Management of recurrent disease risk in patients with FSGS after kidney transplantation

Approved January 21, 2020

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ABBREVIATIONS

AKI	Acute kidney injury
CVL	Central venous line (catheter)
DCD	Donation after circulatory death declaration
DD	Deceased donor
DGF	Delayed graft function
ESRD	End-stage renal disease
FFP	Fresh frozen plasma
FSGS	Focal segmental glomerulosclerosis
HD	Hemodialysis
IL2R Ab	Interleukin-2 receptor antibody (basiliximab)
IV	Intravenous
LD	Live donor
MMF	Mycophenolate mofetil
NS	Nephrotic syndrome
PD	Peritoneal dialysis
PLEX	Plasma exchange
uPCR	Urinary protein to creatinine ratio

GUIDING PRINCIPLES

Primary focal segmental glomerulosclerosis (FSGS) that is not due to congenital or familial (genetic) causes of nephrotic syndrome (NS) is associated with a high risk of recurrence. The pathophysiology of recurrence is incompletely understood, but relapse of nephrotic syndrome is presumed to be associated with the underlying disease process associated with idiopathic FSGS. There is currently no means to identify definitively those children who will experience a relapse of nephrotic syndrome with transplantation. Risk for graft loss in children end-stage renal disease (ESRD) from primary FSGS is associated with donor age and early delayed graft function (1).

- To identify individuals who are at risk for recurrent disease after transplantation in the setting of primary FSGS
- To institute pre-emptive strategies to mitigate the severity of potential recurrent disease and avoid acute kidney injury (AKI)
- To manage post-transplant as if high risk for recurrent disease, until no recurrence has been confirmed
- To institute definitive treatment of recurrence early and fully, once recurrent disease has been confirmed.

FSGS RECURRENT DISEASE GUIDELINES

Pre-transplant considerations

Post-transplant recurrence of FSGS is common – 20-40% in adult populations - and is associated with poor 5-year graft survival. Identification of patients at high-risk of relapse with transplantation, either within the first few days after transplant or later, may help with choosing induction therapy and preventative strategies. Of those patients with primary, non-hereditary FSGS, factors that are associated with relapse include the following general criteria (2, 3)

1) Younger age at diagnosis
2) Rapid progression to ESRD (controversial – multiple papers showing yes *and* no)
3) Lower serum albumin at initial diagnosis
4) Absence of a genetic diagnosis
5) Loss of previous allograft from recurrent FSGS

Donor selection

There is data that suggests that the survival advantage of living donation (over deceased donors) is lost in patients who are transplanted with FSGS, although graft survival is not worse than with a deceased donor. The risk is presumed to relate to inherited risk characteristics shared between a living donor (e.g. parent/sibling) and the recipient. It is unclear whether living-related donors should be avoided, but a preference to living unrelated donors may be considered by utilizing living donor paired exchange. For deceased donors, avoidance of donation after circulatory death (DCD) donors is preferred, due to the increased risk of delayed graft function. In this setting, it is difficult to distinguish delayed graft function (DGF) or AKI that is caused by ischemic injury vs. that which may be an early manifestation of FSGS relapse.

Access considerations

Patients at high risk of recurrence may require prophylaxis with plasma exchange pre-transplant, and will therefore require hemodialysis (HD) access. Depending on what access they have pre-transplant (peritoneal dialysis (PD) catheter, HD catheter, implanted venous access device), discussion and planning is required pre-transplant to determine an access plan for transplantation. Note that patients with a HD catheter who require PLEX may require an additional central venous catheter (CVL) in order to provide continuous fluids therapy while receiving PLEX treatments.

Induction and initial immunosuppression

In general, use otherwise standard-of-care induction immunosuppression. There is not any reported study that indicates superiority of one induction therapy over another. Registry analyses indicate similar utilization of anti-ILR blockade and lymphocyte depleting induction therapy with transplant. Similarly, there are no studies that suggest superiority of cyclosporine over tacrolimus as initial immunosuppression, and contemporary utilization is also similar. (4-6)

1) Recommend using the standard induction and maintenance immunosuppression protocol, with basiliximab and intravenous (IV) steroid induction, tacrolimus, MMF and prednisone.
2) Begin tacrolimus and MMF on the day prior to transplant as per standard protocol.
3) Use standard tacrolimus starting dose. Titrate tacrolimus dose to achieve a target trough level of ~15 µg/L, which is higher than the standard protocol: acceptable trough levels are considered within the range of 12-18 µg/L.

4) Consider TID tacrolimus dosing with a similar overall exposure if using large doses or having side effects. TID dosing gives similar overall exposure with lower peaks.

Monitoring for nephrotic syndrome recurrence

In the case of recurrence of nephrotic syndrome in patients with primary FSGS, early detection and initiation of intensive treatment is a priority. Early detection may be confounded by proteinuria detected along with gross hematuria (stent) and by post-operative decline in serum albumin due to volume resuscitation and capillary leak from ischemia/reperfusion injury. Obvious recurrence of FSGS is defined by clinical criteria for Nephrotic Syndrome (hypoalbuminemia, edema, proteinuria $\geq$5 g/L). Note that urinary protein:creatinine ratio (uPCR) may also be elevated with low urine creatinine, so total urine protein concentration may be more reliable indicator. Relapse may have more insidious presentation and may also present as delayed or slow allograft function, which in high risk patients should be viewed as highly suspicious of relapse. Biopsy confirmation is required for definitive diagnosis, but should not delay initiation of treatment in the setting of relapse diagnosis based on clinical criteria (7-11).

Freedom from relapse is defined by progressive recovery of renal function to expected level post-transplant, improving serum albumin and absence of significant proteinuria.

1) Monitor daily serum albumin, urinalysis, urine protein concentration, urine protein:creatinine ratio and renal function post-transplant. Monitor urine osmolarity (not SG) to test for urinary concentration.
2) Clinical signs of possible relapse should prompt consideration of urgent kidney biopsy with electron microscopy, if the diagnosis of relapse is uncertain. The goal of biopsy is then to rule out acute rejection and identify histologic signs to confirm effacement of glomerular basement membrane.
    - Delayed/slow graft function (early plateau above expected Cr)
    - Rising creatinine
    - Developing oliguria
    - Worsening proteinuria

Nephrotic syndrome prophylaxis with PLEX

There is no universally recognized standard of care for prophylactic treatment to prevent FSGS recurrence, nor has any therapy conclusively been demonstrated to be effective. Research to properly evaluate FSGS prophylaxis is limited due to number of cases. The most common measure that has been utilized is plasma exchange (PLEX), which is limited to uncontrolled studies. A potential advantage in absence of prophylactic efficacy is the immediate readiness to perform/continue therapeutic PLEX upon detection of FSGS relapse (see below). Risks associated with prophylactic PLEX include coagulopathy, alkalosis and management of calcium homeostasis.

Other prophylactic treatments have been proposed, and overlap with treatment used to treat recurrence. They include LDL apheresis (not available at BCCH) and rituximab, but neither has shown efficacy in preventing recurrence. (7, 12-15)

Discuss the PLEX treatment plan with the PLEX consultant in order to plan treatment and write PLEX orders (i.e. Dr. Mammen or Dr. Strahlendorf); and to coordinate PLEX treatments with dialysis considerations (see below).

1) Recommend to provide 3 consecutive daily PLEX treatments starting on the day before transplant, on the day of transplant post-operatively, and on the day after transplant (i.e. Days -1, 0, +1).
2) Start prophylactic PLEX on Day -1 (pre-transplant) for all patients at high risk for FSGS relapse. Preparation for prophylactic PLEX must include placement of a hemodialysis catheter immediately upon admission to hospital (deceased donor) or in the week prior to transplant (living donor).
3) Refer to pre-formatted PLEX order set. PLEX prescription to include 1.5x exchange volumes with 5% albumin, and 10-20 ml/kg FFP at the end of each course (to mitigate coagulopathy). For the pre-transplant dose, consider 20 ml/kg if rushed to the operating room.
4) Basiliximab to be given immediately after PLEX treatment, to avoid removal.
5) Coordinate the PLEX #2 for the post-operative period (transplant Day 0), once the patient has stabilized and there are no concerns about electrolytes (e.g. Ca, Mg) or bleeding risk.
6) Continue PLEX for a minimum of three treatments: PLEX #3 provided on Day +1 post-transplant.

After PLEX #3:

- If no evidence of relapse: Discontinue PLEX after 3rd dose and resume standard post-transplant protocol.
- If there is evidence of relapse, or the diagnosis of relapse is uncertain: Continue PLEX on a M-W-F schedule as per treatment of FSGS relapse recommendations.
- If considering further PLEX, order PT, PTT, INR, and fibrinogen prior to next PLEX session. Also recall that CBC is required (for HCT) prior to each PLEX session.

Dialysis considerations

PLEX can result in fluid, electrolyte and acid-base disturbances and so in some cases the preference is to provide dialysis after PLEX treatment. However, because of the use of heparin anticoagulation the case of hemodialysis, it may sometimes be preferable to complete the dialysis treatment first. FFP can be used post-PLEX to reverse coagulation abnormalities. There are also logistical issues for timing of access both to PLEX and hemodialysis that must be factored in. For this reason, the timing of dialysis and PLEX should be decided upon in collaboration with the PLEX provider and in consideration of timing of surgery or other procedures where there is a bleeding risk.

Treatment of nephrotic syndrome recurrence

In adult populations, the standard of care follows from Canaud et al, who describe intensive combined therapy leading to drastically improved results over previous studies or a mixed control group (16). In patients without relapse, discontinue PLEX and continue standard post-transplant immunosuppression and monitoring. In the case of histologically confirmed relapse or clinically obvious relapse (without immediate biopsy confirmation), initiate treatment protocol for FSGS recurrence. (4, 17, 18)

1) Continue PLEX with Albumin 5% replacement, 1.5x exchange volume, 3 times per week for 3-6 months. Review requirement for replacing FFP with PLEX/dialysis team. If complete and sustained remission is obtained (>2 weeks), wean frequency of PLEX every 2-4 weeks and assess for relapse at each stage. In the case of partial remission (sustained reduction of uPCR by >50%), continue PLEX 3 times weekly. If treatment unresponsive by 3 months (uPCR reduced by <50%), then consider discontinuation of PLEX.

2) PLEX monitoring: CBC and Mg prior to every PLEX treatment (for HCT). After 3rd dose of PLEX, order PT, PTT, INR, and fibrinogen prior to next PLEX session (4th). INR, PTT, fibrinogen weekly on Monday.
3) Rituximab (375 mg/m2/dose): 2 doses one week apart. Administer immediately after PLEX treatment to avoid removal.
4) Optimize high-dose steroids (60 mg/m^2/day) x4-6 weeks minimum (similar to standard NS protocol), to assess steroid responsiveness. If unresponsive, wean steroids every 2 weeks to until a dose of 3 mg/m2 (40, 30, 20, 10, 5, 3 mg/m2). If partial or complete remission within 4-6 weeks, then wean as above q.2-4 weeks according to the same schedule, and hold wean if evidence of relapse during wean. Ensure therapeutic levels of MMF and TAC prior to instituting wean.
5) Optimize tacrolimus: Modify tacrolimus trough target at 15 mcg/L (range 12-18 mcg/L). Consider TID dosing if requiring large doses, or to mitigate adverse effects.
6) Optimize MMF: Verify MPA trough level at day 4 (per protocol) and at weeks 1, 2. If ongoing high-grade proteinuria, increase MMF dosage to 900 mg/m2/dose to account for excess urinary drug loss from protein binding. Consider PK studies once titrated to higher dose, to verify drug exposure achieved. Continue to monitor MPA trough every 2 weeks during high-dose treatment. As proteinuria is diminishing, monitor carefully for MMF toxicity and consider empiric dose reduction if trough MPA levels are consistently elevated (>5).
7) Maintain good urinary flow to avoid AKI. If developing oliguria (which may be associated with increased TAC exposure or ADH effect with nephrosis), increase urinary flow with addition of loop diuretics to inhibit urinary dilution. Avoid severe fluid restriction, rather maintain effective diuresis with diuretics and employ only modest fluid restriction if required to control edema.
8) If considering use of ARB for hypertension/proteinuria, discuss first with the PLEX team due to caution with ongoing PLEX and risk for adverse reactions.

Other treatments (not standard)

Calcineurin Inhibition

CNIs are a mainstay of therapy for primary, non-genetic FSGS at BCCH, and are second line treatment after failure of prednisone. There is mixed evidence in primary FSGS, with some studies showing it might not be useful. That being said, the Canaud method of intensive combined therapy for FSGS relapse makes use of Cyclosporine, and there has long been evidence for high dose CNI in FSGS relapse.
One head-to-head trial of Cyclosporine vs Tacrolimus with only 18 patients total showed equal response (8/9 vs 9/9 remission). Early trials were all based on Cyclosporine, and it is often used as a result, even in centres that have since otherwise switched to Tacrolimus. See Kang et al, and Canaud et al for some indication that Tac is non-inferior to Cyclosporine. In the setting where cyclosporine may be preferred to tacrolimus, the following protocol may be preferred: IV Cyclosporine 2mg/kg (target level 200-400 ng/mL) x2 weeks. (7-11, 19)

LDL apheresis

LDL apheresis is a form of apheresis, using a column with antibodies against apolipoprotein B. It is used similarly to Plasma Exchange, in multiple doses over weeks. It has been used to ameliorate proteinuria, and to induce renal function in anuric FSGS patients, but not successfully reported as treatment or prophylaxis. **Not available at BCCH (15)

Abatecept/Belatacept
Abatacept is a B7-1 inhibitor, a pathway that has been implicated in FSGS recurrence. Initially was shown to be effective in patients in whom staining of their initial biopsy had shown positive staining of B7-1. It has had mixed results in trials, with many negative follow-up attempts. (20, 21)
Others

Hemoadsorption
with CytoSorb (PE adjunct – removes suPAR) has been shown to decrease urinary suPAR levels, but recent advances from the suPAR team (Wei et al) have shown that suPAR levels independently are not necessarily indicative of increased risk of relapse. (22)

Ofatumumab
A second-generation anti-CD20 monoclonal antibody, has been reported once with (partial) success in treating recurrence (20, 23). Despite the similarity to rituximab, it has been used successfully in patients who have failed to respond to rituximab.

Bleselumab (a.k.a. ASKP1240)
An investigational anti-CD40 monoclonal antibody that is currently in clinical trials for treatment of patients at risk of FSGS recurrence (24-26). It provides co-stimulatory blockade and also may have dual-purpose eficacy for induction immunosuppression at transplant (27).

RELATED DOCUMENTS

None

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DOCUMENT HISTORY

VERSION	EFFECTIVE DATE	WRITER	REASON
Initial draft	May 15, 2018	IE/TBH/CM/KH	Draft- Initial creation of guideline
V1.0	Jan 3, 2020 For approval	TBH/CM/LB/LP/KF	Multiple updates based on experience with initial draft.
	Jan 21, 2020 Approved		Approved at MOT Council: Jan 21, 2020

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