov/34757669/

- A retrospective, multicenter study evaluating weight-based dosing requirements of tacrolimus XR in de novo obese patients
- Of the 254 kidney transplant recipients, 81 (31%) were obese. The median therapeutic dose on POD7 was 0.1 vs. 0.12 vs. 0.14 mg/kg/day in the BMI > 30 kg/m2, BMI 25–30 kg/m2, and BMI < 25 kg/m2, respectively, (p = .0001).There was found to be strong linear relationship between ideal body weight (IBW) and therapeutic dose (r = .929)
- In both the non-obese and obese population, IBW was more strongly correlated to a therapeutic dose for tacrolimus XR

Fernandez Rivera, et al (2022). Bioavailability of once-daily tacrolimus formulations used in clinical practice in the management of De Novo kidney transplant recipients: the better study. *Clinical transplantation*. 36(3), e14550. https://pubmed.ncbi.nlm.nih.gov/34851532/

- A multicenter, prospective, observational study to compare the bioavailability of once-daily tacrolimus formulations in de novo kidney transplant recipients
- LCPT group (n=129) had a higher relative bioavailability, with similar Cmin, and 30% lower total daily dose compared against prolonged release-Tac (n=89) (P<0.001)

- Reported adverse events and renal function were similar between agents in the 6 month study period

Ficher, et al (2022). Long-term Efficacy and Safety of Everolimus Versus Mycophenolate in Kidney Transplant Recipients Receiving Tacrolimus. *Transplantation*, 106(2):381-390. https://pubmed.ncbi.nlm.nih.gov/33988338/

- 5-year follow-up post hoc analysis of a prospective trial including 288 patients comparing low dose tacrolimus combined with everolimus compared to standard of care with tacrolimus, mycophenolate, and prednisone
- The use of everolimus is associated with similar efficacy compared to mycophenolate in low-to-moderate immunologic risk kidney transplant recipients receiving tacrolimus
- The use of everolimus combined with reduced tacrolimus concentrations was associated similar rates of acute rejection, dnDSA, graft loss, and death, and stable renal function up to 5 years compared with the standard of care immunosuppressive regimen

Kaufman, et al (2021). Belatacept for simultaneous calcineurin inhibitor and chronic corticosteroid immunosuppression avoidance: two-year results of a prospective, randomized multicenter trial. *Clin J Am Soc Nephrol*. 2021; 16(9): 1387-1397. https://pubmed.ncbi.nlm.nih.gov/34233921/

- Randomized, multicenter trial with all recipients using rapid steroid withdrawal and grouped 1:1:1 to receive either belatacept with alemtuzumab, belatacept with rATG, or tacrolimus with rATG to assess the 2-year composite outcome of death, kidney allograft loss, or an eGFR <45 m/min/1.73m^2
- The composite outcome had no significant difference between groups, reflective of order above, 10%, 13%, and 21%
- Lower incidence of eGFR <45 occurred in both belatacept groups compared to tacrolimus (8%, 8%, and 19%), but significantly higher incidence of BPAR (19%, 25%, 7%)

Werbel, et al (2021). Early steroid withdrawal in HIV-infected kidney transplant recipients: utilization and outcomes. *Am J Transplant*. 2021; 21(2): 717-726. https://pubmed.ncbi.nlm.nih.gov/32681603/

- Analysis of the Scientific Registry of Transplant Recipients for HIV+ recipients to compare those with early steroid withdrawal (ESW) to steroid continuation
- ESW was utilized less in high-volume centers vs moderate-volume centers. The patient population was similar between both types of centers with regard to demographics and immunologic characteristics
- Moderate-volume centers had higher rates of zero HLA mismatch and DGF
- Acute rejection was more common with ESW, but there was no difference in death or graft failure

Pipeleers, et al (2021). 5-year outcomes of the prospective and randomized CISTCERT study comparing steroid withdrawal to replacement of cyclosporine with everolimus in de novo kidney transplant patients. *Transpl Int*. 2021; 34(2): 313-326. https://pubmed.ncbi.nlm.nih.gov/33277746/

- Multicenter, randomized control trial with 151 *de novo* recipients who received cyclosporine, mycophenolic acid, and steroids for 3-months and then were either grouped into early steroid withdrawal or cyclosporine replacement with everolimus with continued steroid use
- No difference in 5-year patient and graft survival, cardiovascular outcomes, and malignancy. There was no difference in GFR at 1- or 5-years posttransplant in the intention-to-treat analysis; however, on-treatment analysis showed superior clearance in the everolimus cohort
- Everolimus group had significantly more incidence of and more severe rejection and higher incidences of posttransplant diabetes

Ciancio, et al (2020). Randomized trial of 3 maintenance regimens (TAC/SRL vs TAC/MMF vs CSA/SRL) with low-dose corticosteroids in primary kidney transplantation: 18-year results. *Clin Transplant.* 2020; 34(12): e14123. https://pubmed.ncbi.nlm.nih.gov/33070366/

- 18-year follow-up of a randomized trial of 150 kidney transplant recipients, comparing 1:1:1 tacrolimus/sirolimus vs. tacrolimus/mycophenolate motif vs. cyclosporine/sirolimus. All patients received daclizumab induction
- BPAR occurred less often in tacrolimus/mycophenolate group at 26% (vs. 36% in tacrolimus/sirolimus and 34% in the cyclosporine/sirolimus groups) with higher eGFR

Schmitz, et al (2020). Kidney transplantation using alemtuzumab, belatacept, and sirolimus: five-year follow-up. *Am J Transplant*. 2020; 20(12): 3609-3619. https://pubmed.ncbi.nlm.nih.gov/32515087/

- 5-year follow up study of low-risk, live-donor kidney transplant recipients who received alemtuzumab induction with maintenance belatacept and sirolimus therapy. Patients without evidence of rejection or donor-specific antibodies were eligible to wean to belatacept monotherapy at 12 months.
- There was stable allograft function (mean eGFR 71 ± 19 mL/min/1.73 m^2) and no allograft loss due to rejection at 5 years. 12/40 patients were weaned to belatacept monotherapy with controlled CMV and EBV reactivations, but 9/12 experienced transient BK in the first year with no clinical rejection

Woodle ES, et al. (2020) BEST Study Group. Belatacept-Based Immunosuppression With Simultaneous Calcineurin Inhibitor Avoidance and Early Corticosteroid Withdrawal: A Prospective, Randomized Multicenter Trial. American Journal of Transplantation. 2020; 00:1–17. https://pubmed.ncbi.nlm.nih.gov/31680394/

- This prospective, randomized, open-label trial compared two belatacept-based calcineurin inhibitor avoidance/early corticosteroid withdrawal regimens with tacrolimus-based early corticosteroid withdrawal regimens.
- Patients were randomized to receive alemtuzumab/belatacept, rATG/belatacept, or rATG/tacrolimus. Superiority was not found for the primary composite endpoint of patient death, renal graft loss, or MDRD eGFR < 45 at 12 months.
- No significant differences were found for antibody-mediated rejection, biopsy-proven mixed acute rejection, de-novo DSA production, death, death-censored graft loss, eGFR < 45. There were statistically significant higher rates of acute cellular rejection in the belatacept groups versus the tacrolimus group. Additionally, there was a lower incidence of neurologic and electrolyte abnormalities with belatacept.

Manzia TM, Carmellini M, et al. (2020) A 3-month, Multicenter, Randomized, Open-label Study to Evaluate the Impact on Wound Healing of the Early (vs Delayed) Introduction of Everolimus in De Novo Kidney Transplant Recipients, With a Follow-up Evaluation at 12 Months After Transplant (NEVERWOUND Study). Transplantation. 2020; 104(2), 374. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7004468/

- This multicenter, randomized, open-label study of 394 kidney transplant recipients evaluated whether a delayed EVR-based regimen reduced the risk of wound-healing complications versus EVR started immediately post-kidney transplant.
- Patients were randomized to either EVL with low-dose cyclosporine and steroids immediately post-transplant or were converted from cyclosporine, MMF, and steroids at 28 ± 4 days.
- At 3 months, WHC-free rates in the immediate EVR vs. delayed EVR arm were 0.68 (95% confidence interval [CI], 0.62-0.75) versus 0.62 (95% CI, 0.55-0.68) (log-rank *P* = 0.56). There were no significant differences between the 3- and 12-month treatment failure rates, delayed graft function and renal function, and patient and graft survival rates.

Berger S, Sommerer C, Witzke O, et al. (2019) Two-year outcomes in de novo renal transplant recipients receiving everolimus-facilitated calcineurin inhibitor reduction regimen from the TRANSFORM study. Am J Transplant. 2019; 19(11): 3018 3034. https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.15480

- Two year results of a prospective open label trial looking at reduced exposure of CNI + everolimus vs. standard CNI and mycophenolate and impact on a composite of BPAR and eGFR <50
- Everolimus + reduced CNI was non-inferior in primary end point, and was associated with less DSAs, CMV infections and BK virus infections

Fructuoso, AS et al. (2019). Effectiveness and safety of the conversion to MeltDose® extended-release tacrolimus from other formulations of tacrolimus in stable kidney transplant patients: a retrospective study. Clinical Transplantation. e13767. https://www.ncbi.nlm.nih.gov/pubmed/31815310

- Analysis of the efficacy and safety of conversion from immediate-release tacrolimus or prolonged-release tacrolimus to once-daily MeltDose® extended-release tacrolimus in kidney transplant recipients. The total daily dose was reduced by 35% after 3 months with a cost reduction of 63% observed. There were no changes in renal function, no cases of biopsy proven acute rejection, and reports of tremors decreased after the conversion to the MeltDose®.

Bray RA et al. (2018) De novo donor-specific antibodies in belatacept-treated vs cyclosporine-treated kidney-transplant recipients: Post hoc analyses of the randomized phase III BENEFIT and BENEFIT-EXT studies. Am J Transplant. 2018; 18(7): 1783-1789. https://www.ncbi.nlm.nih.gov/pubmed/29509295

- Post Hoc analysis of the BENEFIT and BENEFIT-EXT trials where kidney transplant recipients had the presence or absence of HLA-specific antibodies determined at baseline and at certain time points up to the end of 84 month follow up including times of clinically suspected acute rejection episodes. In this analysis, samples were further tested to determine presence/absence of DSAs and mean fluorescence intensity (MFI)
- In the BENEFIT and BENEFIT EXT trials DSAs developed in a significantly higher amount of cyclosporine treated patients vs. belatacept groups over 7 years in both studies. In patients developing de novo DSAs, belatacept group had a numerically lower MFI vs. cyclosporine group.

Tremblay S et al. (2017) A steady-state head-to-head pharmacokinetic comparison of all FK-506 (tacrolimus) formulations (ASTCOFF): an open label, prospective, randomized, two-arm, three-period crossover study. Am J Transplant. 2017;17(2):432-442. https://www.ncbi.nlm.nih.gov/pubmed/27340950

- An open label single center trial evaluating pharmacokinetics of all three available tacrolimus formulations (IR-Tac, ER-Tac and LCPT). AUC and overall bioavailability were significantly higher for LCPT vs. IR-Tac and ER-Tac formulations. Intraday fluctuations in peak to trough were lower for LCPT vs. IR-Tac and ER-Tac formulations and there were lower concentration peaks. IR-Tac and ER-Tac formulations displayed similar pharmacokinetic profiles. No deaths, episodes of biopsy proven rejection, graft loss or serious adverse events were observed.
- Conversion factors of 1:1:0.80 for IR-Tac:ER-Tac:LCPT were utilized in this study

Trofe-Clark J et al. (2017) Results of ASERTAA, a Randomized Prospective Crossover Pharmacogenetic Study of Immediate-Release Versus Extended-Release Tacrolimus in African American Kidney Transplant Recipients. Am J Kidney Dis. 2017: 71(3); 315-326. https://www.ajkd.org/article/S0272-6386(17)30897-1/fulltext

- Evaluated the relationship between CYP3A5 genotype and AUC of tacrolimus IR vs. LCPT in 50 African American kidney transplant patients in a pharmacokinetic study
- 80% of population were CYP3A5 expressers, no differences in AUC or Cmin when LCPT or IR-Tac was administered, however the Cmax of IR-Tac was 33% higher in expressers vs. non-expressers. This effect was not observed with LCPT, indicating that the delayed absorption profile of LCPT may attenuate risk of peak related side effect.

Budde K et al. (2017) Everolimus with cyclosporine withdrawal or low exposure cyclosporine in kidney transplantation from month 3: a multicenter randomized trial: HERAKLES study group. Nephrol Dial Transplant. 2017:32(6):1060-1070. https://www.ncbi.nlm.nih.gov/pubmed/28605781

- Prospective, randomized, multicenter trial with 499 kidney transplant patients who were randomized at month 3 to remain on standard CNI with cyclosporine (+ MPA), convert to everolimus with MPA or start everolimus with reduced CNI and no MPA.
- eGFR using the Nankivell equation at 12 month was significantly greater in CNI-free arm vs. standard CNI therapy and low CNI group with a mean difference of 5.6 mL/min/1.73 m2 and 5.5 mL/min/1.73 m2 respectively. There were no differences in BPAR between groups.

Adams AB et al. (2017) Belatacept combined with transient calcineurin inhibitor therapy prevents rejection and promotes improved long-term renal allograft function. Am J Transplant. 2017; 17(11): 2922-2936. https://www.ncbi.nlm.nih.gov/pubmed/

- A retrospective analysis of 745 patients undergoing renal transplant and receiving Belatacept compare d to a historical cohort receiving a tacrolimus-based immunosuppression regimen. Patient and graft survival were similar between groups. Belatacept treatment was associated with superior renal function and there were no differences in serious infections. In the early Belatacept groups treated with the regimen from the BENEFIT trial, an increased rate of acute rejection was observed. With the addition of a transient course of tacrolimus, rejection rates reduced and were similar to the historical cohort.

Huh KH et al. (2017). De novo low-dose sirolimus versus mycophenolate mofetil in combination with extended-release tacrolimus in kidney transplant recipients: a multicenter, open-label, randomized, controlled, non-inferiority trial. Nephrol Dial Transplant; 32(8):1415-1424. https://www.ncbi.nlm.nih.gov/pubmed/28810721

- 158 renal transplants randomized to receive low-dose sirolimus or MMF in combination with ER tacrolimus. Low dose sirolimus with ER tacrolimus was not inferior to MMF and ER tacrolimus with respect to safety and efficacy.

Vincenti F. (2017) Ten-year outcomes in a randomized phase II study of kidney transplant recipients administered belatacept 4-weekly or 8-weekly. Am J Transplant. 2017; 17(12): 3219-3227. https://www.ncbi.nlm.nih.gov/pubmed/28758341

- Estimated GFR values 10 years from randomization for 4-weekly belatacept, 8-weekly belatacept, and cyclosporine were 67, 68.7, and 42.7 mL/min per 1.73m2 respectively. The rate of biopsy proven acute rejection was 2 times higher in patients receiving belatacept every 8 weeks compared to every 4 weeks.

Haller MC, Royuela A, Nagler EV, Pascual J, Webster AC. (2016) Steroid avoidance or withdrawal for kidney transplant recipients. Cochrane Database Syst Rev. 2016;(8):CD005632. https://www.ncbi.nlm.nih.gov/pubmed/27546100

- Cochrane review of 48 studies (n=7803 patients) evaluated three different comparisons: steroid avoidance or withdrawal vs. steroid maintenance and steroid avoidance vs. steroid withdrawal.
- No significant difference in mortality or graft loss, but steroid avoidance and withdrawal was associated with significant increase in the risk of acute rejection. Long-term consequences of steroid avoidance and withdrawal remains unclear due to lack of prospective long-term studies.

Thierry A, Lemeur Y, Ecotière L, et al. (2016) Minimization of maintenance immunosuppressive therapy after renal transplantation comparing cyclosporine A/azathioprine or cyclosporine A/mycophenolate mofetil bitherapy to cyclosporine A monotherapy: a 10-year postrandomization follow-up study. Transpl Int. 2016;29(1):23-33. https://www.ncbi.nlm.nih.gov/pubmed/26729582

- Multicenter study of 204 low immunological risk kidney transplant recipients were randomized post-transplantation to receive either cyclosporine (CsA) + azathioprine (AZA), CsA + mycophenolate mofetil (MMF), or CsA monotherapy. At 3 years, the occurrence of biopsy for graft dysfunction was similar in bitherapy and monotherapy groups, P = 0.25. At 10 years, patients' survival, death-censored graft survival, and mean eGFR were similar between

groups. CsA monotherapy after 1 year is safe and associated with prolonged graft survival in low immunological risk kidney transplant recipients.

Durrbach A, Pestana JM, Florman S, et al. (2016) Long-Term Outcomes in Belatacept- Versus Cyclosporine-Treated Recipients of Extended Criteria Donor Kidneys: Final Results From BENEFIT-EXT, a Phase III Randomized Study. Am J Transplant. 2016;16(11):3192-3201. https://www.ncbi.nlm.nih.gov/pubmed/27130868

- Extended criteria donor kidney recipients were randomized to receive belatacept-based (more intense [MI] or less intense [LI]) or cyclosporine-based immunosuppression. Mean eGFR was 53.9, 54.2, and 35.3 mL/min per 1.73 m2 for belatacept MI, belatacept LI and cyclosporine, respectively ($p < 0.001$). Acute rejection rates, graft loss, and death were similar between groups.

Rostaing L, Bunnapradist S, Grinyó JM, et al. (2016) Novel Once-Daily Extended-Release Tacrolimus Versus Twice-Daily Tacrolimus in De Novo Kidney Transplant Recipients: Two-Year Results of Phase 3, Double-Blind, Randomized Trial. Am J Kidney Dis. 2016;67(4):648-59. https://www.ncbi.nlm.nih.gov/pubmed/26717860

- Multicenter, phase 3 non-inferiority trial of 543 de novo kidney recipients randomized to once daily vs. twice daily tacrolimus. Treatment failure (death, transplant failure, biopsy-proven acute rejection, or loss to follow up) and safety (adverse events, serious adverse events, new-onset diabetes, kidney function, opportunistic infections, and malignancies) was similar between the two groups at 24 months.

Vincenti F. (2016) Belatacept and Long-Term Outcomes in Kidney Transplantation. N Engl J Med. 2016;374(26):2600-1. https://www.ncbi.nlm.nih.gov/pubmed/27355541

- 666 renal transplant recipients were randomized to a more-intensive belatacept regimen, a less-intensive belatacept regimen, or a cyclosporine regimen. Seven years after transplantation, patient and graft survival and the mean eGFR were significantly higher with belatacept groups compared with cyclosporine.

Wagner M, et al. (2015) Mycophenolic acid versus azathioprine as primary immunosuppression for kidney transplant recipients. Cochrane Database Syst Rev. 2015;(12):CD007746. https://www.ncbi.nlm.nih.gov/pubmed/26633102

- Cochrane review of 23 studies (n=3301) comparing mycophenolate (MMF) and azathioprine (AZA). MMF reduced the risk for graft loss and any acute rejection, biopsy-proven acute rejection, and antibody-treated acute rejection compared to AZA. No statistically significant difference for MMF versus AZA treatment was found for all-cause mortality.

Xie X, et al. (2015) mTOR inhibitor versus mycophenolic acid as the primary immunosuppression regime combined with calcineurin inhibitor for kidney transplant recipients: a meta-analysis. BMC Nephrol. 2015;16:91. https://www.ncbi.nlm.nih.gov/pubmed/26126806

- Review of 11 randomized controlled trials (n=4930 patients) comparing mTOR to MPA as the primary immunosuppressive regimen in combination with CNI. No significant difference in risk of biopsy-proven acute rejection and patient death between the two groups. However, the mTOR group had increased risk of graft loss and inferior graft function compared to MPA. Patients treated with mTOR had a higher risk of new-onset diabetes mellitus, dyslipidemia, proteinuria, peripheral edema, and thrombocytopenia. MPA group had higher risk of cytomegalovirus infection, malignancy, and leucopenia.

Budde K, Lehner F, Sommerer C, et al. (2015) Five-year outcomes in kidney transplant patients converted from cyclosporine to everolimus: the randomized ZEUS study. Am J Transplant. 2015;15(1):119-28. https://www.ncbi.nlm.nih.gov/pubmed/25521535

- Multi-center study of kidney allograft recipients randomized to continuing cyclosporine (CsA) or converting to everolimus at 4.5 months post-transplant (n=300). At 5 years, adjusted eGFR was 66.2 mL/min/ 1.73m2 with everolimus vs 60.9 mL/min/1.73m2 with CsA; $p<0.001$.

- Cumulative incidence of biopsy-proven acute rejection was 13.6% with everolimus vs. 7.5% with CsA (p< 0.095); although this difference did not affect long-term graft function.
- Conversion to everolimus is associated with a significant improvement in renal function that is maintained to at least 5 years.
- Original ZEUS: https://www.ncbi.nlm.nih.gov/pubmed/25070687

Cantarovich D, Rostaing L, Kamar N, et al. (2014) Early corticosteroid avoidance in kidney transplant recipients receiving ATG-F induction: 5-year actual results of a prospective and randomized study. Am J Transplant. 2014;14(11):2556-64. https://www.ncbi.nlm.nih.gov/pubmed/25243534

- Randomized 197 patients to ≥6-month corticosteroids(CS) or no CS. One- and five-year graft survival (censored for death), freedom from clinical and biopsy-proven rejection, and renal function was similar between both groups. In patients receiving CS, rejections occurred later and with a higher risk for subsequent graft failure, whereas rejections in no-CS patients occurred early after transplantation and did not impair long-term renal function. More CS patients developed diabetes, dyslipidemia and malignancies

Chadban SJ, Eris JM, Kanellis J, et al. (2014) A randomized, controlled trial of everolimus-based dual immunosuppression versus standard of care in de novo kidney transplant recipients. Transpl Int. 2014;27(3):302-11. https://www.ncbi.nlm.nih.gov/pubmed/24279685

- Prospective, multinational, controlled trial randomized 126 de novo kidney transplant recipients to: (1)CNI-withdrawal (WD): cyclosporine +mycophenolate + steroids for the first 14 days then everolimus + mycophenolate; (2)everolimus +mycophenolate (terminated prematurely due to excess discontinuation); (3)Control: cyclosporine + mycophenolate +steroids. Mean eGFR at 1 year for CNI-WD vs control was non-inferior (65.1 ml/min/1.73 m2 vs. 67.1 ml/min/1.73 m2, P = 0.026). CNI-WD group had a higher rate of BPAR (31% vs. control 13%, P = 0.048). At 1 year, CNI-WD was non-inferior in eGFR, but was associated with higher rates of acute rejection.

Lim WH, Eris J, Kanellis J, et al. (2014) A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. Am J Transplant. 2014;14(9):210-19. https://www.ncbi.nlm.nih.gov/pubmed/25088685

- Systematic review of 29 randomized controlled trials comparing delayed conversion of mTOR for CNIs versus CNI continuation in kidney transplantation. Patients converted to mTOR up to 1year post-transplant had higher GFR compared with those remaining on CNI, p < 0.001. However, the risk of rejection at 1 year and discontinuation secondary to adverse events was higher for mTORs.

Masson P, Henderson L, Chapman JR, Craig JC, Webster AC. (2014) Belatacept for kidney transplant recipients. Cochrane Database Syst Rev. 2014;(11):CD010699. https://www.ncbi.nlm.nih.gov/pubmed/25416857

- Cochrane review of five studies (n=1535) comparing belatacept and CNIs. Up to three years following transplant, belatacept and CNI-treated recipients were at similar risk of graft loss, acute rejection, and death. Belatacept is associated with better kidney transplant function, blood pressure and lipid profile and a lower incidence of diabetes versus treatment with a CNI.

Silva HT, Felipe CR, Garcia VD, et al. (2013) Planned randomized conversion from tacrolimus to sirolimus-based immunosuppressive regimen in de novo kidney transplant recipients. Am J Transplant. 2013;13(12):3155-63. https://www.ncbi.nlm.nih.gov/pubmed/24266969

- Multicenter study of 297 patients initially treated with tacrolimus, mycophenolate sodium and prednisone randomized to convert to sirolimus (SRL) or continue with tacrolimus. Planned conversion to SRL at 3 months after kidney transplantation was not associated with improved renal function at 24 months. Higher mean urinary protein-to-creatinine ratio and higher incidence of treated acute rejection was observed in SRL compared to TAC group.

Ho, ET et al. (2013). Once-daily extended-release versus twice-daily standard-release tacrolimus in kidney transplant recipients: a systematic review. Transplantation, 95, 1120-28. http://www.ncbi.nlm.nih.gov/pubmed/23542469.

- Systematic review (6 randomized, controlled trials; 15 observational studies) comparing once-daily to twice-daily tacrolimus in de novo or conversion studies in renal transplant recipients. Once-daily tacrolimus was found to be comparable to standard dosing at 12 months post-transplant with regards to biopsy-proven acute rejection, patient survival, and graft survival.

Rostaing, L et al. (2011). Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study. Clinical Journal of the American Society of Nephrology, 6, 430-9. http://www.ncbi.nlm.nih.gov/pubmed/21051752.

- Conversion from a calcineurin inhibitor-based regimen to belatacept in kidney transplant recipients (≥6 but ≤36 months post-transplant, estimated glomerular filtration rates 35-75 ml/min/1.73m2) improved renal function at 12 months but was associated with a low risk of rejection (7%) that resolved with treatment.

Durrbach, A et al. (2010). A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT Study). American Journal of Transplantation, 10, 547-57. http://www.ncbi.nlm.nih.gov/pubmed/20415898.

- In extended criteria donor (ECD) kidney transplant recipients, de novo belatacept regimens improved renal function at 1 year post-transplant and metabolic endpoints compared to cyclosporine-treated patients with similar patient and graft survival and acute rejection episodes. Belatacept was associated with more cases of post-transplant lymphoproliferative disorders (PTLD), particular in patients that were EBV seronegative.

Vincenti, F et al. (2010). A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT Study). American Journal of Transplantation, 10, 535-46. http://www.ncbi.nlm.nih.gov/pubmed/20415897.

- Kidney transplant recipients (non-ECD or DCD, PRA < 50%, re-transplant PRA < 30%) were randomized to a more intensive (MI) belatacept regimen, less intensive (LI) belatacept regimen, or cyclosporine in addition to basiliximab induction, mycophenolate mofetil, and corticosteroids. Belatacept was associated with superior renal function, lower prevalence of chronic allograft nephropathy, improved metabolic endpoints, and similar patient and graft survival at 1 year post-transplant. Belatacept patients experienced a higher incidence of acute rejection episodes (although rejection defined as histologically-confirmed or treatment based on clinical suspicion).

Schena, FP et al. (2009). Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation, 87, 233-42. http://www.ncbi.nlm.nih.gov/pubmed/19155978.

- Eligible kidney transplant recipients (6 to 120 months post-transplant, receiving a calcineurin inhibitor after transplantation along with corticosteroids and an anti-metabolite, estimated glomerular filtration rate (GFR) > 20 ml/min/1.73m2) were stratified according to their baseline GFR and randomly assigned to either sirolimus conversion or calcineurin inhibitor continuation. At 2 years, patients that remained on sirolimus had higher GFR, particularly in those patients with baseline GFR > 40 ml/min, and there were no differences in rejection episodes, graft survival, or patient survival. Sirolimus discontinuation rates were high and conversion was associated with more treatment-emergent adverse events.

KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. (2009). Supplement 3, Volume 9. http://www.ncbi.nlm.nih.gov/pubmed/19845597

- Guidelines released from the Journal of the American Society of Transplantation (AST) and the American Society of Transplant Surgeons (ASTS). Chapters 2 and 3 describe recommendations for initial and long-term maintenance immunosuppression medications, respectively.

Knight, SR et al. (2009). Mycophenolate mofetil decreases acute rejection and may improve graft survival in renal transplant recipients when compared with azathioprine: a systematic review. http://www.ncbi.nlm.nih.gov/pubmed/19300178.

- Systematic review of mycophenolate mofetil versus azathioprine in calcineurin inhibitor-containing regimens (cyclosporine, cyclosporine microemulsion, tacrolimus). Mycophenolate mofetil significantly reduced the risk of acute rejection episodes regardless of calcineurin inhibitor (RR 0.62, p<0.01), and improved graft survival (RR 0.76, p=0.04).

Vincenti, F et al. (2008). A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. American Journal of Transplantation, 8, 307-16. http://www.ncbi.nlm.nih.gov/pubmed/18211506.

- Non-highly sensitized kidney transplant recipients (first transplant, PRA < 20%, cold ischemia time < 24 hours, non-DCD) were randomized to receive no steroids, steroids until day 7 post-transplant, or standard steroid therapy. Renal function at 12 months was not significantly different; while complete steroid avoidance was associated with significantly higher rates of rejection, similar outcomes were observed with early steroid withdrawal and standard steroid therapy. Early steroid withdrawal may be an option for kidney transplant recipients not at a high rejection risk.

Woodle, ES et al. (2008). A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 days) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Annals of Surgery, 248, 564-77. http://www.ncbi.nlm.nih.gov/pubmed/18936569.

- Non-highly sensitized kidney transplant recipients (PRA < 25%, first transplant, non-DGF) were randomized to receive prednisone or early corticosteroid withdrawal at seven days post-transplant. While there were improvements in cardiovascular outcomes and similar long-term graft survival and function, early corticosteroid withdrawal was associated with an increased risk of rejection episodes.

Ekberg, H et al. (2007). Reduced exposure to calcineurin inhibitors in renal transplantation. New England Journal of Medicine, 357, 2562-75. http://www.ncbi.nlm.nih.gov/pubmed/18094377.

- Evaluation of the safety and efficacy of various immunosuppressive regimens, including standard-dose cyclosporine, standard-dose tacrolimus, low-dose tacrolimus, or low-dose sirolimus, in combination with daclizumab induction, mycophenolate mofetil, and corticosteroids. Renal function and biopsy-proven acute rejection rates were statistically lower in the low-dose tacrolimus group and, moreover, this group experienced the best overall graft survival.

Webster, AC et al. (2005). Tacrolimus versus cyclosporine as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomized trial data. British Medical Journal, 331, 810. http://www.ncbi.nlm.nih.gov/pubmed/16157605.

- Systematic review of tacrolimus versus cyclosporine for initial maintenance immunosuppression. Tacrolimus-treated patients had lower rates of graft loss at 6 months and up to 3 years post-transplant and acute rejection at 12 months post-transplant; however, tacrolimus regimens were associated with more diabetes mellitus requiring insulin, tremor, headache, and GI upset.

Woodle, ES et al. (2005). Multivariate analysis of risk factors for acute rejection in early corticosteroid cessation regimens under modern immunosuppression. American Journal of Transplantation, 5, 2740-44. http://www.ncbi.nlm.nih.gov/pubmed/16212635.

- Risk factors for acute rejection with early corticosteroid withdrawal within 7 days included African American race, DGF, any number of HLA mismatches, PRA > 25%, re-transplantation, Thymoglobulin induction, type 1 diabetes, and deceased donor kidney transplantation.

Halloran, PF et al. (2004). Immunosuppressive drugs for kidney transplantation. New England Journal of Medicine, 351, 2715-29. http://www.ncbi.nlm.nih.gov/pubmed/15616206.

- Review article of the immune response and common immunosuppressive agents used for maintenance and induction therapy in kidney transplantation. Describes the classic three-signal model of T-helper cell activation and the role of immunosuppressants within this response.

Gonwa, T et al. (2003). Randomized trial of tacrolimus + mycophenolate mofetil or azathioprine versus cyclosporine + mycophenolate mofetil after cadaveric kidney transplantation: results at three years. Transplantation, 75, 2048-53. http://www.ncbi.nlm.nih.gov/pubmed/12829910.

- A comparison of initial immunosuppressive regimens in kidney transplant recipients. Patients receiving tacrolimus-based regimens experienced superior renal function at 1 and 3 years; in African Americans and patients with delayed graft function (DGF), the combination of tacrolimus and mycophenolate mofetil was associated with superior graft outcomes.

1.3 Desensitization therapy

Vincenti, F., Bestard, O., Brar, A., Cruzado, J. M., Seron, D., Gaber, A. O., Ali, N., Tambur, A. R., Lee, H., Abbadessa, G., Paul, J.-A., Dudek, M., Siegel, R. J., Torija, A., Semiond, D., Lépine, L., Ternes, N., Montgomery, R. A., & Stegall, M. (2023). Isatuximab Monotherapy for Desensitization in Highly Sensitized Patients Awaiting Kidney Transplant. *Journal of the American Society of Nephrology: JASN*. https://doi.org/10.1681/ASN.0000000000000287

- Single-arm phase I/II study of isatuximab, an anti-CD38 monoclonal antibody approved for relapsed/refractory multiple myeloma, for desensitization in two cohorts, Cohort A with CPRA >99.9% (n=12) and Cohort B with CPRA 80.0-99.9% (n=11).
- 83.3% of Cohort A and 81.8% of Cohort B met the primary outcome of either reduction of CPRA sufficient to double the likelihood of finding a compatible donor, the reduction >2 antibody titers to reach target CPRA, or the elimination of anti-HLA antibody to MFI <2000. However, the clinical significance of this is unclear as only 39% of patients had CPRA reductions to target levels.

Wilson, N., Reese, S., Ptak, L., Aziz, F., Parajuli, S., Jucaud, V., Denham, S., Mishra, A., Cascalho, M., Platt, J. L., Hematti, P., & Djamali, A. (2023). Ixazomib for Desensitization (IXADES) in Highly Sensitized Kidney Transplant Candidates: A Phase II Clinical Trial. *Kidney360*, *4*(6), e796–e808. https://doi.org/10.34067/KID.0000000000000113

- Phase II, open-label study of 12 monthly cycles of ixazomib, an oral second-generation proteasome inhibitor approved for refractory multiple myeloma in desensitization of kidney transplants candidates with CPRA >80% who have been on the waiting list for > 24 months.
- While immunodominant alloantibody MFIs declined for some subjects, there was no significant decline in CPRA after treatment with ixazomib. 2 of 10 patients were transplanted by the end of follow-up.

Couzi L, Malvezzi P, Amrouche L, et al. Imlifidase for Kidney Transplantation of Highly Sensitized Patients With a Positive Crossmatch: The French Consensus Guidelines. *Transpl Int*. 2023;36:11244. 10.3389/ti.2023.11244

- French Consensus guidelines for the desensitization of highly-sensitized KTRs with imlifidase, which has recently gained early access authorization in the EU.
- This group recommends that imlifidase be considered in patients with a cPRA ≥ 98% (due to low likelihood of transplantation), age ≤ 65 years (due to increased infectious risk), ≥ 3 years on the waiting list, ≤ 2 prior kidney transplants, and at low risk of biopsy-related complications.
- Eligible patients may receive imlifidase only if the dominant DSAs have an MFI >6000 but <5000 after 1:10 dilution. A post imlifidase (4-6h after infusion) CDCXM must be negative prior to proceeding with transplant.
- Imlifidase should be considered only after exhausting other strategies, like living donors, paired donation, and delisting unacceptable HLA antigens for which antibodies have disappeared or have low-level MFIs.
- While imlifidase does not cleave horse IgG, it does cleave rabbit IgG, and so rATG must be separated from imlifidase by 96 hours.

Vo, et al (2022). Clazakizumab for desensitization in highly sensitized patients awaiting transplantation. *Am J Transplant*. 22(4):1133-1144. https://pubmed.ncbi.nlm.nih.gov/34910841/

- A single-center, phase 2, open-label, single-arm exploratory study exploring the safety and limited efficacy of clazakizumab, a humanized anti-IL-6 monoclonal antibody, on highly sensitized patients (cPRA ≥ 50%) awaiting kidney transplant
- Highly sensitized patients (n=20) received PLEX, IVIg, and clazakizumab 25 mg monthly for 6 months
- Clazakizumab was well tolerated and associated with significant reductions in class I and II donor specific antibodies (DSA) in 18 out of 20 patients with low incidence of DSA rebound. Three patients experienced an antibody-medicated rejection. At 12 months, patient survival was 100% and there was one case of graft loss due to surgical complications.

NasrAllah, et al (2022). Obinutuzumab in Kidney Transplantation: Effect on B-cell Counts and Crossmatch Tests. *Transplantation*, 106(2):369-372. https://pubmed.ncbi.nlm.nih.gov/33577249/

- A retrospective, single-center trial comparing Obinutuzumab vs standard of care (Rituximab) on the effect of B-cell depletion and impact on crossmatch results in highly sensitized kidney transplant candidates (n=8) or kidney transplant recipients presenting with antibody-mediated rejection (n=4)
- Obinutuzumab effectively depleted B-lymphocytes in highly sensitized kidney transplant candidates and had no effect on the CDC crossmatch test results as opposed to rituximab

Jordan, et al. (2021). Imlifidase desensitization in crossmatch-positive highly sensitized kidney transplant recipients: results of an international phase 2 trial (Highdes). *Transplantation*. 2021; 105(8): 1808-1817. https://pubmed.ncbi.nlm.nih.gov/33093408/

- Open-label, single-arm, phase 2 trial at 5 transplant centers to evaluate if 24-hour negative crossmatch occurred with median cPRA of 99.83%
- Conversion of positive to negative crossmatch occurred in 89.5% of transplants with varying occurrences of donor-specific antibodies that rebounded 3-14 days post-dose. Patient survival was 100% and graft survival was 88.9% with 38.9% BPAR with 2-19 days onset post-transplant.
- Overall, this enabled patients with high cPRA to successfully undergo transplant

Kjellman, et al. (2021). Outcomes at 3 years post-transplant in imlifidase-desensitized kidney transplant patients. *Am J Transplant*. 2021. https://pubmed.ncbi.nlm.nih.gov/34236770/

- AMR occurred in 38% of patients within the first month. Comparing AMR+ to AMR-, allograft survival was 93% vs 77% and patient survival was 85% vs 94% with higher eGFR in the AMR- group (49 vs 61 ml/min/1.73m^2)
- Confirms that imlifidase is an option for patients with significant immunologic barriers to undergo a successful kidney transplant

Jouve, et al. (2021). Immune responses following tocilizumab therapy to desensitize HLA-sensitized kidney transplant candidates. *Am J Transplant*. 2021. https://pubmed.ncbi.nlm.nih.gov/34080291/

- A single-center prospective study with 13 highly sensitized (cPRA >95%) with well-tolerated results in all but one patient who presented with spondylodiscitis
- No difference in percent of lymphocyte subsets and Tfh cell subsets, but a significant increase in naïve B-cells, IL-6 levels, and sIL-65R; and significant decrease in plasmablasts
- Minimal effect on anti-HLA antibodies (class I and II)

Sasaju, et al. (2021). Long-term outcome of ABO-incompatible kidney transplantation in patients treated with low-dose rituximab regimen. *Transplant Proc*. 2021; 53(3): 989-994. https://pubmed.ncbi.nlm.nih.gov/33272650/

- 10-year follow up of patients who received rituximab or underwent splenectomy
- Patient and graft survival was similar with rates between 94-95%, and similar AMR rates of 10.2% vs. 12.5%; of those who with AMR 3 lost their grafts (1 rituximab and 2 splenectomy)
- Patients who underwent splenectomy had higher rates of cytomegalovirus and incidences of late-onset neutropenia

Tremblay, et al. (2020) A prospective, iterative, adaptive trial of carfilzomib-based desensitization. American Journal of Transplantation. 2020; 20(2), 411-421. https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.15613

- This prospective, non-randomized study evaluated the efficacy of carfilzomib for desensitization in 16 highly sensitized kidney transplant candidates. KTR in group A received 12 increasing doses of carfilzomib from 20 mg/m2 to 36 mg/m2, preceded by 50 – 100 mg methylprednisolone. Following the last carfilzomib dose, patients underwent 3 sessions of plasmapheresis. KT candidates in group B received the same regimen with additional plasmapheresis once weekly prior to carfilzomib.
- The safety profile of carfilzomib was found to be similar to bortezomib, but neurotoxicity was not present with carfilzomib. There was a significant reduction in HLA immunodominant antibodies in group A. Rebound occurred, with antibody levels returning to baseline values at days 81 and 141. 69.2% of bone-marrow plasma cells were depleted following carfilzomib monotherapy.

Lonze, et al. (2018). IdeS (Imlifidase): A novel agents that cleaves human IgG and permits successful kidney transplantation across high-strength donor-specific antibody. Ann Surg; 268(3):488-496. https://www.ncbi.nlm.nih.gov/pubmed/20004918

- Single-center experience with 7 highly sensitized kidney transplant candidates with positive crossmatches who received IdeS prior to transplant.
- All crossmatches became negative. 3 patients had DSA rebound and AMR, which was treated. 3 had delayed graft function that resolves. At the 235 day follow-up mark, all had functioning allografts.

Jordan, et al. (2017). IgG Endopeptidase in highly sensitized patients undergoing transplantation. N Engl J Med; 377(5):442-453. https://www.ncbi.nlm.nih.gov/pubmed/28767349

- IdeS was administered to 25 highly sensitized patients before receiving a kidney from a HLA-incompatible donor.
- IdeS was found to reduce/eliminate donor specific antibodies in 24 of 25 patients. Antibody mediated rejection occurred in 10 patients, but all responded to treatment. There was one graft loss due to non-HLA antibodies.

Jeong, et al. (2016) Desensitization Using Bortezomib and High-dose Immunoglobulin Increases Rate of Deceased Donor Kidney Transplantation. Medicine (Baltimore). 2016;95(5):e2635. https://www.ncbi.nlm.nih.gov/pubmed/26844479

- Prospective, open-label clinical trial of 36 patients comparing rate of DDRT between sensitized patients; IVIG (2 g/kg x 2 doses), rituximab (375 mg/m2 x 1 dose), bortezomib (1.3 mg/m2 x 4 doses) vs. control (no desensitization).
- Multivariate time-varying covariate Cox regression analysis showed that desensitization increased the probability of DDRT (hazard ratio, 46.895; 95% confidence interval, 3.468–634.132; P=0.004).
- Desensitization was well tolerated, and acute rejection occurred only in the control group.

Vo, et al. (2014) Benefits of rituximab combined with intravenous immunoglobulin for desensitization in kidney transplant recipients. Transplantation. 2014;98(3):312-9. https://www.ncbi.nlm.nih.gov/pubmed/24770617

- Renal transplant recipients (n=13) were randomized to IVIG + placebo versus IVIG + rituximab

- No significant differences were seen in DSA levels at transplant. ABMR episodes and DSA rebound occurred in the IVIG+placebo group 43% vs 0% in IVIG + rituximab group, P=0.06. Renal function at 6 and 12 months showed a significant benefit for IVIG + rituximab, P=0.04.
- IVIG + rituximab appeared more effective in preventing DSA rebound, ABMR and development of transplant glomerulopathy.

Vo, et al. (2013). Efficacy, outcomes, and cost-effectiveness of desensitization using IVIG and rituximab. Transplantation, 95(6), 852-8. http://www.ncbi.nlm.nih.gov/pubmed/23511212.

- 71% of sensitized patients were transplanted using the desensitization protocol of IVIG 2 g/kg x 2 doses plus rituximab 1 g
- Each transplanted patient saved the U.S. healthcare system an estimated $18,753 as compared to remaining on dialysis

Bentall, et al. (2013). Five-year outcomes in living donor kidney transplants with a positive crossmatch. American Journal of Transplantation, 13 (1), 76-85. http://www.ncbi.nlm.nih.gov/pubmed/23072543.

- Actual 5-year death-censored graft survival was lower in positive crossmatch kidney transplant recipients versus negative crossmatch kidney transplant recipients (70.7% vs. 88.0%, p<0.01); transplant glomerulopathy was present in 54.5% of surviving grafts
- Graft survival was higher in recipients with antibody against donor class I only compared to antibody against class II, alone or in combination with class I (85.3% vs. 62.6%, p=0.05)

Huber, et al. (2012) Identification and therapeutic management of highly sensitized patients undergoing renal transplantation. Drugs, 72, 1335-54. http://www.ncbi.nlm.nih.gov/pubmed/22747448.

- A thorough review regarding the management of highly sensitized patients undergoing renal transplantation

Montgomery, et al. (2011). Desensitization in HLA-incompatible kidney recipients and survival. New England Journal of Medicine, 365, 318-26. http://www.ncbi.nlm.nih.gov/pubmed/21793744.

- 8-year Kaplan-Meier estimates of patient survival greater for desensitization treatment vs. dialysis-only and dialysis-or-transplantation (80.6% vs. 30.5% or 49.1%, p<0.001)

Marfo, et al (2011). Desensitization protocols and their outcome. Clinical Journal of the American Society of Nephrology, 6, 922-936. http://www.ncbi.nlm.nih.gov/pubmed/21441131.

- In-depth review of desensitization treatment modalities and clinical outcomes of various protocols

Stegall, et al. (2011). Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. American Journal of Transplantation, 11, 2405-13. http://www.ncbi.nlm.nih.gov/pubmed/21942930.

- Eculizumab (1200 mg POD 0, 600 mg POD 1, and then 600 mg weekly for 4+ weeks) used for prevention of AMR in positive crossmatch living-donor kidney transplant recipients resulted in AMR in 7.7% at 3 months vs. 41.2% among historical controls
- One-year protocol biopsy showed transplant glomerulopathy in 6.7% of eculizumab-treated recipients vs. 35.7% of control patients (p=0.044)

Montgomery RA (2010). Renal transplantation across HLA and ABO antibody barriers: integrating paired donation into desensitization protocols. American Journal of Transplantation, 10, 449-57. http://www.ncbi.nlm.nih.gov/pubmed/20121749.

- Review of kidney transplantation options for sensitized patients by integrating paired donation with desensitization protocols

Lefaucheur, et al (2010). Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. Journal of American Society of Nephrology, 21, 1398-406. http://www.ncbi.nlm.nih.gov/pubmed/20634297.

- 8-year graft survival significantly worse (61%) among patients with pre-existing HLA-DSA compared with both sensitized patients without HLA-DSA (93%) and non-sensitized patients (84%)

- Patients with MFI >6000 had >100-fold higher risk for AMR than patients with MFI <465

Lemy, et al (2010). Bortezomib: a new player in pre- and post-transplant desensitization? Nephrology Dialysis Transplantation, 25, 3480-9. http://www.ncbi.nlm.nih.gov/pubmed/20826741.
- Review of the use of bortezomib as part of a desensitization protocol

Akalin, et al. (2008). Addition of plasmapheresis decreases the incidence of acute antibody-mediated rejection in sensitized patients with strong donor-specific antibodies. Clinical Journal of the American Society of Nephrology, 2008, 3, 1160-7. http://www.ncbi.nlm.nih.gov/pubmed/18337549.
- In CDC and/or flow cytometry crossmatch positive kidney transplant recipients receiving induction of thymoglobulin 1.5 mg/kg daily for five days plus high-dose IVIG (1 g/kg during transplant and 500 mg/kg POD 1 and 2), 66% of those with strong (MFI > 6000) DSA had acute rejection whereas 0% of those with weak-moderate (>1500-5999) DSA had acute rejection
- Subsequently, recipients with strong DSA also received peri-transplant plasmapheresis (4-8 sessions prior to transplant) until DSA reduced to weak-moderate, resulting in reduction of acute rejection to 7%

Burns, et al. (2008). Alloantibody levels and acute humoral rejection early after positive crossmatch kidney transplantation. American Journal of Transplantation, 8, 2684-94. http://www.ncbi.nlm.nih.gov/pubmed/18976305.
- AMR occurs at a wide spectrum of baseline DSA as determined by T- and B-cell flow cytometry crossmatch levels, including those associated with a negative T-cell AHG crossmatch
- Risk of AMR generally increases with increasing baseline DSA, but is unpredictable

Vo, et al. (2008). Rituximab and intravenous immune globulin for desensitization during renal transplantation. New England Journal of Medicine, 359, 242-51. http://www.ncbi.nlm.nih.gov/pubmed/18635429.
- Desensitization with high-dose IVIG 2 g/kg on days 0 and 30 plus rituximab 1 g on days 7 and 22 resulted in significant reduction of mean panel reactive antibody (77 ± 19% before to 44 ± 30% after, $p<0.001$)
- 16 of 20 (80%) patient received a transplant and patient and graft survival at 12 months were 100% and 94%, respectively

Stegall, et al. (2006). A comparison of plasmapheresis versus high-dose IVIG desensitization in renal allograft recipients with high levels of donor specific alloantibody. American Journal of Transplantation, 2006, 346-51. http://www.ncbi.nlm.nih.gov/pubmed/16426319.
- A negative crossmatch was achieved in 38% of patients receiving high-dose IVIG, 84% of patients receiving low-dose IVIG, plasmapheresis, and rituximab, and 88% of patients receiving low dose IVIG, plasmapheresis, rituximab, and pre-transplant Thymoglobulin combined with post-transplant DSA monitoring
- Even with a negative crossmatch, rejection rates were 80% vs. 37% vs. 29%, respectively ($p<0.05$, high-dose IVIG vs. low-dose IVIG, plasmapheresis, and rituximab)
- Multiple plasmapheresis treatment sessions leads to more reproducible desensitization and lower rates of AMR

Jordan, et al. (2004). Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IGO2 trial. Journal of American Society of Nephrology, 15, 3256-62. http://www.ncbi.nlm.nih.gov/pubmed/15579530.
- IVIG 2 g/kg monthly for 4 months significantly reduces PRA levels after one year
- More patients who received IVIG were transplanted and subsequently developed rejection as compared to those receiving placebo

Jordan, et al. (2003) Intravenous immune globulin treatment inhibits crossmatch positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients. Transplantation, 76(4):631-636. http://www.ncbi.nlm.nih.gov/pubmed/12973100.

- Discusses the use of IVIG to decrease or eliminate cross match positivity and allow for successful transplantation.

Glotz, et al. (2002). Desensitization and subsequent kidney transplantation of patients using intravenous immunoglobulins (IVIG). American Journal of Transplantation, 2002, 2, 758-60. http://www.ncbi.nlm.nih.gov/pubmed/12243496.

- Desensitization with 3 monthly courses of IVIG 2 g/kg resulted in a transplantation rate of 87% (13/15)
- One graft was lost due to thrombosis and one due to rejection at one year follow up

1.4 Management of rejection

Lionet, A., Van Triempon, M., Figeac, M., Fages, V., Gibier, J. B., Provot, F., Maanaoui, M., Pottier, N., Cauffiez, C., & Glowacki, F. (2024). Extracorporeal Photopheresis Reduces Fibrotic and Inflammatory Transcriptomic Biological Marker of Chronic Antibody-mediated Kidney Rejection. *Transplantation direct*, *10*(3), e1587. https://doi.org/10.1097/TXD.0000000000001587

- Retrospective, single-center case series of 8 kidney transplant recipients investigating the effects of extracorporeal photopheresis (ECP) in biopsy-proven chronic antibody-mediated rejection (cABMR)
- Mean duration of ECP treatment was 3.9 months w, receiving on average 23 total sessions
- Renal function remained stable after ECP for 3 patients, decreased for 1 patient, and increased for 4 patients
- Comparison of microvascular inflammation scores on biopsies before and after treatment showed an improvement in 5, stability in 1 patient and a worsening in 2 patients
- Transcriptomic analysis of the graft biopsies identified a significant ($p<0.05$) increase in CAV1 mRNA (antifibrotic biologic marker) in all patients and a significant decrease in CD19, IL21, PAX5, and SFTPA2 mRNAs (fibrotic and inflammatory biological markers) in 7 of 8 patients.

Moein, M., Gao, S. X., Martin, S. J., Farkouh, K. M., Li, B. W., Ball, A. S., Dvorai, R. H., & Saidi, R. F. (2023). Conversion to Belatacept in kidney transplant recipients with chronic antibody-mediated rejection (CAMR). *Transplant Immunology*, *76*, 101737. https://doi.org/10.1016/j.trim.2022.101737

- Retrospective analysis of 48 patients diagnosed with chronic antibody-mediated rejection comparing those who had been converted to belatacept (n=19) vs those who had not (n=29)
- Preservation of kidney function did not differ between groups. One patient in each group had biopsy-proven acute rejection and there was no difference in de novo DSA formation (12.5% in belatacept group vs 15%, P=0.90).

Boonpheng, B., De Castro, I. C. C., Ng, Y.-H., Blosser, C., Bakthavatsalam, R., Gimferrer, I., Smith, K., & Leca, N. (2023). Tocilizumab for treatment of chronic active antibody-mediated rejection in kidney transplant recipients. Clinical Transplantation, 37(5), e14936. https://doi.org/10.1111/ctr.14936

- 11 adult KTRs with biopsy-proven chronic antibody-mediated rejection and preserved kidney function (eGFR 57 ± 18) were treated with monthly tocilizumab
- Patients treated with tocilizumab had significant reductions in dd-cfDNA of 29% (p=0.05) at 6 months and 47% (P=0.047) at 12 months compared to baseline. In those with DSAs at baseline, DSAs were reduced by 29% at 12 months (P=0.047). No graft loss was experienced, but two patients had moderate to severe infections.

Jordan, S. C., Ammerman, N., Choi, J., Huang, E., Najjar, R., Peng, A., Sethi, S., Sandhu, R., Atienza, J., Toyoda, M., Ge, S., Lim, K., Gillespie, M., Zhang, X., Haas, M., & Vo, A. (2022). Evaluation of Clazakizumab (Anti–Interleukin-6) in Patients With Treatment-Resistant Chronic Active Antibody-

Mediated Rejection of Kidney Allografts. *Kidney International Reports*, 7(4), 720–731. https://doi.org/10.1016/j.ekir.2022.01.1074

- Phase 2, open-label study of monthly subcutaneous clazakizumab in patients with biopsy proven chronic antibody-mediatred rejection.
- Patient's treated with clazakizumab had stabilization of eGFR at 12 and 24 months with reductions in g+ptc and C4d scores on biopsy. 2 graft losses occurred, both in patients who had discontinued clazakizumab therapy.

Heo S, Park Y, Lee N, et al. Lack of Efficacy and Safety of Eculizumab for Treatment of Antibody-Mediated Rejection Following Renal Transplantation. *Transplantation Proceedings*. 2022;54(8):2117-2124. doi:10.1016/j.transproceed.2022.08.008

- Multicenter, open-label, prospective, randomized trial that compared eculizumab to standard of care (PLEX and IVIG) for the treatment of antibody-mediated rejection in KTRs. 7 patients received eculizumab and 4 received standard of care.
- With 12 months of follow-up, eculizumab did not appear to be effective at treating AMR. 2 of 4 standard of care patients and 0 of 12 eculizumab patients experienced reversal of rejection. No patient in either group experienced graft loss.
- Though no statistical analysis was performed, the strength of DSA titers generally decreased after treatment in both groups.

Sood, et al (2021). Kidney allograft rejection: diagnosis and treatment practices in USA - A UNOS survey. *Clin Transplant*. 2021; 35(4): e14225. https://pubmed.ncbi.nlm.nih.gov/33455009

- Web-based questionnaire distributed to nephrologists and transplant surgeons on immunosuppression management
- Response rate of 37% (104 responses from 88/235 programs) with thymoglobulin (84%) as the most common induction, 67% of responders using belatacept maintenance immunosuppression, and 72% with rapid steroid withdrawal protocols
- All responders use indication biopsies for T-cell mediated rejection and 99% for antibody mediated rejection with wide variations in occurrence of protocol and biomarker driven biopsy. Common treatments for TCMR included IV/PO steroids and PP/IVIG for ABMR. Use of rituximab, bortezomib, and eculizumab increased for recurrent ABMR compared to C4D+ ABMR. Harmonization of practice management for rejection is needed.

Kumar, et al (2021). Impact of belatacept conversion on renal function, histology, and gene expression in kidney transplant patients with chronic active antibody-mediated rejection. *Transplantation*. 2021; 105(3): 660-667. https://pubmed.ncbi.nlm.nih.gov/32510913/

- Single-center study of 19 patients with biopsy-proven chronic active antibody-mediated rejection converted to belatacept with 90 day tacrolimus taper. Median time to conversion was 44 months (range 5-141 months).
- At average 29 month follow-up (IQR 16-46), 89% graft survival and 95% patient survival occurred
- Compared to a propensity-matched INSERM U970 registry, patients converted to belatacept had significant improvement in eGFR post-conversion (33.9 at baseline to 38.5 at 12 months), while control therapy had a decline in eGFR. No difference in biopsy results.

Massat, et al (2021). Do anti-IL-6R blockers have a beneficial effect in the treatment of antibody-mediated rejection resistant to standard therapy after kidney transplantation? *Am J Transplant*. 2021; 21(4): 1641-1649.https://pubmed.ncbi.nlm.nih.gov/33141487/

- Monthly tocilizumab was given to patients with AMR resistant to apheresis, rituximab, and IVIg with no difference in graft survival or renal function and overall did not alter the AMR course

Bailly, et al. (2020) An extension of the RITUX-ERAH study, multicenter randomized clinical trial comparing rituximab to placebo in acute antibody-mediated rejection after renal transplantation. Transplant International 2020. https://www.ncbi.nlm.nih.gov/pubmed/32279367

- 7 year outcomes of the RITUX-ERAH study (11 patients received placebo and 27 patients with ≥ 1 dose of rituximab)
- Death-censored kidney allograft survival and renal function not significantly different between the groups
- Similar development of anti-HLA sensitization in both groups
- NS difference in neoplastic complications but 7 cancers in 6 patients s/p rituximab

Pottebaum, et al. (2020) Efficacy and Safety of Tocilizumab in the Treatment of Acute Active Antibody Mediated Rejection in Kidney Transplant Recipients. Transplantation Direct 2020; 6(4). https://www.ncbi.nlm.nih.gov/pubmed/32309629

- Single-center, observational study of kidney transplant recipients s/p ≥ 1 dose tocilizumab for acute AMR
- 7 patients received tocilizumab 8 mg/kg (max dose 800 mg) monthly, leading to ≥ 50% reduction in immunodominant DSAs in 4/6 patients
- Stabilization of renal function during therapy
- Extended follow-up: 1 patient with mixed rejection and 2 patients with ACR 6-24 mos s/p tocilizumab

Marks, et al. (2019) Safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in living-donor kidney transplant recipients requiring desensitization therapy: A randomized trial. American Journal of Transplantation 2019; 19(10), 2876-2888. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6790671/

- Phase 2, randomized, multicenter, open-label, double-arm study
- Evaluated the safety and efficacy of eculizumab in for prevention of AMR in sensitized recipients of living donor kidney transplants
- Post-transplant 51 patients received standard of care (PLEX/IVIg) and 51 patients received eculizumab
- Eculizumab dosing: 1200 mg immediately before reperfusion; 900 mg on post-transplant days 1, 7, 14, 21, and 28; and 1200 mg at weeks 5, 7, and 9
- Significantly decreased treatment failure inclusive of grade I AMR in eculizumab (11.8%) vs. standard of care (29.4%) groups

Tan, et al. (2019) Use of Eculizumab for Active Antibody-mediated Rejection That Occurs Early Post kidney Transplantation: A Consecutive Series of 15 Cases. Transplantation 2019; 103(11), 2397-2404. https://journals.lww.com/transplantjournal/Fulltext/2019/11000/Use_of_Eculizumab_for_Active_Antibody_mediated.34.aspx

- This observational retrospective study of kidney transplant recipients investigated the role of eculizumab for AMR treatment within the first 30 days post-transplant
- 15 patients with AMR (13/15 biopsy-proven AMR) treated with eculizumab + plasmapheresis
- Within 1 week of eculizumab treatment, eGFR significantly increased and persistent AMR in 16.7% at 4-6 months

Glotz, et al. (2019) Safety and efficacy of eculizumab for the prevention of antibody-mediated rejection after deceased-donor kidney transplantation in patients with preformed donor-specific antibodies. American Journal of Transplantation 2019; 19(10), 2865-2875. https://www.ncbi.nlm.nih.gov/pubmed/31012541

- Open-label, single-arm trial to determine safety and efficacy of eculizumab in prevention AMR in deceased-donor kidney transplants with preformed DSA
- Eculizumab dosing: 1200 mg immediately before reperfusion; 900 mg on post-transplant days 1, 7, 14, 21, and 28; and 1200 mg at weeks 5, 7, and 9

- Treatment failure rate (composite of biopsy-proved grade II/III AMR (Banff 2007 criteria), graft loss, death, or loss to follow-up) by 9 weeks post-transplant significantly lower with eculizumab (8.8%) versus standard of care (40%)
- Patient and graft survival rates 91.5% and 83.4% in cohort

Schinstock, et al. (2019) Long-term outcomes of eculizumab-treated positive crossmatch recipients: Allograft survival, histologic findings, and natural history of the donor-specific antibodies. American Journal of Transplantation 2019; 19(6), 1671-1683. https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.15175

- This observational, retrospective study determined long-term outcomes of eculizumab-treated positive crossmatch kidney transplant recipients vs. positive cross-match and negative cross-match controls
- Death-censored allograft survival rates similar in both positive cross-match groups but significantly reduced vs. negative cross-match controls
- Eculizumab-treated group:
    - 57.9% allografts developed chronic AMR
    - Death-censored allograft survival 76.6% at 5 years and 75.4% at 7 years
    - IgG3, BFXM $\geq$ 300, and C1q positivity associated with allograft loss

Schinstock, et al. (2019) Recommended Treatment for Antibody-mediated Rejection After Kidney Transplantation: The 2019 Expert Consensus From the Transplantion Society Working Group. Transplantation, 104(5), 911-922. https://journals.lww.com/transplantjournal/Fulltext/2020/05000/Recommended_Treatment_for_Antibody_mediated.11.aspx?context=LatestArticles

- The pre-publication TTS guidelines for management of AMR in kidney transplant recipients describes consensus recommendations for appropriate treatment of active and chronic AMR. Treatment recommendations are based on expert opinion, as well as evidence that is currently available in kidney transplant

Choi, et al. (2017). Assessment of Tocilizumab (Anti–Interleukin-6 Receptor Monoclonal) as a Potential Treatment for Chronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients. American Journal of Transplantation, 17(9): 2381-2389. https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.14228

- Tocilizumab patients demonstrated graft survival and patient survival rates of 80% and 91% at 6 years. Significant reductions in DSAs and stabilization of renal function were seen at 2 years.

Moresco, et al. (2017). Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: A multicenter, prospective, randomized, double-blind clinical trial. American Journal of Transplantation, 18(4): 927-935. https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.14520

- Multicenter, prospective, randomized, placebo-controlled, double-blind trial to evaluate efficacy and safety of intravenous immunoglobulins (IVIG) combined with rituximab (RTX)
- The combination of IVIG and RTX is not useful in patients displaying transplant glomerulopathy and DSA

Sautenet, Blancho, Büchler, et al. (2016) One-year Results of the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation: RITUX ERAH, a Multicenter Double-blind Randomized Placebo-controlled Trial. Transplantation. 2016;100(2):391-9. https://www.ncbi.nlm.nih.gov/pubmed/26555944

- Multicenter, double-blind, placebo-controlled trial, randomized 38 patients with biopsy proven AMR to receive rituximab (375 mg/m2) or placebo at day 5. All patients received PE, IVIg, and CS. Primary endpoint (composite of graft loss or no improvement in renal function at day 12) frequency was similar in both groups. Both groups showed improved histological features of AMR

and decreased mean fluorescence intensity of donor-specific antibodies. This study was underpowered, but concluded that rituximab had no additional benefit in patients for AMR.

Montgomery, et al. (2016) Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study. Am J Transplant. 2016:16(12);3468-3478. https://www.ncbi.nlm.nih.gov/pubmed/27184779

- Phase 2B randomized placebo-controlled pilot study evaluating human plasma derived C1-esterase inhibitor (C1 INH) vs. placebo in 18 patients.
- The primary end point of a difference between groups in day 20 pathology or graft survival was not achieved, however the C1 INH group had a trend toward sustained improvement in renal function. There were no graft losses, deaths or serious study drug related ADE.

Kim, Martin, Townsend, Gabardi, et al. (2014) Antibody-mediated rejection in kidney transplantation: a review of pathophysiology, diagnosis, and treatment options. Pharmacotherapy. 2014;34(7):733-44. https://www.ncbi.nlm.nih.gov/pubmed/24753207

- Review of the standard of care for AMR, including; plasmapheresis, intravenous immunoglobulin, rituximab and alemtuzumab, bortezomib, and eculizumab

Cooper, et al. (2014) High dose intravenous immunoglobulin therapy for donor-specific antibodies in kidney transplant recipients with acute and chronic graft dysfunction. Transplantation. 2014;97(12):1253-9. https://www.ncbi.nlm.nih.gov/pubmed/24937199

- Retrospective analysis of 28 kidney transplant recipients with de novo DSA and graft damage (chronic graft dysfunction or AMR) given standard regimen of high-dose (5 g/kg) IVIG dosed over 6 months. High-dose IVIG resulted in modest DSA MFI reductions in patients with previous graft damage, mostly class I DSA in patients with AMR. There was no clinical benefit in patients with chronic graft damage, whereas high-dose IVIG may reduce the risk of chronic graft dysfunction in those with an acute AMR event.

Eskandary, Bond, Schwaiger, et al. (2014) Bortezomib in late antibody-mediated kidney transplant rejection (BORTEJECT Study): study protocol for a randomized controlled trial. Trials. 2014;15:107. https://www.ncbi.nlm.nih.gov/pubmed/24708575

- Single center study of intravenous bortezomib on the course of late AMR randomized 44 patients to two cycles of bortezomib (4 × 1.3 mg/m2 over 2 weeks; 3-month interval between cycles) vs. placebo. Primary end point will be the course of eGFR over 24 months. Secondary endpoints will be DSA levels, protein excretion, measured glomerular filtration rate, transplant and patient survival, and the development of acute and chronic morphological lesions in 24-month protocol biopsies.
- Results: To be determined (24 month follow-up study)

van den Hoogen, et al. (2013). Treatment of steroid-resistant acute renal allograft rejection with alemtuzumab. American Journal of Transplantation, 13, 192-6. http://www.ncbi.nlm.nih.gov/pubmed/23167538.

- Comparison of steroid-resistant kidney rejection of patients treated with alemtuzumab (15-30 mg subcutaneously on two subsequent days) vs. previous patients treated with rATG (2.5-4.0 mg/kg IV for 10-14 days), in which similar incidence of treatment failure was observed (27% vs. 40%, p=0.70)
- More infusion-related side-effects were observed in rATG treated patients (27% vs. 85%, p=0.013)

Joudeh, et al (2013). Pathologic basis of antibody-mediated organ transplant rejection: from pathogenesis to diagnosis. Current Opinion in Organ Transplantation, 18(4), 478-85. http://www.ncbi.nlm.nih.gov/pubmed/23838653.

- Review of the diagnosis and pathogenesis of acute and chronic AMR

Waiser, et al. (2012). Comparison between bortezomib and rituximab in the treatment of antibody-mediated renal allograft rejection. Nephrology Dialysis Transplantation, 27, 1246-51. http://www.ncbi.nlm.nih.gov/pubmed/21852274.

- Kidney transplant recipients with AMR treated with bortezomib (1.3 mg/m2 x 4 doses) compared to historical patients treated with rituximab (500 mg x 1 dose); all recipients treated with plasmapheresis (6 sessions) and IVIG 30 g after last plasmapheresis
- 9 months after treatment renal function was superior in the bortezomib group (SCr: 2.5 ± 0.6 vs. 5.1 ± 2.1, p=0.0008)
- 18 months after treatment, graft survival was superior in the bortezomib group (6/10 vs. 1/9, p=0.071)

Levine, et al. (2012). Treatment options and strategies for antibody mediated rejection after renal transplantation. Seminars in Immunology, 24, 136-42. http://www.ncbi.nlm.nih.gov/pubmed/21940179.

- In-depth review of AMR and treatment modalities

Mengel, et al. (2012). Banff 2011 meeting report: new concepts in antibody-mediated rejection. American Journal of Transplantation, 12, 563-70. http://www.ncbi.nlm.nih.gov/pubmed/22300494.

- Updates from the 2011 Banff meeting, with a focus on refining criteria for AMR

Roberts, et al. (2012). The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. Transplantation, 94, 775-83. http://www.ncbi.nlm.nih.gov/pubmed/23032865.

- Systematic review of heterogeneous studies examining the treatment of acute AMR

Puttarajappa, et al. (2012). Antibody-mediated rejection in kidney transplantation: a review. Journal of Transplantation, 193724. http://www.ncbi.nlm.nih.gov/pubmed/22577514.

- Review of histopathological and clinical manifestations of AMR, as well as treatment modalities

Jordan, et al. (2011). Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. American Journal of Transplantation, 2011, 11, 196-202. http://www.ncbi.nlm.nih.gov/pubmed/21219579.

- Review of the clinical application of IVIG in solid organ transplant recipients

Mulley, et al. (2011). Understanding crossmatch testing in organ transplantation: a case-based guide for the general nephrologist. Nephrology, 16, 125-33. http://www.ncbi.nlm.nih.gov/pubmed/21272123.

- Case-based guide of the various crossmatching techniques

Nankivell, et al. (2010). Rejection of the kidney allograft. New England Journal of Medicine, 363, 1451-62. http://www.ncbi.nlm.nih.gov/pubmed/20925547.

- Review of the mechanisms and clinical features of cellular and antibody mediated rejection

Raghavan R, Jeroudi A, Achkar K, Gaber AO, Patel SJ, Abdellatif A. (2010) Bortezomib in kidney transplantation. J Transplant. 2010. https://www.ncbi.nlm.nih.gov/pubmed/20953363

- Literature review of bortezomib for desensitization and treatment of AMR

Flechner, et al. (2010). the role of proteasome inhibition with bortezomib in the treatment of antibody-mediated rejection after kidney-only or kidney-combined organ transplantation. Transplantation, 90, 1486-92. http://www.ncbi.nlm.nih.gov/pubmed/21042239.

- Case series of 20 kidney transplant recipients with AMR who received rescue therapy with IV corticosteroids followed by a 2-week cycle of plasmapheresis on days 1, 4, 8, and 11, and bortezomib 1.3 mg/m2, then IVIG 0.5 mg/kg for four doses
- Patients had substantial reduction in DSA, but only 10% had undetectable DSA after treatment
- Each treated patient had an initial improvement in serum creatinine, but only 25% returned to baseline renal function

Sis, et al. (2010). Banff '09 meeting report: antibody mediated graft deterioration and implementation of Banff working groups. American Journal of Transplantation, 10, 464-71. http://www.ncbi.nlm.nih.gov/pubmed/20121738.

- Updates from the 2009 Banff meeting, with a focus on alloantibody responses, roles of endothelial cells in rejection, non-invasive markers of rejection, and updates on kidney, pancreas, heart, liver, lung, and composite tissue graft pathology

KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients (2009). Chapter 6: treatment of acute rejection. American Journal of Transplantation, 9 (suppl 3), S21-S22. http://www.kdigo.org/pdf/KDIGO%20Txp%20GL%20publ%20version.pdf.

- Evidence-based recommendations for the treatment of acute rejection

Lefaucheur, et al. (2009). Comparison of combination Plasmapheresis/IVIg/anti-CD20 versus high-dose IVIg in the treatment of antibody-mediated rejection. American Journal of Transplantation, 9, 1099-107. http://www.ncbi.nlm.nih.gov/pubmed/19422335.

- Kidney transplant recipients with AMR treated with either (Group A) high-dose IVIG (2 g/kg over 2 days every 3 weeks for 4 doses) or (Group B) plasmapheresis (4 sessions) plus low-dose IVIG (100 mg/kg after plasmapheresis) plus high-dose IVIG (2 g/kg over 2 days every 3 weeks for 4 doses) and rituximab (375 mg/m2 once weekly for two weeks) after the last plasmapheresis
- Graft survival at 36 months was 91.7% with combination therapy (Group B) vs. 50% with high-dose IVIG alone (Group A) (p=0.02)

Kurtkoti, et al. (2008). The utility of 1- and 3-month protocol biopsies on renal allograft function: a randomized controlled study. American Journal of Transplantation, 8, 317-23. http://www.ncbi.nlm.nih.gov/pubmed/18093273.

- Graft function (serum creatinine and MDRD eGFR) was superior at 6 months and 1 year amongst patients who underwent protocol biopsies, but no difference in the incidence of clinical acute rejection

Everly, et al. (2008). Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. Transplantation, 86, 1754-61. http://www.ncbi.nlm.nih.gov/pubmed/19104417.

- Case series of 6 patients with concomitant AMR and ACR, refractory to with plasmapheresis ± IVIG ± rATG ± methylprednisolone ± rituximab, received addition of bortezomib therapy (1.3 mg/m2 for four doses)
- Bortezomib therapy provided resolution of refractory ACR, marked and sustained reduction in DSA within 2-4 weeks, regardless of initial DSA level, improved renal function, and suppression of recurrent rejection for at least 5 months

Solez K, et al (2008). Banff 07 classification of renal allograft pathology: updates and future directions. American Journal of Transplantation, 8, 753-60. http://www.ncbi.nlm.nih.gov/pubmed/18294345.

- Updates from the 2007 Banff meeting, with a focus on PTC grading, C4d scoring, interpretation of C4d deposition without morphological evidence of active rejection, application of the Banff criteria to zero-time and protocol biopsies, and introduction of a new scoring for total interstitial inflammation (ti-score)

Zarkhin V, et al. (2008). A randomized, prospective trial of rituximab for acute rejection in pediatric renal transplantation. American Journal of Transplantation, 8, 2607-17. http://www.ncbi.nlm.nih.gov/pubmed/18808404.

- Prospective study of pediatric kidney transplant recipients with acute rejection (BPAR and > 1 B-cell-infiltrating clusters with absolute count > 100 CD20+ cells/hpf) treated with standard therapy of pulsed steroid +/- thymoglobulin (1.5 mg/kg/dose x 6 doses) +/- the addition of rituximab (375 mg/m2 weekly for 4 weeks)
- Rituximab treated recipients showed a higher trend in creatinine clearance (p=0.026) and showed significant improvement in 1-month follow up biopsy scores (p=0.0003)

Solez K, et al. (2007). Banff '05 meeting report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). American Journal of Transplantation, 7, 518-26. http://www.ncbi.nlm.nih.gov/pubmed/17352710.

- Updates from the 2005 Banff meeting, with a major topic of discussion being the elimination of the term "chronic allograft nephropathy" from the Banff schema for diagnosis and grading of renal allograft rejection

Colvin RB, et al. (2007). Antibody-mediated renal allograft rejection: diagnosis and pathogenesis. Journal of American Society of Nephrology, 18, 1046-56. http://www.ncbi.nlm.nih.gov/pubmed/17360947.

- Review of the diagnosis and pathogenesis of acute and chronic AMR

Webster AC, et al. (2006). Monoclonal and polyclonal antibody therapy for treating acute rejection in kidney transplant recipients: a systemic review of randomized trial data. Transplantation, 81(7), 953-65. http://www.ncbi.nlm.nih.gov/pubmed/16612264.

- Comprehensive systematic review of trials utilizing monoclonal antibody (muromonab-CD3) and polyclonal antibody (ATG, ALG) therapies to treat acute rejection in kidney transplant recipients

Jordan SC, et al. (2005). Post-transplant therapy with high-dose intravenous gammaglobulin: Applications to treatment of antibody-mediated rejection. Pediatric Transplantation, 9, 155-61. http://www.ncbi.nlm.nih.gov/pubmed/15787786.

- Review of AMR and experience of high-dose IVIG at Cedars-Sinai Medical Center

Lehrich RW, Rocha PN, Reinsmoen N, et al. (2005) Intravenous immunoglobulin and plasmapheresis in acute humoral rejection: experience in renal allograft transplantation. Hum Immunol. 2005;66(4):350-8. https://www.ncbi.nlm.nih.gov/pubmed/15866697

- Retrospective review classifying patients according to biopsy results into three groups: AHR, (n=23) ACR (n=75), and no rejection. AHR was treated with IVIG and PP resulting in similar IVIG graft survival to patients with ACR.

Shah A, Nadasdy T, Arend L, et al. (2004) Treatment of C4d-positive acute humoral rejection with plasmapheresis and rabbit polyclonal antithymocyte globulin. Transplantation. 2004;77(9):1399-405. https://www.ncbi.nlm.nih.gov/pubmed/15167598

- Case series of 7 patients with AMR treated with PPH (mean of 6.8 treatments) in combination with rATG (0.75 mg/kg/day 5–10 days) until the serum creatinine returned to 120% of nadir. For 6 patients, nadir posttreatment creatinine was significantly lower than pretreatment creatinine ($P<0.007$) with only one episode of graft loss. Combination therapy using PPH an rATG is an effective means of reversing AHR in renal allograft

Becker YT, et al. (2004). Rituximab as treatment for refractory kidney transplant rejection. American Journal of Transplantation, 2004, 996-1001. http://www.ncbi.nlm.nih.gov/pubmed/15147435.

- Kidney transplant recipients diagnosed with steroid-resistant BPAR given rituximab (375 mg/m2) and methylprednisolone +/- plasmapheresis and thymoglobulin resulted in graft loss in only 3/27
- In the 24 successfully treated recipients, serum creatinine declined from 5.6 ± 1.0 to 0.95 ± 0.7 at discharge

Montgomery RA, Zachary AA, Racusen LC, et al. (2000) Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. Transplantation. 2000;70(6):887-95. https://www.ncbi.nlm.nih.gov/pubmed/11014642

- Live donor kidney transplant recipients (n=7) who experienced AHR and had donor-specific Ab (DSA) were segregated into two groups: treated for established AHR (rescue group, n=3) and received therapy before transplantation (preemptive group, n=4). Using PP/IVIG we have successfully reversed established AHR in three patients. Combined therapies of PP/IVIG were successful in reversing AHR mediated by Ab specific for donor HLA antigens.

Gaber AO, et al. (1998). Results of the double-blind, randomized, multicenter, phase III clinical trial of thymoglobulin versus Atgam in the treatment of acute graft rejection episodes after renal transplantation. Transplantation, 66(1), 29-37. http://www.ncbi.nlm.nih.gov/pubmed/9679818.

- Thymoglobulin was superior to Atgam in reversing acute rejection (88% vs. 76%, p=0.027) and preventing recurrent rejection (17% vs. 36%, p=0.011)

Rush D, et al. (1998). Beneficial effects of treatment of early subclinical rejection: a randomized study. Journal of American Society of Nephrology, 9, 2129-34. http://www.ncbi.nlm.nih.gov/pubmed/9808101.

- Corticosteroid treatment of early subclinical rejection is associated with a decrease in early (month 2 and 3) and late (months 7 to 12) clinical rejection, a decrease in chronic tubulointerstitial score at 6 months, and a lower serum creatinine at 24 months

Alarcon-zurita A, Ladefoged J. (1976) Treatment of acute allograft rejection with high doses of corticosteroids. Kidney Int. 1976;9(4):351-4. https://www.ncbi.nlm.nih.gov/pubmed/781384

- 55 kidney transplant patients were treated with high doses of corticosteroids, either prednisone (oral 150 – 600mg/day); methylprednisolone (IV 0.5 to 1g/day [total dose: 2 to 8 g]); methylprednisone (same dose + heparin 5000 U/day). Acute rejection was reversed in 60% of patients without any difference between the three treatment groups. Nineteen patients died from steroid-related complications. Authors suggests that total methylprednisolone dosage exceeding 3 to 5 g did not lead to significant improvement and therefore does not warrant the additional risk.

1.5 Retransplantation and Graft Failure

DiFranza, et al. (2024). Collapsing glomerulopathy is likely a major contributing factor for worse allograft survival in patients receiving kidney transplants from black donors. Frontiers in medicine, 11, 1369225. https://doi.org/10.3389/fmed.2024.1369225

- Retrospective clinical-pathological study of kidney transplant recipients who received kidney allografts from either Black (n = 407) or White (n = 1,494) donors at Columbia University Irving Medical Center from 2005 to 2018, with median follow-up of 4.5 years post-transplantation.
- Black donor race was independently associated with allograft failure (adjusted HR = 1.34, p = 0.02) and recipients of kidney allografts from Black donors had a higher incidence of collapsing glomerulopathy [7.4% vs. 1.9%, OR = 4.17, p < 0.001].
- When causes of allograft failure were examined, only allograft failure following development of collapsing glomerulopathy was more frequent in recipients of allografts from Black donors [15% vs. 5%, OR = 3.16, p = 0.004]. Notably, when patients who developed collapsing glomerulopathy were excluded from analysis, receiving kidney allografts from Black donors was not independently associated with allograft failure (adjusted HR = 1.24, p = 0.10).
- These findings revealed that, compared with recipients of kidney allografts from White donors, recipients of kidneys from Black donors have modestly shorter allograft survival and a higher probability of developing collapsing glomerulopathy, which negatively impacts allograft outcome.

Noguchi, et al. (2024). A Single-Center Retrospective Study of Re-Transplantation After Allograft Failure in Kidney Transplant Recipients. Transplantation proceedings, S0041-1345(24)00049-6. Advance online publication. https://doi.org/10.1016/j.transproceed.2024.01.053

- Study aimed to examine the outcomes of kidney retransplantation in patients with allograft failure at Kyushu University
- Donor-specific anti-HLA antibody (DSA) had been detected in a greater percentage of patients in the second KT group than in the first (31% vs 11%, respectively; P < .001).
- There were no significant differences in 5-year death-censored/overall graft survival rates, rates of surgical complications, or incidence of delayed graft function between the groups

- During the study period, significantly more candidates for second than first KT were rejected for this procedure because of their high immunologic risk (20% vs 2%, P < 001).
- Seven of the 42 patients in the second KT group required the removal of the primary graft during the second transplantation.

Noelle, et al. (2023). Impact of Calcineurin Inhibitor-Based Immunosuppression Maintenance During the Dialysis Period After Kidney Transplant Failure on the Next Kidney Graft Outcome: A Retrospective Multicenter Study With Propensity Score Analysis. *Transplant international : official journal of the European Society for Organ Transplantation*, *36*, 11775. https://pubmed.ncbi.nlm.nih.gov/37799669/

- Retrospective, multicenter review of 205 patients undergoing second kidney transplant (KT) who either received calcineurin inhibitor (CNI)-based immunosuppression (G-CNI) or no immunosuppression (G-STOP) throughout the dialysis period prior to re-transplantation
- Among the G-CNI patients, 36 (61%) were treated with tacrolimus and 23 (39%) were treated with cyclosporine. Per the investigators, residual CNI levels were rarely measured in patients after graft failure and therefore were not collected.
- Of the 59 total patients in the G-CNI group:
    - 19 (32.2%) were maintained on CNI monotherapy
    - 30 (50.8%) were maintained on CNI combined with antimetabolite or corticosteroid therapy
    - 10 (17.0%) received triple immunosuppression
- During the second KT follow-up period, rejection episodes were similar in both groups
    - The G-STOP group experienced longer median pre-transplant dialysis time in the intergraft period than the G-CNI group (37 vs. 16 months; p<0.001), had a greater proportion of hyperimmunized patients (defined as cPRA ≥85%; 55.2% vs. 23.9%; p<0.001), and used more expanded criteria donors (43.2% vs. 29.9%; p=0.01)
- 10-year survival rates without death and dialysis were 98.7% and 59.5% in the G-CNI and G-STOP groups, respectively. Multi-variable analysis associated the G-CNI group with better survival (HR 0.08; 95% CI 0.01-0.58, p=0.01).
- Maintaining CNI-based immunosuppression through the dialysis period after kidney transplant failure may improve re-transplantation outcomes.

Hickey, et al. (2023). Continuation of immunosuppression vs. immunosuppression weaning in potential repeat kidney transplant candidates: a care management perspective. *Frontiers in nephrology*, *3*, 1163581. https://pubmed.ncbi.nlm.nih.gov/37746029/

- Review article summarizing evidence for the following with regards to immunosuppression reduction: effect on HLA sensitization, factors for selecting patients for reduction, strategies for reduction or interchange to belatacept, and monitoring of patients with graft failure undergoing reduced immunosuppression.

Leeaphorn, et al (2021). Outcomes of kidney retransplantation in recipients with prior post transplant lymphoproliferative disorders: an analysis of the 2000-2019 UNOS/OPTN database. *Am J Transplant*. 2021; 21(2): 846-853. https://pubmed.ncbi.nlm.nih.gov/33128832/

- UNOS database analysis of posttransplant lymphoproliferative disease (PTLD).
- PTLD occurrence in second kidney transplant was significantly higher in patients with a history of PTLD, but no difference in graft failure, all-cause mortality, and acute rejection

Leeaphorn, et al (2020). Outcomes of kidney retransplantation after graft loss as a result of BK virus nephropathy in the era of newer immunosuppressant agents. *Am J Transplant*. 2020; 20(5): 1334-1340. https://pubmed.ncbi.nlm.nih.gov/31765056/

- Utilizing OPTN to assess retransplant after first graft loss due to BK virus associated nephropathy (BKVAN) compared to those without BKVAN. There was no difference in graft survival, acute rejection, and patient survival. Subgroup analysis showed that patients with graft loss due to BKVAN had better graft survival than patients with prior failure due to acute rejection and recurrent disease
- BKVAN should not be a contraindication to retransplant

Sandal, et al (2021). Comparing outcomes of third and fourth kidney transplantation in older and younger patients. *Am J Transplant*. 2021. https://pubmed.ncbi.nlm.nih.gov/34355512/

- Younger patients (18-64 years old) and older patients (≥65 years old) did not have significant differences in DGF, primary non-function, 1-year acute rejection or 5-year graft failure; 5-year mortality was higher in older recipients
- Results support improving access to 3 and 4 retransplants in older patients

Petrun, et al (2020). Graft survival of fourth-time renal transplant recipients is similar to third-time recipients: a SRTR database analysis. *Clin Transplant*. 2020; 34(7): e13884. https://pubmed.ncbi.nlm.nih.gov/32301524/

- Graft and patient survival was comparable between 3 and 4 transplant events, but inferior to 1 and 2
- Life expectancy of fourth transplant increased compared to those waitlisted for fourth transplant

Benko, et al. (2019). Long-term outcome of third, fourth, and fifth kidney transplantation: technical aspects and immunological challenges. *Clin Kidney J* ; 12(6):895-900. https://www.ncbi.nlm.nih.gov/pubmed/31807305

- Kidney recipients that underwent a third, fourth, or fifth kidney transplant were compared to a historical cohort of recipients transplanted a second time. No differences in graft and patient survival were observed, suggesting that survival after more than three transplants is similar to that of second graft recipients.

Ahmed, et al. (2008). Influence of number of retransplants on renal graft outcome. Transplantation Proceedings, 40, 1349–52. http://www.ncbi.nlm.nih.gov/pubmed/18589103.

- Single-center, retrospective analysis of graft outcomes amongst patients with a history of multiple (>2) kidney transplants compared to a cohort of patients receiving their first graft during the same period.
- Graft survival rates were not different among patients with a history of two compared to more than two transplants; the authors suggest that kidney retransplantation can yield acceptable graft survival rates, albeit significantly lower than primary transplantation.

Marcen, et al. (2008). Patient outcomes after kidney allograft loss. Transplantation Reviews, 22, 62-72. http://www.ncbi.nlm.nih.gov/pubmed/18631859.

- Review article of kidney graft failure, including considerations for the management of patients after graft loss, patient outcomes, and retransplantation.

Magee, et al. (2007). Repeat organ transplantation in the United States, 1996–2005. American Journal of Transplantation, 7: 1424–33. http://www.ncbi.nlm.nih.gov/pubmed/17428290.

- Compared to other organ types, the number of repeat kidney transplants has grown most significantly over the past 10 years (absolute increase 40%, represented 12.4% of all kidney transplants in 2005). However, graft survival rates at 1-, 3-, and 5 years following retransplantation are significantly lower than those observed for primary transplants.

Miles, et al. (2007). Mortality experience in recipients undergoing repeat transplantation with expanded criteria donor and non-ECD deceased-donor kidneys. American Journal of Transplantation, 7, 1140-47. http://www.ncbi.nlm.nih.gov/pubmed/17331109.

- Data from the Scientific Registry of Transplant Recipients (SRTR) of all adult kidney transplant recipients who experienced graft failure and were relisted for transplantation between 1995 and 2004.
- While a survival benefit was observed with non-ECD kidneys, retransplantation with ECD kidneys did not offer a significant survival benefit over remaining on dialysis.

Meier-Kriesche, et al. (2004). Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. American Journal of Transplantation, 4, 378-83. http://www.ncbi.nlm.nih.gov/pubmed/14961990.

- Analysis of Scientific Registry of Transplant Recipients (SRTR) data of all adult first renal transplants between 1995 and 2000.
- While the authors noted a decrease in acute rejection rates post-transplant (6-months, 12-months, and late rejections), there was no significant improvement in overall graft survival.

Ojo, et al. (1998). Prognosis after primary renal transplant failure and the beneficial effects of repeat transplantation: multivariate analyses from the United States Renal Data System. Transplantation, 27, 1651-59. http://www.ncbi.nlm.nih.gov/pubmed/9884254.

- United States Renal Data System (USRDS) data evaluating survival outcomes of 19,208 kidney transplant recipients who experienced primary graft loss between 1985 and 1995, as evidenced by return to maintenance dialysis, wait-listing for repeat transplantation, or receipt of a second kidney transplant.
- Repeat transplantation was associated with a substantial improvement in 5-year mortality rates

1.6 Kidney diseases

1.6.1 Glomerular disease

Garnier, et al. (2024). Drug-induced glomerular diseases. Therapie, 79(2), 271–281. https://doi.org/10.1016/j.therap.2023.10.010

- Review article focusing on drug-induced glomerular diseases, more precisely podocytopathies - minimal change diseases (MCD), focal segmental glomerulosclerosis (FSGS) - and membranous nephropathies (MN), from a physiological and a pharmacological point of view.

Obata, et al. (2024). Recurrent C3 glomerulopathy after kidney transplantation. Transplantation reviews (Orlando, Fla.), 38(2), 100839. https://doi.org/10.1016/j.trre.2024.100839

- Review article focusing on recurrence of C3 glomerulopathy after kidney transplant, as well as pathogenesis and therapy options

de Sousa MV et al. (2024). Post-Transplant Glomerulonephritis: Challenges and Solutions. International journal of nephrology and renovascular disease, 17, 81–90. https://doi.org/10.2147/IJNRD.S391779

- Review article discussing the challenges and solutions of the management of immunoglobulin A nephropathy, membranous nephropathy, Focal Segmental Glomerulosclerosis, membranoproliferative glomerulonephritis, and viral glomerulopathies.

Gilani, et al. (2024). IgG4-related kidney disease: Clinicopathologic features, differential diagnosis, and mimics. Seminars in diagnostic pathology, 41(2), 88–94. https://doi.org/10.1053/j.semdp.2023.12.001

- Review article discussing the different types types of autoimmune and plasma cell-rich interstitial nephritis, mass forming inflammatory diseases of the kidney, and other mimics of IgG4-TIN, in particular ANCA-associated disease.

Noris, et al. (2024). C3G and Ig-MPGN-treatment standard. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 39(2), 202–214. https://doi.org/10.1093/ndt/gfad182

- Review article discussing current standards of treatment and discuss novel developments in the pathophysiology, diagnosis, outcome prediction and management of C3 glomerulopathy (C3G) and immunoglobulin-associated membranoproliferative glomerulonephritis (Ig-MPGN.)

Keskinyan, VS et al. (2023). Glomerulonephritis. Pediatrics in review, 44(9), 498–512. https://doi.org/10.1542/pir.2021-005259

- Review article focusing on lupus nephritis, IgA nephropathy, IgA vasculitis, and postinfectious GN.

Anders, HJ et al. (2023). CKD therapy to improve outcomes of immune-mediated glomerular diseases. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 38(Supplement_2), ii50–ii57. https://doi.org/10.1093/ndt/gfad069

- Review article focusing on the management of immunoglobulin A nephropathy, membranous nephropathy, lupus nephritis, anti-neutrophil cytoplasmic antibody–associated vasculitis, C3 glomerulonephritis, autoimmune podocytopathies and other immune-mediated glomerular disorders. Article discusses non-drug and drug interventions to attenuate CKD progression in immune-mediated kidney disorders.

Rovin, et al (2021). KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney International, 100(4), S1–S276. https://doi.org/10.1016/j.kint.2021.05.021

- Therapeutic guidelines containing chapters on various glomerular diseases (lupus nephritis, membranous nephropathy, focal segmental glomerulosclerosis, infection-related glomerulonephritis, IgA nephropathy, etc) and recommended treatment approaches
- Chapters are updated on a rolling basis and should be checked with the KDIGO website frequently

Infante B, et al. (2020). Recurrent glomerulonephritis after renal transplantation: the clinical problem. *Int J Mol Sci*. 2020; 21(17): 5954. https://pubmed.ncbi.nlm.nih.gov/32824988/

- Review article focusing on recurrence of disease after transplant as well as pathogenesis, biomolecular mechanisms, and therapy options
- Glomerulonephritis (GN) has changed from a minor contributor to graft loss to the 3rd most common cause of 10-year graft failure

Lim, W. H., Shingde, M., & Wong, G. (2019). Recurrent and *de novo* Glomerulonephritis After Kidney Transplantation. *Frontiers in immunology*, *10*, 1944. https://pubmed.ncbi.nlm.nih.gov/31475005/

- Review article examining management of patients with high risk glomerulonephritis, including pre-transplant assessment, post-transplant monitoring, and treatment options for recurrence.
- Specific forms of glomerulonephritis reviewed include IgA nephropathy, primary FSGS, primary MPGN, and idiopathic membranous GN.

Chadban, SJ et al. (2005). Glomerulonephritis. The Lancet, 365, 1797-806. http://www.ncbi.nlm.nih.gov/pubmed/15910953.

- Review article of the epidemiology, pathophysiology, and initial management of various types of glomerular diseases.

Hricik, DE et al. (1998). Glomerulonephritis. New England Journal of Medicine, 24, 888-99. http://www.ncbi.nlm.nih.gov/pubmed/9744974.

- Review article of the pathophysiology and clinical presentation of acute, rapidly progressing, and chronic glomerulonephritis.

1.6.2 Focal Segmental Glomerulosclerosis

Shoji, et al. (2024). Efficacy and Safety of Bleselumab in Preventing the Recurrence of Primary Focal Segmental Glomerulosclerosis in Kidney Transplant Recipients: A Phase 2a, Randomized, Multicenter Study. Transplantation, 10.1097/TP.0000000000004985. Advance online publication. https://doi.org/10.1097/TP.0000000000004985

- A phase 2a, randomized, multicenter, open-label study of adult recipients (aged ≥18 y) of a living or deceased donor kidney transplant with a history of biopsy-proven primary FSGS.
- The study assessed the efficacy of bleselumab combined with tacrolimus and corticosteroids as maintenance immunosuppression in the prevention of rFSGS >12 mo posttransplantation, versus standard of care (SOC) comprising tacrolimus, mycophenolate mofetil, and corticosteroids. All patients received basiliximab induction.
- The primary endpoint was rFSGS, defined as proteinuria (protein-creatinine ratio ≥3.0 g/g) with death, graft loss, or loss to follow-up imputed as rFSGS, through 3 mo posttransplant.
- In at-risk kidney transplant recipients, bleselumab numerically reduced proteinuria occurrence versus SOC, but no notable difference in occurrence of biopsy-proven rFSGS was observed.

Ahmad, et al. (2024). Current approaches to overcome recurrent focal segmental glomerulosclerosis after kidney transplantation. Current opinion in nephrology and hypertension, 33(1), 61–66. https://doi.org/10.1097/MNH.0000000000000946

- Review article that provides an overview of the role of circulating permeability factors in disease pathogenesis and treatment options for recurrent FSGS.

Mirioglu, et al. (2024). Management of adult patients with podocytopathies: an update from the ERA Immunonephrology Working Group. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association, 39(4), 569–580. https://doi.org/10.1093/ndt/gfae025

- Review article providing a perspective of the Immunonephrology Working Group (IWG) of the European Renal Association (ERA) and discusses the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases focusing on the management of MCD and primary forms of FSGS in the context of recently published evidence, with a special emphasis on the role of rituximab, cyclophosphamide, supportive treatment options and ongoing clinical trials in the field.

Raina, et al. (2024). Post-transplant recurrence of focal segmental glomerular sclerosis: consensus statements. Kidney international, 105(3), 450–463. https://doi.org/10.1016/j.kint.2023.10.017

- Review article that focuses on the definition, epidemiology, risk factors, pathogenesis, and management of recurrent FSGS.

Angeletti, et al. (2023). Efficacy of combined rituximab and daratumumab treatment in posttransplant recurrent focal segmental glomerulosclerosis. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, S1600-6135(23)00910-3. https://pubmed.ncbi.nlm.nih.gov/38101474/

- Report of five cases of early post-transplant FSGS recurrence which were resistant to plasma exchange and rituximab that subsequently resolved after combined therapy with rituximab and daratumumab.
- Rituximab was administered at 375 mg/m^2 (single dose). Daratumumab was administered at 16 mg/kg (single dose) fifteen days after rituximab.

- Treatment was well-tolerated in all patients. Minor or moderate respiratory symptoms occurred during 43% of daratumumab infusions, requiring slowing or temporary interruption of infusion. Two patients developed CMV positivity which promptly responded to valganciclovir.
- Remission was observed in all patients. Two patients experienced relapse which responded to a second course of combined therapy (with subsequent relapse responsive to daratumumab alone)

Kwon, et al. (2023). Post-operative recurrence of focal segmental glomerulosclerosis according to pre-transplant treatment after kidney transplantation. *BMC nephrology*, *24*(1), 53. https://pubmed.ncbi.nlm.nih.gov/36922759/

- Single-center, retrospective study including 99 patients with primary FSGS transplanted between 2007 and 2018. Patients were divided into the pre-treatment group (n=53) and no pre-treatment group (n=46)
- Of the 53 patients in the pre-treatment group, n=22 underwent two sessions of prophylactic plasmapheresis prior to living donor KT, n=28 with flow cytometry crossmatch-positive and ABO incompatibility received desensitization with rituximab and plasmapheresis, and n=3 underwent prophylactic plasmapheresis the day after deceased donor KT.
- Recurrence was defined as reappearance of nephrotic-range proteinuria (>3.0 g/day). Immediate post-operative recurrence was defined as recurrence of FSGS within two weeks of transplant.
- Rate of immediate post-operative recurrence was significantly higher in the no pre-treatment group (P=0.002). The three cases of graft failure due to recurrent FSGS were in the no pre-treatment group. After adjusting for confounding factors, the significant factors associated with FSGS recurrence were age and pre-transplant treatment. Death-censored graft survival was significantly superior in the pre-transplant treatment group (P=0.042).

Al Shamsi, et al. (2022). Management of recurrent focal segmental glomerulosclerosis (FSGS) post renal transplantation. *Transplantation reviews (Orlando, Fla.)*, *36*(1), 100675. https://pubmed.ncbi.nlm.nih.gov/34952298/

- Literature review (23 articles assessed from between 2000-2021) evaluating management of adult patients with post-transplant FSGS recurrence (prophylactic plasmapheresis; prophylactic rituximab; effectiveness of plasmapheresis and rituximab in treatment of recurrent FSGS via assessing proteinuria; other modalities for treatment of recurrent FSGS)
- Current evidence suggests:
    - Prophylactic plasmapheresis may not help with post-transplant recurrence of FSGS
    - More data is required to conclude whether prophylactic rituximab can be recommended to prevent post-transplant recurrence of FSGS
    - Current evidence (primarily systematic reviews and meta-analyses) support the effectiveness of both plasmapheresis and rituximab in inducing remission of post-transplant FSGS recurrence
    - The optimal plasmapheresis prescription to induce remission of recurrent FSGS is unknown. A typical prescription is 1-2 times plasma volume exchanges, 3-4 treatments per week (total of 8-12 treatments until remission achieved). More data is needed to determine if intensive, prolonged plasmapheresis provides better remission outcomes.
    - Rituximab dosing to induce remission ranged from 100 mg (single dose) to 375 mg/m^2. An optimal number of doses is yet to be determined.
    - Other treatment modalities (immunoadsorption, high dose cyclosporine, RAS inhibition, cyclophosphamide, abatacept, belatacept, acthar gel, etc.) require more studies to confirm their role in prevention and treatment of recurrent FSGS

Kurian SM, et al (2021). UNOS/OPTN Data-guided assessment of focal segmental glomerulosclerosis after kidney transplantation and evaluation of immunosuppressive protocols in a steroid-free center. *Transplant Direct*. 2021; 7(9): e738. https://pubmed.ncbi.nlm.nih.gov/34386576/

- Single-center, retrospective study of renal transplant recipients with primary diagnosis of FSGS. Patients at Scripps Center for Organ Transplantation (SCOT) using a rapid low-dose steroid withdrawal were compared to UNOS database of patients with FSGS
- Graft failure and recipient death did not differ between SCOT SF cohort and UNOS SF cohort. There was a lower rate of FSGS recurrence in the SCOT cohort compared to previously published studies
- Concluding that steroid avoidance and steroid-free protocols may not be detrimental when considering steroid adverse effects and toxicities

Ochi, A et al. (2012). Rituximab treatment for adult patients with focal segmental glomerulosclerosis. Internal Medicine, 51, 759-796. http://www.ncbi.nlm.nih.gov/pubmed/22466834.

- Case series of single-dose rituximab administration in the setting of steroid-resistant (n=2) and steroid-dependent FSGS (n=2). Patients with steroid-dependent FSGS responded to rituximab therapy while those with steroid-resistant FSGS did not.

D'Agati, VD et al. (2011). Focal segmental glomerulosclerosis. New England Journal of Medicine, 365, 2398-411. http://www.ncbi.nlm.nih.gov/pubmed/22187987.

- Review article of the pathophysiology, clinical presentation, therapeutic options, and treatment algorithm for focal segmental glomerulosclerosis. The article concludes with considerations of disease recurrence following renal transplantation.

Fernandez-Fresnedo, G et al. (2009). Rituximab treatment of adult patients with steroid-resistant focal segmental glomerulosclerosis. Clinical Journal of the American Society of Nephrology, 4, 1317-23. http://www.ncbi.nlm.nih.gov/pubmed/19578004.

- Eight patients with biopsy-proven FSGS and had received rituximab (375 mg/m2 weekly x 4) for disease resistant to corticosteroids and other therapies (including cyclosporine, tacrolimus, mycophenolate, cyclophosphamide, chlorambucil) were included. At the end of follow-up, patients experienced a modest reduction in proteinuria (14.0 vs. 10.5 g/24h) but serum creatinine increased and only two patients achieved a remarkable and sustained reduction in proteinuria.

Burgess, E et al. (1999). Management of focal segmental glomerulosclerosis: Evidence-based recommendations. Kidney International, 70, S26-32. http://www.ncbi.nlm.nih.gov/pubmed/10369192.

- Graded recommendations developed by the International Society of Nephrology for the treatment of FSGS. Steroids are the first-line treatment approach, with resistance being declared only if patients do not achieve remission after a six-month trial; second-line options include cyclosporine, cytotoxic therapy (cyclophosphamide, azathioprine, chlorambucil), and plasmapheresis for kidney transplant recipients with recurrent FSGS.

1.6.3 Lupus Nephritis

Chakravarty EF, et al. (2024). Mycophenolate mofetil withdrawal in patients with systemic lupus erythematosus: a multicentre, open-label, randomised controlled trial. The Lancet. Rheumatology, 6(3), e168–e177. https://doi.org/10.1016/S2665-9913(23)00320-X

- Multicenter, open-label, randomized trial to determine the effects of mycophenolate mofetil withdrawal on the risk of clinically significant disease reactivation in patients with quiescent SLE on long-term mycophenolate mofetil therapy.
- 102 were randomly allocated to the maintenance group (n=50) or the withdrawal group (n=52).
- The risk of clinically significant disease reactivation was 11% (95% CI 5-24) in the maintenance group and 18% (10-32) in the withdrawal group. The estimated increase in the risk of clinically significant disease reactivation with mycophenolate mofetil withdrawal was 7% (one-sided upper 85% confidence limit 15%).
- Similar rates of adverse events were observed in the maintenance group (45 [90%] of 50 participants) and the withdrawal group (46 [88%] of 52 participants). Infections were more frequent in the mycophenolate mofetil maintenance group (32 [64%]) compared with the withdrawal group (24 [46%]).

Wuttiputhanun, et al. (2024). Therapeutic drug monitoring of mycophenolic acid and clinical outcomes of lupus nephritis: a systematic review and meta-analysis. Lupus science & medicine, 11(1), e001093. https://doi.org/10.1136/lupus-2023-001093

- A systematic review and meta-anyalsis to review and summarize current knowledge of therapeutic drug monitoring of mycophenolic acid in the treatment of lupus nephritis.
- This meta-analysis emphasised the meaningful correlation between MPA AUC and C_0 with renal response in LN treatment

Jiang W, et al. (2024). Graft survival and mortality outcomes after kidney transplant in patients with lupus nephritis: a systematic review and meta-analysis. Renal failure, 46(1), 2296000. https://doi.org/10.1080/0886022X.2023.2296000

- Review article that describes the effect of lupus nephritis on graft survival in renal transplant patients.
- The findings suggest that the presence of LN might have a negative impact on both the graft survival and the overall patient survival of post-transplant ESRD patients.

Rovin et al (2024). KDIGO 2024 Clinical Practice Guideline for the management of LUPUS NEPHRITIS. *Kidney International*. 2024;105(1):S1-S69. doi:10.1016/j.kint.2023.09.002

- Focused update of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases regarding the management of lupus nephritis
- Guidelines and recommendations provided for diagnosis of lupus nephritis, initial management and pharmacotherapy, definitions for appropriate response to therapy, an algorithm to approach unsatisfactory response to therapy, and treatment of complicated populations (relapsed, pregnancy, associated TMA)

Parikh SV, et al (2020). Update on lupus nephritis: core curriculum 2020. *Am J Kidney Dis*. 2020; 76(2): 265-281. https://pubmed.ncbi.nlm.nih.gov/32220510/

- Review of current epidemiology, pathogenesis, diagnosis, and treatment. Additional updates on management in pregnant patients, timing of transplant, and the role of corticosteroids

Hahn, BH et al. (2012). American College of Rheumatology (ACR) guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care and Research, 64, 797-808. http://www.ncbi.nlm.nih.gov/pubmed/22556106.

- Guidelines and recommendations developed by the American College of Rheumatology to provide guidance to physicians managing patients with lupus nephritis.

Roving, BH et al. (2012). Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis and Rheumatism, 64, 1215-26. http://www.ncbi.nlm.nih.gov/pubmed/22231479.

- Patients with lupus nephritis were randomized to receive placebo or rituximab (1 g IV on days 1, 15, 168, and 182) in addition to mycophenolate mofetil and corticosteroids. Although rituximab resulted in significant improvements in C3, C4, and anti-dsDNA levels and higher response rates (46% vs. 57%, p=0.18), clinical outcomes at one year were similar. In an underpowered subgroup analysis, African American patients achieved better outcomes with rituximab.

Dooley, MA t al. (2011). Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. New England Journal of Medicine, 365, 1886-1895. http://www.ncbi.nlm.nih.gov/pubmed/22087680.

- Patients with active class III, IV, or V lupus nephritis were randomized to maintenance therapy with mycophenolate (1 g oral BID) or azathioprine (2 g/kg/day) in combination with corticosteroids (10 mg of prednisone per day or less). Mycophenolate was superior to azathioprine with respect to time to treatment failure (defined by renal flare, end-stage renal disease, doubling of the serum creatinine, or need for rescue therapy).

Appel, GB et al. (2009). Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. Journal of the American Society of Nephrology, 20, 1103-12. http://www.ncbi.nlm.nih.gov/pubmed/19369404.

- Patients with biopsy-proven lupus nephritis were randomized to treatment with mycophenolate mofetil (target dose 1.5 g oral BID) or cyclophosphamide (0.5 - 1 g/m2 monthly) in combination with oral steroids. Mycophenolate was non-inferior to cyclophosphamide in terms of reduction in urine protein:creatinine ratio, change in serum creatinine, or tolerability. Mycophenolate allows for convenient oral dosing and eliminates the risk of ovarian dysfunction associated with cyclophosphamide.

1.6.4 Membranous Glomerulonephritis

Podestà, MA et al. (2024). Ofatumumab in Rituximab-Resistant and Rituximab-Intolerant Patients With Primary Membranous Nephropathy: A Case Series. American journal of kidney diseases : the official journal of the National Kidney Foundation, 83(3), 340–349.e1. https://doi.org/10.1053/j.ajkd.2023.08.010

- Review of case series to assess whether ofatumumab, a fully human second-generation anti-CD20 antibody, could be a valuable alternative to rituximab in this population.

Hullekes, et al. (2024). Recurrence of membranous nephropathy after kidney transplantation: A multicenter retrospective cohort study. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, S1600-6135(24)00126-6. Advance online publication. https://doi.org/10.1016/j.ajt.2024.01.036

- Retrospective multicenter cohort study examining the MN recurrence rate, risk factors, and response to treatment within the Post-Transplant Glomerular Disease Consortium.
- During a median follow-up period of 5.9 years (interquartile range [IQR], 3.2-8.6 years), 43 patients experienced recurrent MN.
- Patients receiving rituximab for MN recurrence had a higher likelihood of achieving remission than patients receiving renin-angiotensin-aldosterone system inhibition alone. In sum, MN recurs in one-third of patients posttransplant, and measurement of serum anti-PLA2R antibody levels shortly before transplant could aid in risk-stratifying patients for MN recurrence. Moreover, patients receiving rituximab had a higher rate of treatment response.

Ruggenenti, P et al. (2012). Rituximab in idiopathic membranous nephropathy. Journal of the American Society of Nephrology, 23, 1416-25. http://www.ncbi.nlm.nih.gov/pubmed/22822077.

- Outcomes following rituximab administration (375 mg/m2 weekly x 4) in the setting of idiopathic membranous nephropathy with persistent proteinuria. During a median follow-up of 29 months, 65 of 100 patients achieved complete (<0.3 g/day) or partial remission (<3 g/day) at a median of 7.1 months after administration, while 4 patients progressed to ESRD. The magnitude of proteinuria significantly correlated with a slower decline in eGFR.

Waldman, M et al. (2012). Treatment of idiopathic membranous nephropathy. Journal of the American Society of Nephrology, 23, 1617-30. http://www.ncbi.nlm.nih.gov/pubmed/22859855.

- Review article of the pathophysiology, pharmacologic options, and current approach to treatment for idiopathic membranous nephropathy.

1.6.5 IgA Nephropathy

Barratt, et al. (2024). Phase 2 Trial of Cemdisiran in Adult Patients with IgA Nephropathy: A Randomized Controlled Trial. Clinical journal of the American Society of Nephrology : CJASN, 19(4), 452–462. https://doi.org/10.2215/CJN.0000000000000384

- Phase 2, 36-week, double-blind study, in adult patients with IgA nephropathy and urine protein ≥1 g/24 hours. Patients were randomized (2:1) to subcutaneous cemdisiran 600 mg or placebo every 4 weeks in combination with the standard of care.
- The primary end point was percentage change from baseline at week 32 in urine protein-to-creatinine ratio (UPCR) measured by 24-hour urine collection. Cemdisiran-treated patients had a

placebo-adjusted geometric mean change in 24-hour UPCR of -37.4% (cemdisiran-adjusted geometric mean ratio to baseline [SEM], 0.69 [0.10]) at week 32.
- Additional end points included change from baseline in UPCR measured by spot urine, serum C5 level, and safety assessments. Spot UPCR was consistent with 24-hour UPCR placebo-adjusted change of -45.8% (cemdisiran-adjusted geometric mean ratio to baseline [SEM], 0.73 [0.11]). Mean (SD) change in serum C5 level from baseline at week 32 was -98.7% (1.2) with cemdisiran and 25.2% (57.7) with placebo. Over 36 weeks, most adverse events were mild or moderate and transient; the most common adverse event after cemdisiran treatment was injection-site reaction (41%).

Mathur, et al. (2024). A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy. The New England journal of medicine, 390(1), 20–31. https://doi.org/10.1056/NEJMoa2305635
- Phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group. Adults with biopsy-confirmed IgA nephropathy who were at high risk for disease progression, despite having received standard-care treatment, were randomly assigned in a 1:1:1:1 ratio to receive intravenous sibeprenlimab at a dose of 2, 4, or 8 mg per kilogram of body weight or placebo once monthly for 12 months.
- The primary end point was the change from baseline in the log-transformed 24-hour urinary protein-to-creatinine ratio at month 12. At 12 months, the geometric mean ratio reduction (±SE) from baseline in the 24-hour urinary protein-to-creatinine ratio was 47.2±8.2%, 58.8±6.1%, 62.0±5.7%, and 20.0±12.6% in the sibeprenlimab 2-mg, 4-mg, and 8-mg groups and the placebo group, respectively.
- Secondary end points included the change from baseline in the estimated glomerular filtration rate (eGFR) at month 12. Safety was also assessed. At 12 months, the least-squares mean (±SE) change from baseline in eGFR was -2.7±1.8, 0.2±1.7, -1.5±1.8, and -7.4±1.8 ml per minute per 1.73 m2 in the sibeprenlimab 2-mg, 4-mg, and 8-mg groups and the placebo group, respectively. The incidence of adverse events that occurred after the start of administration of sibeprenlimab or placebo was 78.6% in the pooled sibeprenlimab groups and 71.1% in the placebo group.
- In patients with IgA nephropathy, 12 months of treatment with sibeprenlimab resulted in a significantly greater decrease in proteinuria than placebo.

El Karoui, et al. (2024). Treatment of IgA Nephropathy: A Rapidly Evolving Field. Journal of the American Society of Nephrology : JASN, 35(1), 103–116. https://doi.org/10.1681/ASN.0000000000000242
- Review article discussing the pathophysiology and comprehensive approach that tackles the different targets in the pathophysiology of IgA nephropathy according to their relevance in the individual patient.

Aydin-Ghormoz, et al. (2024). Outcomes of kidney transplantation in patients with IgA nephropathy based on induction: A UNOS data analysis. Clinical transplantation, 38(1), e15225. https://doi.org/10.1111/ctr.15225
- Retrospective analysis of the UNOS database in adults with ESKD secondary to IgAN who received kidney transplants between January 2000 and June 30, 2022.
- Patients with thymoglobulin (ATG), alemtuzumab, or basiliximab/daclizumab induction with calcineurin inhibitor (CNI) and mycophenolate mofetil (MMF) with or without prednisone maintenance were analyzed.
- Compared to ATG with steroid maintenance, alemtuzumab with steroid increased the odds of IgAN recurrence in DDKTs (OR 1.90, $p < .010$, 95% CI [1.169-3.101]). Alemtuzumab with and without steroid increased the odds of recurrence by 52% ($p = .036$) and 56% ($p = .005$), respectively, in LDKTs. ATG without steroids was associated with less risk of IgAN recurrence (HR .665, $p = .044$, 95% CI [.447-.989]), graft failure (HR .758, $p = .002$, 95% CI [.633-.907]), and death (HR .619, $p < .001$, 95% CI [.490-.783]) in DDKTs.
- Recurrence was strongly associated with risks of graft failure in DDKTs and LDKTs and death in LDKTs.

- In patients with IgAN requiring a kidney transplant, Alemtuzumab induction correlates with increased IgAN recurrence. Relapse significantly affects graft survival and mortality. ATG without steroids is associated with the least graft loss and mortality.

Aydin-Ghormoz, et al. (2023). Outcomes of kidney transplantation in patients with IgA nephropathy based on induction: A UNOS data analysis. *Clinical transplantation*, e15225. https://pubmed.ncbi.nlm.nih.gov/38127110/

- Retrospective database analysis of 11,679 patients with ESRD secondary to IgA nephropathy who received a renal transplant between January 2000 and June 30, 2022. Multivariate logistic regression was performed to assess for factors correlated with IgA recurrence.
- Induction with thymoglobulin (n=6,391, 56.4%), alemtuzumab (n=1,910, 16.8%), basiliximab (n=2,580, 22.8%), or daclizumab (n=460, 4.1%) was assessed. Patients were excluded if they received any other form of induction or received a combination of induction agents.
- Patients received CNI + MMF for maintenance therapy either with prednisone (n=7,944, 70.1%) or without prednisone (n=3,397, 29.9%)
- Recurrence occurred in 5.38% of transplanted patients. Other notable outcomes included:
    - Alemtuzumab with and without steroid increased odds of recurrence by 52% (p=0.36) and 56% (p=0.005), respectively in living donor KTs
    - ATG without steroids was associated with less risk of IgAN recurrence (HR 0.665, p=0.044), graft failure (HR 0.758, p=0.002), and death (HR 0.619, p<0.001) in deceased donor KTs
    - Recurrence was strongly associated with risk of graft failure in DDKT (HR 2.463, p<0.001) and LDKT (HR 3.016, p<0.001), as well as death in LDKT (HR=1.697, p=0.006)

Lafayette, et al. (2023). Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. *Lancet (London, England)*, *402*(10405), 859–870. https://pubmed.ncbi.nlm.nih.gov/37591292/

- This multicenter study included patients aged ≥18 years with primary IgA nephropathy, eGFR 35-90 ml/min/1.73 m^2, and persistent proteinuria (UPCR ≥ 0.8 g/g or proteinuria ≥1 g/24 hours) despite optimized RAAS blockade.
- Patients were assigned to 16 mg/day of targeted-release budesonide or placebo for 9 months followed by a 15-month observational follow-up period. The primary efficacy endpoint was time-weighted average of eGFR over 2 years.
- Targeted-release budesonide showed statistically significant improvement in time-weighted average of eGFR over 2 years when compared to placebo (-2.47 ml/min/1.73 m^2 vs. -7.52 ml/min/1.73 m^2 – difference of 5.05 ml/min/1.73 m^2, p<0.001).
- Concluded that a 9-month treatment period with targeted-release budesonide provided clinically relevant reduction in eGFR decline and durable reduction in proteinuria compared to placebo.

Noor, et al. (2023). IgA nephropathy: a review of existing and emerging therapies. *Frontiers in nephrology*, *3*, 1175088. https://pubmed.ncbi.nlm.nih.gov/37675358/

- A review of current and emerging therapies for IgA nephropathy, including supportive care, SGLT2i, sparsentan, hydroxychloroquine, and immunosuppression.

Hou, et al (2023). Effectiveness of Mycophenolate Mofetil Among Patients With Progressive IgA Nephropathy: A Randomized Clinical Trial. *JAMA network open*, *6*(2), e2254054. https://pubmed.ncbi.nlm.nih.gov/36745456/

- Single center, randomized control trial conducted to evaluate safety and efficacy of mycophenolate mofetil in 170 patients with IgA nephropathy at high risk for loss of kidney function (proteinuria >1.0 g/day plus eGFR >30 and <60 mL/min/1.73 m^2 **or** persistent hypertension)
- Patients with secondary, familial, or crescentic IgAN, presence of other CKD, any prior immunosuppressive therapy, or eGFR <30 mL/min/1.73 m^2 were excluded
- Patients were randomized 1:1 to receive MMF (1,500 mg/day for 12 months, maintained at 750-1,000 mg/day for at least 6 months) plus standard of care OR standard of care alone
- Standard of care included RAS inhibition (with losartan) to reduce BP to <130/80 mmHg, lifestyle modifications, and treatment with erythropoietin or statin where necessary
- The first primary outcome (composite of doubling of serum creatinine, ESRD, or death secondary to renal or cardiovascular cause) occurred significantly less in the group receiving MMF (7.1% vs. 21.2%, aHR 0.23; 95% CI, 0.09-0.63)
- The second primary outcome (progression of CKD, defined as decrease in eGFR of 30% or more if baseline eGFR >60 mL/min/1.73 m^2 or 50% if baseline eGFR was <60 mL/min/1.73 m^2) occurred significantly less in the group receiving MMF (8.2% vs. 27.1%, aHR 0.23; 95% CI 0.10-0.57)
- Pneumonia was observed more frequently in the MMF group, but the difference was not statistically significant. Infections occurred more frequently overall in the MMF group (16.5%) vs. the no MMF group (10.6%).
- Addition of MMF to standard of care significantly reduces risk of disease progression among patients with high risk for progressive IgA nephropathy

Lv, et al (2022). Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. *JAMA*, *327*(19), 1888–1898. https://pubmed.ncbi.nlm.nih.gov/35579642/

- International, multicenter, double-blind, randomized clinical trial that enrolled 503 patients with IgA nephropathy, proteinuria ≥1 g/day, and eGFR of 20-120 mL/min/1.73 m^2 after at least 3 months of optimized background care
- Patients were randomized 1:1 to receive oral methylprednisolone (n=136; 0.6-0.8 mg/kg/day, maximum 48 mg/day, weaning by 8 mg/day each month) or placebo (n=126). After this initial randomization, an excess of serious infections led to reduced methylprednisolone dosing (0.4 mg/kg/day, maximum 32 mg/day, weaning by 4 mg/day each month) and addition of antibiotic prophylaxis for PCP in subsequent participants (n=121 for methylprednisolone, n=120 for placebo).
- Duration of intervention period was 6 to 9 months; mean follow-up was 4.2 years. 85.7% of patients were able to complete the full treatment course.
- The primary endpoint a composite of 40% decline in eGFR, kidney failure (dialysis or transplant), or death due to kidney disease) occurred less frequently in the methylprednisolone group compared to the placebo group (28.8% vs. 43.1%; HR 0.53, 95% CI, 0.39-0.72, p<0.001)
- Risk of kidney failure requiring dialysis or transplant was significantly lower in the methylprednisolone group (19.5% vs. 27.2%; HR 0.59, 95% CI, 0.40-0.87, p=0.008)
- Time-averaged mean 24-hour urine protein excretion was significantly lower during follow-up in the methylprednisolone group, but the difference was no longer apparent by 3 years of follow-up
- Annual rate of loss of kidney function was significantly less with the methylprednisolone group (mean difference 2.46 mL/min/1.73 m^2 per year, P=0.002). This effect was present in both the full-dose and reduced-dose regimen groups.
- More serious adverse events occurred in the methylprednisolone group (10.9% vs. 2.8%), which were primarily hospitalization or serious infection. This difference was primarily observed in the full-dose methylprednisolone group.

Wyatt, RJ et al. (2013). IgA nephropathy. New England Journal of Medicine, 368, 2402-14. http://www.ncbi.nlm.nih.gov/pubmed/23782179.

- Review article of the pathophysiology, clinical outcomes, and treatment options for IgA nephropathy. IgA nephropathy is considered a glomerular disease as well as autoimmune disease.

1.6.6 Post-Infectious Glomerulonephritis

Rodriguez-Iturbe, B et al. (2008). The current state of poststreptococcal glomerulonephritis. Journal of the American Society of Nephrology, 19, 1855-64. http://www.ncbi.nlm.nih.gov/pubmed/18667731.

- Post-streptococcal glomerulonephritis is becoming increasingly rare in industrialized countries, though the incidence in developing nations remains high and prophylactic antibiotic treatment in endemic regions may be warranted. Genome sequencing may allow for recognition of strains likely to cause disease and improved clinical research.

1.6.7 Membranoproliferative Glomerulonephritis

Paula, L. C. de, Mazzali, M., & Sousa, M. V. de. (2023). Recurrent Membranoproliferative Glomerulonephritis After Kidney Transplantation: Risk Factors and Impact on Graft Survival. *Annals of Transplantation*, *28*. https://doi.org/10.12659/AOT.940502

- Retrospective review of 28 kidney transplant recipients who had a native kidney diagnosis of membranoproliferative glomerulonephritis aiming to identify risk factors for recurrence of native disease
- 7/28 (25%) patients had recurrence of native disease, with two of them progressing to graft failure. Those with recurrence had higher incidences of nephrotic syndrome, hematuria and C3 complement consumption. At 5 years, the eGFR was 67.5±35.1 in the group with recurrence compared to 52.9±8.4 in the group without (P=0.45).

Sethi, S et al. (2012). Membranoproliferative glomerulonephritis – a new look at an old entity. New England Journal of Medicine, 366, 1119-31. http://www.ncbi.nlm.nih.gov/pubmed/22435371.

- Review article of membranoproliferative glomerulonephritis, including the pathophysiology, disease types (complement-mediated, immune complex-mediated), clinical presentation, and therapeutic management. The underlying process should be identified in order to facilitate appropriate disease management.

1.6.8 Hypertensive nephrosclerosis

Appel, LR et al. (2010). Intensive blood pressure control in hypertensive chronic kidney disease. New England Journal of Medicine, 363, 918-29. http://www.ncbi.nlm.nih.gov/pubmed/20818902.

- African American patients with hypertensive chronic kidney disease were randomized to receive intensive (<130/80mmHg) or standard (<140/90mmHg) blood pressure control in order to evaluate whether blood pressure control can slow the progression of renal disease. Intensive blood pressure control had no effect on kidney disease progression, though patients with baseline proteinuria demonstrated a potential benefit.

Freedman, BI et al. (2008). Hypertension-associated kidney disease: perhaps no more. Journal of the American Society of Nephrology, 19, 2047-51. http://www.ncbi.nlm.nih.gov/pubmed/18923054.

- Article suggesting that hypertension may cause progression renal dysfunction only in genetically susceptible individuals (MYH9 haplotype) or may be the result of a primary renal disease. While it is well-recognized that elevated blood pressure can exacerbate existing chronic kidney disease, essential hypertension as the etiology of kidney damage may not be supported by current data.

Marcantoni, C et al. (2002). Hypertensive nephrosclerosis in African Americans versus Caucasians. Kidney International, 62, 172-80. http://www.ncbi.nlm.nih.gov/pubmed/12081576.

- Retrospective study comparing renal biopsies with a histological diagnosis of hypertensive nephrosclerosis among African American versus Caucasian patients. Though MAP and proteinuria were similar between groups, African American patients were found to have more severe histological findings. This again suggests other contributing factors such as genetics and microvascular disease.

Caetano, ER et al. (2001). Hypertensive nephrosclerosis as a relevant cause of chronic renal failure. Hypertension, 38, 171-76. http://www.ncbi.nlm.nih.gov/pubmed/11509471.

- Study evaluating renal biopsies of hypertensive patients (SBP >160 mmHg and/or DBP >95 mmHg) with moderate renal insufficiency (SCr > 1.5 mg/dL) with no clinical evidence of primary or ischemic renal disease. While hypertension alone contributed to benign and malignant nephrosclerosis, a significant fraction of patients with an initial clinical diagnosis of hypertensive nephrosclerosis were found to have histological evidence of primary renal disease (i.e. FSGS).

Luft, FC et al. (2000). Hypertensive nephrosclerosis: a cause of end-stage renal disease? Nephrology Dialysis Transplantation, 15, 1515-17. http://www.ncbi.nlm.nih.gov/pubmed/11007815.

- Editorial questioning the connection between essential hypertension and nephropathy. The author proposes that many factors contribute to nephropathy, including obesity, hyperlipidemia, and genetics; still, blood pressure is a controllable and treatable factor that can prevent progression of renal disease.

Freedman, BI et al. (1995). The link between hypertension and nephrosclerosis. American Journal of Kidney Disease, 25, 207-21. http://www.ncbi.nlm.nih.gov/pubmed/7847347.

- Review article of the correlation between hypertension and renal processes resulting in nephrosclerosis and end-stage renal disease. Suggests that patients with hypertensive nephrosclerosis have contributing mechanisms that increase their susceptibility to progressive renal disease, including primary renal microvascular diseases, renal artery stenosis, and/or genetic factors.

1.6.9 Renovascular and other vascular diseases

Ruggenenti, et al (2011). Chapter 34: Microvascular and Macrovascular Diseases of the Kidney. Brenner & Rector's The Kidney Ninth Edition; p. 1297-331.

- Review of microvascular diseases: thrombotic microangiopathies (Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura), atheroembolic renal disease, radiation nephropathy, and renal involvement in systemic diseases (Scleroderma, Sickle Cell Disease, and the Antiphospholipid Syndrome)
- Review of macrovascular diseases: acute occlusion of the renal artery, aneurysms of the renal artery, and thrombosis of the renal vein

1.6.10 Tubular and interstitial diseases

Muhammad, et al. (2024). The diagnosis of acute interstitial nephritis caused by infection versus antibiotic-induced interstitial nephritis: a narrative review. Clinical kidney journal, 17(4), sfae054. https://doi.org/10.1093/ckj/sfae054

- This narrative review highlights certain findings that can be typical of infection-associated ATIN compared with antibiotic-associated ATIN based on clinical history and physical examination, clinical presentation of different antibiotic drug classes, histopathological features, classical and novel biomarkers, serum and urine cytokines and chemokines, cellular biomarkers, and genetic biomarkers.

Kelly, et al (2011). Chapter 35: Tubulointerstitial Diseases. Brenner & Rector's The Kidney Ninth Edition; p. 1332-55.

- Review of etiology and pathology of acute interstitial nephritis and chronic tubulointerstitial nephritis

1.6.11 Polycystic kidney disease

Capelli, et al. (2024). Investigational agents for autosomal dominant polycystic kidney disease: preclinical and early phase study insights. Expert opinion on investigational drugs, 10.1080/13543784.2024.2342327. Advance online publication.

- This review aims to analyze the set of preclinical and early phase studies to provide a general view of the current progress on Autosomal Dominant Polycystic Kidney Disease (ADPKD) therapeutic options.

Colbert GB, et al (2021). Update and review of adult polycystic kidney disease. *Dis Mon*. 2020; 66(5): 100887. https://pubmed.ncbi.nlm.nih.gov/31582186/

- An overview of pathophysiology, genetic variants, clinical aspects, and therapeutics. Additional sections of prognosis and future directions.

Mosconi G, et al (2013) Renal Transplant in Patients with Polycystic Disease: The Italian Experience. Transplantation Proceedings; 45:2635-2640. http://www.ncbi.nlm.nih.gov/pubmed/24034011.

- Analysis of outcomes in renal transplant recipients with polycystic kidney disease.

Patel P, et al (2011) Native nephrectomy in transplant patients with autosomal dominant polycystic kidney disease. Ann R Coll Surg Engl; 93:391-395. http://www.ncbi.nlm.nih.gov/pubmed/21943464.

- Clinical outcomes at an institution practicing native nephrectomy in patients with autosomal polycystic kidney disease. The study concluded that native nephrectomy was not needed in the majority of patients.

Jacquet A, et al (2011) Outcomes of renal transplantation in patients with autosomal dominant polycystic kidney disease: a nationwide longitudinal study. Transplant International 24:582-587. http://www.ncbi.nlm.nih.gov/pubmed/21352383.

- Results from a nationwide study showing that patients with autosomal dominant polycystic kidney disease are associated with better graft survival, more thromboembolic complications, more metabolic complications and increases rates of hypertension.

Takier V, et al (2011) Polycystic Kidney Disease: Pathogenesis and Potential Therapies. Biochim Biophys Acta. 1812 (10): 1337-1342. http://www.ncbi.nlm.nih.gov/pubmed/21146605

- Review discussing the pathogenic pathways and therapeutic treatments of polycystic kidney disease.

Serra AL, et al (2010) Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. N Engl J Med 363(9): 820-829. http://www.ncbi.nlm.nih.gov/pubmed/20581391.

- A clinical trial using sirolimus in adults with autosomal dominant polycystic kidney disease. The study showed that 18 months of treatment with sirolimus did not halt polycystic kidney growth.

1.7 Chronic calcineurin inhibitor toxicities

1.7.1 CNI and CAN

Karataş, et al. (2024). Should Calcineurin Inhibitors/Sirolimus Be Ceased Completely In Posterior Reversible Encephalopathy Syndrome?. Transplantation proceedings, 56(1), 93–96. https://doi.org/10.1016/j.transproceed.2023.11.012

- Retrospective study of 4 cases of posterior reversible encephalopathy syndrome to investigate the relationship between immunosuppressive treatments and posterior reversible encephalopathy syndrome (PRES) in transplant patients.

Nausens, et al. (2009). Calcineurin inhibitor nephrotoxicity. Clinical Journal of the American Society of Nephrology, 4, 482-508. http://www.ncbi.nlm.nih.gov/pubmed/19218475.

- Review article of the clinical and histologic features of acute and chronic calcineurin inhibitor nephrotoxicity as well as susceptibility factors for nephrotoxicity, including supratherapeutic levels

of cyclosporine or tacrolimus, older kidney age, use of NSAIDs, and certain genetic polymorphisms. The article also includes considerations for prevention and treatment of calcineurin inhibitor-induced nephrotoxicity.

Flechner, et al. (2008). Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity. Clinical Transplantation, 22, 1-15. http://www.ncbi.nlm.nih.gov/pubmed/18217899.

- Review of acute and chronic nephrotoxicity and cardiovascular morbidity associated with calcineurin inhibitors and the impact of calcineurin-sparing strategies in kidney, liver, and heart transplantation.
- In kidney transplantation, several studies have demonstrated modest improvements in renal function but histological damage is observed for the duration that the calcineurin inhibitors are continued, despite dose minimization.

Ekberg, et al. (2007). Reduced exposure to calcineurin inhibitors in renal transplantation (ELITE-Symphony Study). New England Journal of Medicine, 357, 2562-75. http://www.ncbi.nlm.nih.gov/pubmed/18094377.

- Kidney transplant recipients were randomly assigned to one of four treatment groups: standard-dose cyclosporine, low-dose cyclosporine, low-dose tacrolimus, or low-dose sirolimus group.
- All patients in low-dose groups received daclizumab induction, and maintenance immunosuppression consisted of mycophenolate mofetil and corticosteroids in all groups. Superior graft outcomes were seen with low-dose tacrolimus, with significantly higher eGFR, higher allograft survival, and lower rates of acute rejection episodes at 12 months post-transplant.

Flechner, et al. (2004). De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. American Journal of Transplantation, 4, 1176-85. http://www.ncbi.nlm.nih.gov/pubmed/15476476.

- Kidney transplant recipients were randomized to a cyclosporine-based or sirolimus-based immunosuppressive regimen following basiliximab induction, in combination with mycophenolate mofetil and prednisone.
- Patients on sirolimus-based regimens had a lower incidence of chronic allograft nephropathy (CAN) and better renal function at 2 years, with similar patient outcomes, graft outcomes, and acute rejection rates.

Weir, et al. (2001). Long-term impact of discontinued or reduced calcineurin inhibitor in patients with chronic allograft nephropathy. Kidney International, 59, 1567-73. http://www.ncbi.nlm.nih.gov/pubmed/11260422.

- In patients with declining kidney function due to biopsy-proven chronic allograft nephropathy, calcineurin inhibitor dose was reduced or completely discontinued with the addition, continuation and/or increased dose of mycophenolate mofetil and corticosteroids.
- Although intervention slowed the rate of graft deterioration and was associated with a minimal incidence of acute rejection, concomitant strategies such as intensive blood pressure and glucose control should be considered.

1.7.2 CNI and Metabolic Disorders

Sommerer, et al. (2023). Cardiovascular Outcomes in De Novo Kidney Transplant Recipients Receiving Everolimus and Reduced Calcineurin Inhibitor or Standard Triple Therapy: 24-month Post Hoc Analysis From TRANSFORM Study. *Transplantation*, *107*(7), 1593–1604. https://pubmed.ncbi.nlm.nih.gov/36959121/

- Compared incidence of major adverse cardiac events (MACEs) in kidney transplant recipients receiving everolimus and reduced CNI (EVR+rCNI) versus mycophenolate and standard CNI (MPA+sCNI).
- MACE occurred in 81 of 1014 (8.0%; EVR+rCNI) versus 89 of 1012 (8.8%; MPA+sCNI) kidney transplant recipients (risk ratio, 0.91 [95% CI 0.68-1.21]). Incidence of circulatory death,

myocardial infarction, revascularization, or angina was similar between both arms. Predicted risk of MACE within 3 years of follow-up did not differ between treatment arms.
- Concluded that cardiovascular morbidity and mortality were similar between de novo KTRs receiving EVR+rCNI and MPA+sCNI.

Lim, et al. (2022). The Efficacy and Safety of SGLT2 Inhibitor in Diabetic Kidney Transplant Recipients. *Transplantation*, *106*(9), e404–e412. https://pubmed.ncbi.nlm.nih.gov/35768908/

- Multicenter cohort study including 2083 KTRs with diabetes from 6 transplant centers in Korea. 226 of these patients were prescribed an SGLT2 inhibitor for greater than 90 days with mean follow-up of 62.9 ± 42.2 months. The primary outcome was a composite of all-cause mortality, death-censored graft failure (DCGF), and serum creatinine doubling.
- The SGLT2i group had a lower risk of primary composite outcome than the control in both multivariate and propensity score-matched models (HR 0.43; 95% CI 0.24-0.78; P=0.006 and HR 0.45; 95% CI 0.24-0.85; P=0.013, respectively)
- Multivariate analysis consistently showed decreased risk of DCGF and serum creatinine doubling. A minority (15.6%) of users showed an acute dip in eGFR that recovered thereafter.
- SGLT2i improve a composite of all-cause mortality, DCGF, or serum creatinine doubling in KTRs. SGLT2i are safe and have beneficial effects on preserving graft function in diabetic KTRs

Ertuglu, et al (2021). Glucagon-like-peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors for diabetes after solid organ transplantation. *Transplant Int*. 2021; 34(8): 1341-1359. https://pubmed.ncbi.nlm.nih.gov/33880815/

- This review suggests that GLP-1RA are safe and effective in this patient population, but it is possible that higher rates of gastrointestinal events can occur. SGLT2i data is limited and even less than GLP-1RA and studies have shown high rates of discontinuation due to UTI adverse events and may be limited in the SOT population due to GFR dosing cut offs
- Insulin remains the first-line therapy for transplant patients with DM for the first 1-2 months and then could be considered for patients with other predisposing factors

Wissing, et al. (2018). Prospective randomized study of conversion from tacrolimus to cyclosporine A to improve glucose metabolism in patients with posttransplant diabetes mellitus after renal transplantation. Am J Transplant, 18(7):1726-1734. https://www.ncbi.nlm.nih.gov/pubmed/29337426

- Multicenter, prospective study to assess whether conversion from tacrolimus to cyclosporine can reverse posttransplant diabetes (PTDM) after renal transplantation.
- At 12 months, 39% of patients on cyclosporine were off glucose lowering medications compared to 13% of patients in the tacrolimus group.
- The replacement of tacrolimus with cyclosporine significantly improved glucose metabolism and may reverse PTDM in the first year after converting to cyclosporine.

Holdaas, et al. (2017). Cardiovascular parameters to 2 years after kidney transplantation following early switch to everolimus without calcineurin inhibitor therapy: an analysis of the randomized ELEVATE study. Transplantation; 101(10):2612-2620. https://pubmed.ncbi.nlm.nih.gov/28333860/

- Patients were randomized at 10-14 weeks post-transplant to convert from CNI to everolimus or continue on standard CNI therapy.
- No clinically relevant effects on cardiac endpoints were seen after converting to a CNI-free regimen.

Murakami, et al. (2014) Risk of metabolic complications in kidney transplantation after conversion to mTOR inhibitor: a systematic review and meta-analysis. Am J Transplant. 2014;14(10):2317-27. https://www.ncbi.nlm.nih.gov/pubmed/25146383

- Systematic review of nine trials converting patients from CNI to mTOR (n= 2323) with the primary end points of new-onset diabetes after transplant (NODAT) and hypercholesterolemia.

- Relative risk of NODAT and hypercholesterolemia associated with mTOR inhibitors was lower than with CNI-based regimen, but there was a higher risk of acute rejection, proteinuria and anemia associated with mTOR inhibitor conversion.

Vincenti, et al. (2007). Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. American Journal of Transplantation, 7, 1506-14. http://www.ncbi.nlm.nih.gov/pubmed/17359512.

- Nondiabetic kidney transplant recipients were randomized to cyclosporine microemulsion or tacrolimus in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids.
- NODAT or impaired fasting glucose at 6 months post-transplant was significantly lower though LDL and triglyceride levels were significantly higher with cyclosporine microemulsion compared to tacrolimus
- Overall, both groups had similar graft outcomes, patient outcomes, and rejection rates.

Kasiske, et al. (2003). Diabetes mellitus after kidney transplantation in the United States. American Journal of Transplantation, 3, 178-85. http://www.ncbi.nlm.nih.gov/pubmed/12603213.

- Report of data from the United Renal Data System describing the incidence, risk factors, and clinical relevance of new-onset diabetes after transplantation (NODAT).
- Risk factors for NODAT included age, African American and Hispanic race, male donor, increasing HLA mismatches, BMI > 30 kg/m2, and the use of a tacrolimus-based initial maintenance immunosuppressive regimen.
- Factors that reduce the risk of NODAT included, among others, the use of an antimetabolite.

Artz, et al. (2003). Improved cardiovascular risk profile and renal function in renal transplant patients after randomized conversion from cyclosporine to tacrolimus. Journal of the American Society of Nephrology, 14, 1880-88. http://www.ncbi.nlm.nih.gov/pubmed/12819249.

- Stable kidney transplant recipients (>1 year post-transplant, CrCl > 20 ml/min) were randomized to either continuation of cyclosporine or conversion to tacrolimus, with a follow-up of 6 months.
- Tacrolimus conversion was associated with a significant reduction in blood pressure, LDL cholesterol, and triglycerides.
- While the incidence of NODAT is higher with tacrolimus, glucose and HbA1c levels were similar between groups.

Margreiter, et al. (2002). Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicenter study. Lancet, 359, 741-46. http://www.ncbi.nlm.nih.gov/pubmed/11888584.

- Kidney transplant recipients were randomized to de novo tacrolimus or cyclosporine in combination with azathioprine and corticosteroids.
- Regarding the cardiovascular-risk profile, tacrolimus-based regimens were associated with a lower incidence of hypertension and hypercholesterolemia.

Drachenberg, CB et al. (1999). Islet cell damage associated with tacrolimus and cyclosporine: morphological features in pancreas allograft biopsies and clinical correlation. Transplantation, 15, 396-402. http://www.ncbi.nlm.nih.gov/pubmed/10459544.

- Describes the beta cell structural damage caused by tacrolimus and cyclosporine, particularly at higher levels and with concomitant steroid therapy.