Kidney transplantation in C3G:
Transplant or dialysis ?

Christie P Thomas MD
Professor and Vice Chair, Faculty Advancement
Department of Internal Medicine
Medical Director, Kidney Transplant Program
University of Iowa Carver College of Medicine

1

Objectives

- Recognize that long-term dialysis is an option
- Understand when transplantation is the right step
- Be aware of two versus three drug regimens (steroid sparing)
- Understand the side effects of transplant drugs- what patients should know about these drugs (risk of skin cancer, etc.)
- Understand how we monitor recurrence of C3G vs rejection
- Understand the difference between clinical and histological recurrence and the difference between these terms

2

To appreciate when chronic dialysis might be considered

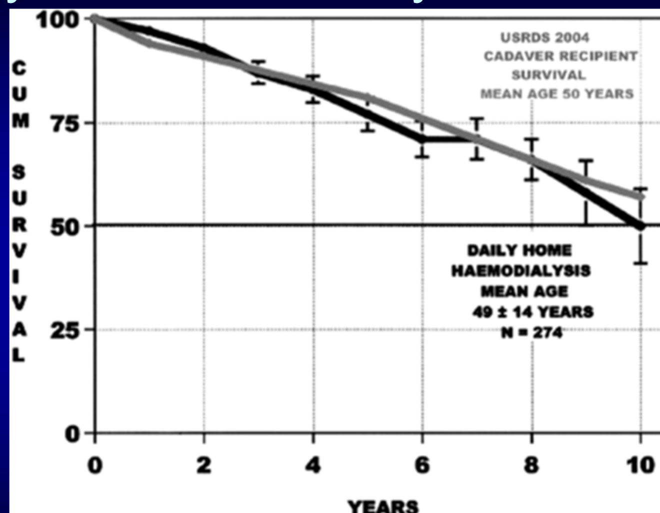
3

Chronic dialysis

- While waiting for a kidney transplant
  - Blood group, lack of living donors, HLA antibodies
- If unable to find a willing transplant center
  - Center concern with C3G recurrence
- If patient wants to wait for better therapy for C3G recurrence
  - Reasonable if prior early recurrent kidney transplant failure

4

Daily home hemodialysis vs transplant

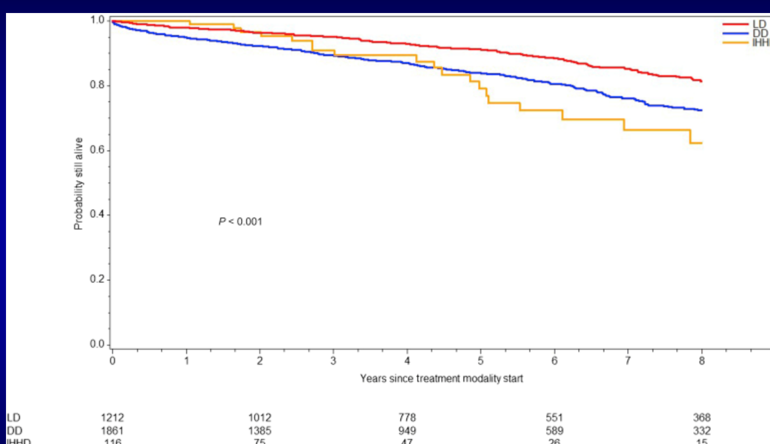


274 multinational SDHD compared to US transplant recipients

Pauly, R.P. Advances in chronic kidney disease, 2009, 16: 169-172

5

Home hemodialysis vs transplant



~3000 transplant recipients and 116 home hemodialysis patients (both from Virginia)
Survival with HD similar to deceased donor recipients

Nishio-Lucar et al., Kidney Int Rep. 2020 Mar; 5(3): 296–306

6

Kidney transplant as the option

7

How to get a kidney transplant

1. You must qualify

- If > 18 yrs old, must have declining kidney function with an eGFR approaching ~20 ml/min/1.73m^2
- If < 18 yrs old, should have declining kidney function and expected to need a transplant or dialysis eventually

2. You must want it

3. A transplant center must accept you

8

Steps in preparing for a transplant - I

- Discuss with your nephrologist as early as possible
- Schedule a visit to a transplant center
- Take your support person (caregiver) with you
- Be prepared for a long visit (1-2 days to complete)

At the transplant center:

Meet with surgeon, nephrologist, social worker, nurse coordinator, dietician, pharmacist, financial counselor, blood tests, X-rays

Sometimes specialists, clinical psychologist, CT scan, stress test

9

Steps in preparing for a transplant -II

- Counseling about dialysis versus transplant for C3G
- Complete any additional visits, tests required (specialists, vaccinations)
- Ask about treatment options for disease recurrence
- Get placed on the transplant waitlist
- Maintain your hemoglobin around 10 gm/dl (avoid transfusion if possible)
- Encourage your living donors to contact transplant center
- Keep your contact information up to date with the transplant center
- Let the transplant center know if you get pregnant, fall sick or need surgery or will be unavailable for an extended period of time

10

Should patients with C3G be transplanted?

- Any patient who has previously not been transplanted should be considered a candidate for a transplant.
- Any patient who has been transplanted but not had early transplant failure from C3G recurrence should also be considered a candidate
- Risk of recurrent disease may be influenced by
  - Sex, age, genetics, autoantibodies, complement activity
- Not all recurrent disease leads to premature kidney loss
- Consequence of early kidney loss
  - early kidney failure from C3G probably predicts recurrent early loss.
  - Exposure to donor kidney leads to development of antibodies to HLA antigens.

Sensitization (HLA antibodies) can make future transplants difficult.

11

When should patients with C3G be transplanted?

- Ideally when the disease appears inactive
  - patient not requiring immunosuppressive therapy
  - Urine testing shows no red cells (blood) or casts
  - Signs of complement activation have resolved
    - Normal C3
    - undetectable C3 nephritic factor (if previously abnormal)
    - MORL assays: Normal CH50, Normal APFA, Normal hemolytic assay
- Adults with monoclonal Ig (MGRS) should first be treated for the plasma cell disease

12

How should C3G patients be transplanted?

- As with other transplants, a living donor is almost always preferable to a deceased donor transplant
- Immunosuppressive regimen should include standard therapy:
  - Induction antibody: Alemtuzumab (Campath®) or anti-thymocyte globulin (Thymoglobulin®) or basiliximab (Simulect®)
  - Maintenance:
    - Std: tacrolimus (Prograf®, Envarsus®), MMF/MPA (mycophenolate, Cellcept®, Myfortic®) +/- prednisone
    - Others: cyclosporin (Gengraf®), azathioprine (Imuran®), sirolimus (Rapamune®), everolimus (Zortress®), belatacept (Nulojix®)
- No data to support pre-operative use of eculizumab, other complement blockers
- Transplant center should have a plan for monitoring for early transplant recurrence
  - Urine for blood (microscopic)
  - Urine protein or albumin

13

Side effects of transplant medications

- Susceptibility to infections – mostly viral, fungal, parasitic
  - Common to transplant – CMV, EBV, BKV, pneumocystis, histoplasmosis
- Susceptibility to some cancers
  - Skin (squamous cell, basal cell, melanoma)
  - Other squamous cell cancers
  - Some lymphomas
  - Kaposi sarcoma
- Increased risk of diabetes (tacrolimus, prednisone)
- Increased risk of CKD (tacrolimus, cyclosporin)
- GI side effects: Nausea, diarrhea (mycophenolate)
- Low blood counts (mycophenolate, azathioprine)
- Hair loss/ excessive hair (tacrolimus, cyclosporin)
- Weight gain (prednisone)

Remember drug drug and drug-food interactions especially with tacrolimus, cyclosporin

14

To understand transplantation options like living donation including directed, non-directed and kidney exchange

15

Types of kidney donors

Deceased Donors

- Patients are listed with UNOS (United Network for Organ Sharing) and wait their turn.
- Waiting times vary based on a variety of factors including; likelihood of benefit (EPTS), time on waitlist, blood group, HLA match and where the donor organ is procured.

Living Donors

- Related (parent, child, sibling)
- Unrelated (spouse, friend, stranger, kidney exchange)

Benefits from a living kidney donor transplant:

- Surgery can be electively scheduled.
- Kidney usually works immediately and lasts longer than from a deceased donor.

16

Types of living donors

- Compatible (Blood type, HLA)
  - Related
  - Unrelated
- Incompatible (Blood type, HLA)
- Compatible but non-ideal (Age, size mismatch)

17

To learn about transplant outcomes for patients with C3G

18

C3G – recurrence after transplant

Summary

- probably universal by biopsy – histological recurrence
- but detectable C3 in biopsy may not always impact kidney function
- clinically meaningful disease: 50% by 3-5 years
- kidney failure in 50% by 7-15 years

19

Summary

- Kidney transplantation is the preferred option for any patient with end stage kidney disease including from C3G
- Get all recommended vaccines prior to transplant if able
- Many vaccines including COVID19 are less effective after transplantation
- Although the risk of recurrent disease is high, it may not occur early or lead to early loss of kidney function
- Although no specific treatment for C3G after transplant is available, new treatments are in clinical trials
- If transplant is not an option or if the wait is expected to be long, consider home hemodialysis rather than center-based dialysis (if able)

20

Questions

21

Treatment options for recurrence

- No FDA approved treatment
- Eculizumab (C5 convertase inhibition) -
  - Has been effective in some C3G cases
  - Most cases prior to transplantation
  - Some required months of therapy prior to response

  Publication bias may be a problem (More reviews than cases)
- C5aR inhibition – Phase 2- Avacopan
- C3 inhibitor: Phase 2 - Pegcetacoplan
- Factor B inhibition-Phase 3 – Iptacopan (LPN023) - MAP

Pediatr Nephrol. 2014 Jun;29(6):1107-11. doi: 10.1007/s00467-013-2711-5. Epub 2014 Jan 10.
Am J Kidney Dis. 2015 Mar;65(3):484-9. doi: 10.1053/j.ajkd.2014.09.025. Epub 2014 Dec 17.
Clin Kidney J. 2015 Aug;8(4):445-8. doi: 10.1093/ckj/sfv044. Epub 2015 Jun 15.
Pediatr Nephrol. 2017 Jun;32(6):1023-1028. doi: 10.1007/s00467-017-3619-2. Epub 2017 Feb 24
Clin J Am Soc Nephrol. 2012 May;7(5):748-56. doi: 10.2215/CJN.12901211. Epub 2012 Mar 8.

22

Should plans for eculizumab be made preemptively?

<u>Options</u>

- Prophylactic use of eculizumab ahead of and following transplant – insufficient data
- Rescue therapy with eculizumab if recurrence occurs and cannot be controlled
  - Contingency planning - ideal
  - Insurance preapproval prior to transplant
  - Required vaccinations prior to transplant

23