UCLA
Proceedings of UCLA Health

Title
Balancing the Efficacy and Toxicity of Maintenance Immunosuppression in a Kidney Transplant Recipient: A Case Report

Permalink
https://escholarship.org/uc/item/8019f6p9

Journal
Proceedings of UCLA Health, 20(1)

Author
Schulze, Carl E.

Publication Date
2016-04-01

eScholarship.org Powered by the California Digital Library
University of California

CLINICAL VIGNETTE

Balancing the Efficacy and Toxicity of Maintenance Immunosuppression in a Kidney Transplant Recipient: A Case Report

Carl E. Schulze, M.D.

A retired engineer who originally had ESRD ascribed to hypertension underwent kidney transplantation from an 8-year-old deceased donor in 1999. His initial post-transplant course was uncomplicated, and there was immediate function of the allograft. His induction immunosuppression consisted of basiliximab, methylprednisolone, and cyclosporine, though the cyclosporine dose was half of the usual dose as part of a clinical trial. His baseline creatinine was initially 1.2. Almost exactly 12 months post-transplant, an increase in creatinine to 1.4 prompted an allograft biopsy, which showed acute tubular injury and no signs of acute cellular rejection. Another biopsy, performed 12 months later (2y post-transplant) due to increasing proteinuria, showed Focal Segmental Glomerulosclerosis (FSGS), IgA deposition, and no rejection; extensive foot process effacement suggested primary FSGS. The proteinuria was treated with an angiotensin receptor blocker and remained subnephrotic. Other complications included post-transplant diabetes (about 1-2y post-transplant with poor control), hypertension (requiring multiple agents), atrial fibrillation (6y post-transplant, on warfarin), legionella pneumonia complicated by non-ST-elevation myocardial infarction and acute kidney injury (about 7y post-transplant), and Parkinson disease (15y post-transplant).

About 2-3 years after the transplant, the maintenance prednisone was stopped (perhaps due to post-transplant diabetes), and mycophenolic acid was added. The creatinine remained about 1.2-1.3 at baseline until about 15 years post-transplant when it started to trend up along with increasing proteinuria. Over the past 2 years, he had worsening edema, and it became increasingly difficult to control hypertension. Now 18 years post-transplant, the creatinine has been around 2.0, and proteinuria has increased to the nephrotic range. Donor-specific antibodies have developed though the time of onset is unclear. He has been advised that his kidney transplant allograft is unlikely to last for more than 12-24 months and that preparation for dialysis access should begin.

Kidney transplantation offers the best quality of life, longest survival, and lowest cost compared to the other forms of renal replacement therapy for end stage renal disease (ESRD).[1] Maximizing allograft survival is critical: 10-12% of transplants each year are retransplants,[2] and many patients waitlisted for kidney transplant do not survive to receive one due to increasingly long waiting times.[3] Indeed, this patient's age, comorbidities, and long waitlist times make him very unlikely to receive another kidney transplant.

Allograft longevity made great leaps forward with introduction of prednisone and azathioprine in the 1960s[4] and cyclosporine in the early 1980s.[5,6] More modest improvements have been seen with mycophenolate in 1998[7,8] and belatacept in 2010.[9] The estimated crude and death-censored half lives for recipients of deceased-donor kidney allografts are now 10 and 15 years, respectively.[2,7] Despite this progress in allograft longevity, the long-term attrition rates remain high and have improved little over time at about 5-7% per year after the first post-transplant year.[7] Antibody-mediated rejection (AMR) and recurrent primary glomerulonephritis are the two most common causes of chronic allograft loss as shown in a recent prospective study.[10] These conditions are treated with higher doses of immunosuppression, but this strategy and indeed all solid organ transplants are limited by the toxicity of chronic immunosuppression.

Kidney transplant patients frequently experience immune-mediated allograft injury and toxicity from immunosuppression at the same time. In this patient, the maintenance corticosteroids were stopped due to the development of new onset diabetes after transplant (NODAT). Though perhaps less feared than opportunistic infections or cancer, NODAT is due in part to immunosuppressive medications and is associated with worse outcomes, including increased rates of cardiovascular events, graft failure, and death.[11] The incidence at 6 months post-transplant was 8.9-16.8% in a recent trial of kidney transplant recipients using modern triple-drug maintenance immunosuppression[12] in comparison to an annual incidence of about 6% for patients on the kidney transplant waitlist.[11] In addition to sharing traditional risk factors for type 2 diabetes, risk factors for NODAT also include glucocorticoids, tacrolimus, cyclosporine, sirolimus, chronic hepatitis C virus infection, HLA-mismatches, and HLA-DR mismatches.[13]

Though stopping the corticosteroids in this patient is a common response to NODAT,[13] this change might have led to formation of the donor-specific antibodies. A multicenter Canadian study comparing glucocorticoid + cyclosporine versus cyclosporine maintenance alone found higher rates of allograft loss in the steroid-free arm at five years.[14] However, a more recent trial using the more potent and widely-used maintenance immunosuppression of tacrolimus and mycophenolate found equivalent rates of patient and allograft survival but a higher rate of acute rejection at 5 years follow up.[15] The recurrent GN occurring in this patient's allograft could have also been worsened by stopping of the steroids.

Retrospective and prospective studies have shown increased rates of allograft loss and recurrent GN both for all types of GN and for IGA nephropathy in patients maintained on steroid-free regimens.[16-18]

Unfortunately, additional treatment options for this patient and the many patients who suffer from chronic allograft nephropathy are limited. There are little clinical trial data for the treatment of chronic AMR.[19] A common strategy is to maximize the dose of the antimetabolite as this usually does not substantially increase the side effects of immunosuppression, although the efficacy is unknown. Prednisone can be re-added to this patient's long list of medications, but this patient's diabetes and sodium retention would probably get worse. His recurrent GN would be unlikely to respond this late. Therefore, this patient's options are limited to increasing the mycophenolate dose and preparing for returning to dialysis.

REFERENCES

1. **Davis AE, Mehrotra S, McElroy LM, Friedewald JJ, Skaro AI, Lapin B, Kang R, Holl JL, Abecassis MM, Ladner DP**. The extent and predictors of waiting time geographic disparity in kidney transplantation in the United States. *Transplantation*. 2014 May 27;97(10):1049-57. doi:10.1097/01.tp.0000438623.89310.dc. PubMed PMID: 24374790.
2. **Matas AJ, Smith JM, Skeans MA, Thompson B, Gustafson SK, Stewart DE, Cherikh WS, Wainright JL, Boyle G, Snyder JJ, Israni AK, Kasiske BL**. OPTN/SRTR 2013 Annual Data Report: kidney. *Am J Transplant*. 2015 Jan;15 Suppl 2:1-34. doi:10.1111/ajt.13195. PubMed PMID: 25626344.
3. **Schold JD, Meier-Kriesche HU**. Which renal transplant candidates should accept marginal kidneys in exchange for a shorter waiting time on dialysis? *Clin J Am Soc Nephrol*. 2006 May;1(3):532-8. Epub 2006 Feb 8. PubMed PMID: 17699256.
4. **Morris PJ**. Transplantation--a medical miracle of the 20th century. *N Engl J Med*. 2004 Dec 23;351(26):2678-80. PubMed PMID: 15616201.
5. **Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D**. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med*. 2000 Mar 2;342(9):605-12. PubMed PMID: 10699159.
6. **Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B**. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *Am J Transplant*. 2004 Mar;4(3):378-83. PubMed PMID:14961990.
7. **Lamb KE, Lodhi S, Meier-Kriesche HU**. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant*. 2011 Mar;11(3):450-62. doi: 10.1111/j.1600-6143.2010.03283.x. Epub 2010 Oct 25. PubMed PMID: 20973913.
8. **Serur D, Saal S, Wang J, Sullivan J, Bologa R, Hartono C, Dadhania D, Lee J, Gerber LM, Goldstein M, Kapur S, Stubenbord W, Belenkaya R, Marin M, Seshan S, Ni Q, Levine D, Parker T, Stenzel K, Smith B, Riggio R, Cheigh J.** Deceased-donor kidney transplantation: improvement in long-term survival. *Nephrol Dial Transplant*. 2011 Jan;26(1):317-24. doi: 10.1093/ndt/gfq415. Epub 2010 Jul 23. PubMed PMID: 20656753.
9. **Vincenti F, Rostaing L, Grinyo J, Rice K, Steinberg S, Gaite L, Moal MC, Mondragon-Ramirez GA, Kothari J, Polinsky MS, Meier-Kriesche HU, Munier S, Larsen CP**. Belatacept and Long-Term Outcomes in Kidney Transplantation. *N Engl J Med*. 2016 Jan 28;374(4):333-43. doi: 10.1056/NEJMoa1506027. Erratum in: N Engl J Med. 2016 Feb 18;374(7):698. PubMed PMID: 26816011.
10. **Sellarés J, de Freitas DG, Mengel M, Reeve J, Einecke G, Sis B, Hidalgo LG, Famulski K, Matas A, Halloran PF**. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant*. 2012 Feb;12(2):388-99. doi: 10.1111/j.1600-6143.2011.03840.x. Epub 2011 Nov 14. PubMed PMID: 22081892.
11. **Ghisdal L, Van Laecke S, Abramowicz MJ, Vanholder R, Abramowicz D**. New-onset diabetes after renal transplantation: risk assessment and management. *Diabetes Care*. 2012 Jan;35(1):181-8. doi: 10.2337/dc11-1230. PubMed PMID: 22187441; PubMed Central PMCID: PMC3241330.
12. **Vincenti F, Friman S, Scheuermann E, Rostaing L, Jenssen T, Campistol JM, Uchida K, Pescovitz MD, Marchetti P, Tuncer M, Citterio F, Wiecek A, Chadban S, El-Shahawy M, Budde K, Goto N; DIRECT (Diabetes Incidence after Renal Transplantation: Neoral C Monitoring Versus Tacrolimus) Investigators**. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. *Am J Transplant*. 2007 Jun;7(6):1506-14. Epub 2007 Mar 12. Erratum in: Am J Transplant. 2008 Jan;8(1):1. Am J Transplant. 2008 Apr;8(4):908. Dosage error in article text. PubMed PMID:17359512.
13. **Pham PT, Pham PM, Pham SV, Pham PA, Pham PC**. New onset diabetes after transplantation (NODAT): an overview. *Diabetes Metab Syndr Obes*. 2011;4:175-86. doi:10.2147/DMSO.S19027. Epub 2011 May 9. PubMed PMID: 21760734; PubMed Central PMCID: PMC3131798.
14. **Sinclair NR**. Low-dose steroid therapy in cyclosporine-treated renal transplant recipients with well-functioning grafts. The Canadian Multicentre Transplant Study Group. *CMAJ*. 1992 Sep 1;147(5):645-57. PubMed PMID: 1521210; PubMed Central PMCID: PMC1336386.
15. **Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P; Astellas Corticosteroid Withdrawal Study Group**. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. *Ann Surg*. 2008 Oct;248(4):564-77. doi: 10.1097/SLA.0b013e318187d1da. PubMed PMID: 18936569.

16. **Von Visger JR, Gunay Y, Andreoni KA, Bhatt UY, Nori US, Pesavento TE, Elkhammas EA, Winters HA, Nadasdy T, Singh N**. The risk of recurrent IgA nephropathy in a steroid-free protocol and other modifying immunosuppression. *Clin Transplant*. 2014 Aug;28(8):845-54. doi: 10.1111/ctr.12389. Epub 2014 Jun 24. PubMed PMID: 24869763.
17. **Clayton P, McDonald S, Chadban S**. Steroids and recurrent IgA nephropathy after kidney transplantation. *Am J Transplant*. 2011 Aug;11(8):1645-9. doi: 10.1111/j.1600-6143.2011.03667.x. PubMed PMID: 21797974.
18. **Kukla A, Chen E, Spong R, Weber M, El-Shahawi Y, Gillingham K, Matas AJ, Ibrahim HN**. Recurrent glomerulonephritis under rapid discontinuation of steroids. *Transplantation*. 2011 Jun 27;91(12):1386-91. doi: 10.1097/TP.0b013e31821bf157. PubMed PMID: 21508898; PubMed Central PMCID: PMC3634349.
19. **Djamali A, Kaufman DB, Ellis TM, Zhong W, Matas A, Samaniego M**. Diagnosis and management of antibody-mediated rejection: current status and novel approaches. *Am J Transplant*. 2014 Feb;14(2):255-71. doi: 10.1111/ajt.12589. Epub 2014 Jan 8. Review. PubMed PMID: 24401076; PubMed Central PMCID: PMC4285166.

Submitted April 1, 2016