Secondry Glomerulonephritis after transplantation

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AAV

- AAV patients should be in remission for 1 year prior to performing RTx.
- The risk of post-transplant relapse is high in:

recipients with PR3 ANCA positivity

Patients with GPA

subjects with positive ANCA at transplant

•The time to relapse after RTx (ranging from only 5 days to > 13 years and a mean time being 31months

- The combination of mycophenolate mofetil, prednisone, and tacrolimus has decreased vasculitis relapse rates post transplant to 5–10% with very few recurrences in the allograft.

Zdenka Hruskova

Kidney Blood Press Res 2020;45:157–165

In the study by Marco et al.

- 38% of relapsing patient had renal involvement
- 48% extrarenal involvement
- and the remaining patients displayed signs of both renal and extra renal involvement.
- extrarenal involvement (particularly of upper and/or lower respiratory tract) being more common in patients with PR3-ANCA

Clin Transplant 2013 DOI: 10.1111/ctr.12084

AAV

Clinical manifestions:

- vasculitis activity should be monitored every 3–6 months clinically and by measurement of serum creatinine and urinalysis.
- Microscopic hematuria can be an early indicator of vasculitis relapse before a rise in serum creatinine becomes.
- *persistent positivity for ANCA or rise in ANCA titer are not reliable predictors of relapse.*

AAV

TREATMENT:

- Treatment of AAV relapse post transplant is similar to the non transplant setting .
- Non severe relapses are often treated with increase in glucocorticoid dosing.
- For treatment of severe relapses, both cyclophosphamide and rituximab are effective for remission induction.

Zdenka Hruskova

Kidney Blood Press Res 2020;45:157-165

AAV

Similar to nontransplant setting, rituximab may be preferred for remission induction in AAV patients :

- who are in reproductive age group
- those with history of malignancy and
- history of relapsing vasculitis
- and higher cumulative cyclophosphamide exposure prior to transplant.

AAV

When cyclophosphamide is used for remission induction:

- stopping mycophenolate mofetil and resuming once remission is achieved.

When using rituximab for remission induction:

- mycophenolate is continued with monitoring of blood count.

The choice of induction therapy should be individualized based on:

- patient age, disease severity, prior exposure to cyclophosphamide, and ANCA type.

Anti GBM

- The incidence of recurrent linear (IgG) staining in the transplant may be as high as 50 percent .
- most patients remain asymptomatic.
- delaying kidney transplantation until circulating anti-GBM antibody levels have been undetectable for at least 12 months and there has been quiescent disease for at least six months post treatment (without cytotoxic agents).
- recurrent anti-GBM disease can range from months to several years posttransplant.

Clin J Am Soc Nephrol

2017 Jul 7 doi: 10.2215/CJN.01380217

AntiGBM

The **diagnosis** is established by :

- the presence of elevated circulating anti- GBM antibody titers
- and a renal allograft biopsy demonstrating positive immunofluorescence.

AntiGBM

TREATMENT:

- perform plasmapheresis as soon as possible to remove the circulating anti-GBMantibody.
- The plasmapheresis prescription and duration of treatment are similar to those used in the treatment of disease in the native kidneys
- start oral cyclophosphamide and discontinue the antimetabolite used for maintenance immunosuppression (mycophenolate or azathioprine).
- The dose of cyclophosphamide and duration of treatment are similar to those used in the treatment of disease in the native kidneys.

Clin Transplant

Jan-Feb 2009;23(1):132-6.

doi: 10.1111

AntiGBM

- high-dose oral prednisone (1 mg/kg per day to a maximum of 60 to 80 mg/day), followed by a taper to the original maintenance dose once remission is induced.

- In patients who present with pulmonary hemorrhage, give pulse methylprednisolone (15 to 30 mg/kg to a maximum dose of 1000 mg) daily for three doses prior to starting daily oral prednisone.
- Augment maintenance immunosuppression by targeting higher trough levels of the calcineurin inhibitor (ie, tacrolimus levels of 7 to 10 ng/mL or
- cyclosporine levels of 100 to 150 ng/mL).

Daniel C Brennan, MD, FACP

Andrew Malone, MB, BCh, MRCPI

AntiGBM

Administer antimicrobial and antiviral prophylaxis for the patient receives cyclophosphamide

This includes :

- prophylaxis against *Pneumocystis pneumonia (PCP).*
- cytomegalovirus (CMV) infection and disease, and herpes simplex infection (in patients who are at low CMV risk).
- antifungal prophylaxis, although this practice may vary by transplant center.

AntiGBM

- anti-GBM antibody levels should be monitored every one to two weeks until they are negative on two occasions.

- periodically monitor anti-GBM levels for up to six months to confirm that remission is maintained or at any time if there are clinical signs suggestive of recurrence.

SLE

- All patients with ESRD due to lupus nephritis be dialyzed for at least three to six months and be on less than 10 mg of prednisone per day before kidney transplantation.
- Recurrent lupus nephritis can occur first week to as late as 16 years after transplantation (median 4.3 years in the large study cited above)
- The reported rate of clinically apparent recurrent lupus nephritis in the kidney transplant is 2 to 11 percent.

SLE

Patients with recurrent lupus nephritis generally present with :

- an increased serum creatinine above their usual baseline
- new-onset or worsening proteinuria of a variable degree
- and new-onset hematuria on routine screening
- ***Serologic parameters are not an accurate assessment of disease activity and do not help in predicting disease recurrence in the allograft.***

IN the study by Burgo et al.

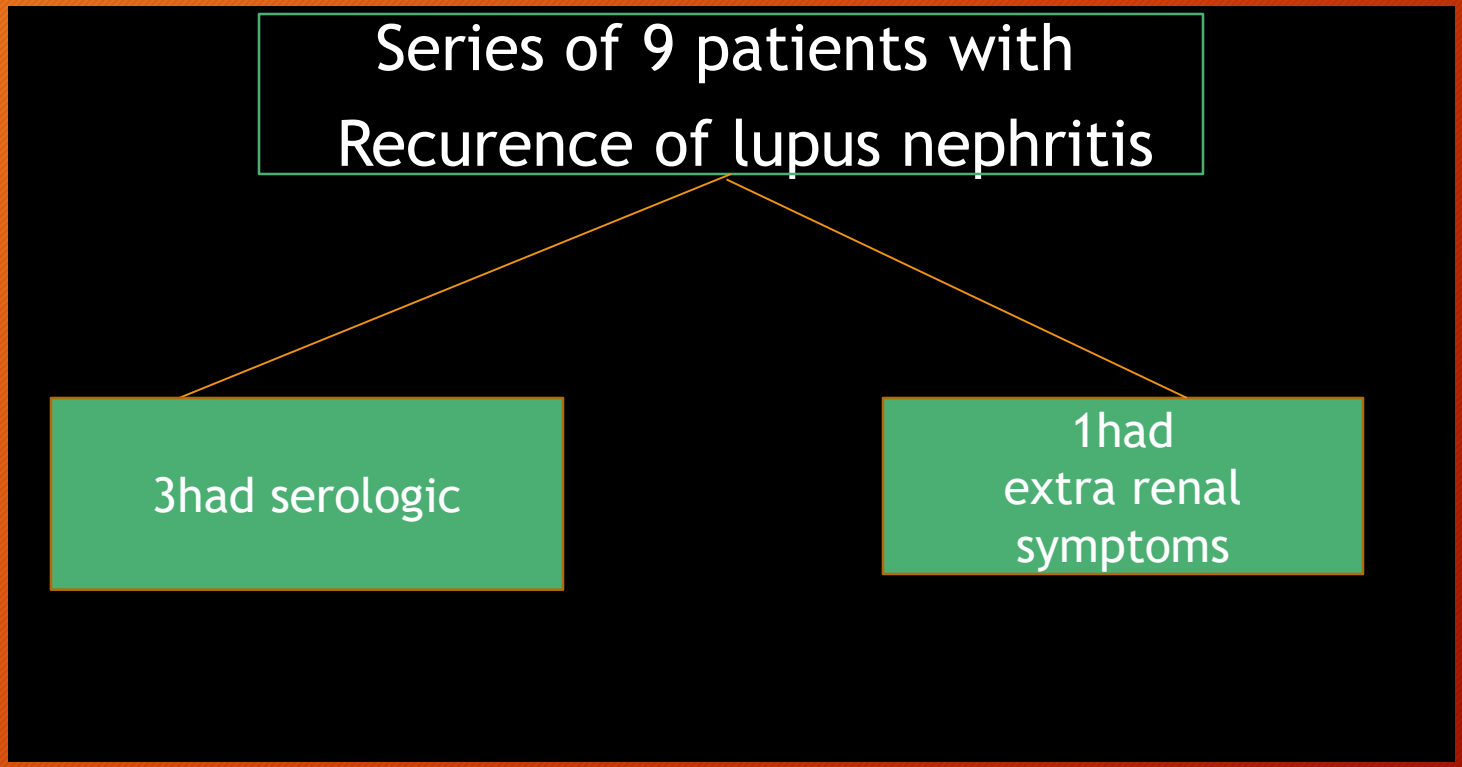
Arthritis Rheum. 2009 September 60(9): 2752766doi:10.1002/art.24776s

A study of 177 patients with lupus nephritis and a kidney transplant followed over a 30- year interval included 20 patients (11 percent) with recurrent nephritis:

In the native kidneys:
proliferative GN (class III or class IV, n = 10)
or membranous nephropathy (class V, n =6).

in the transplanted kidney:
most often mesangial lesion (class II, n =12),
3 patients having proliferative lesions.

In the Study by JOHN H. STONE



SLE

Nonimmuno suppressive treatment of recurrent nephritis

- generally treat all patients who:
- have histopathologic changes of recurrent lupusnephritis and
- proteinuria that is >300 mg/24 hours
- with renin-angiotensin system (RAS)blockade.

SLE

Immunosuppressive treatment of recurrent nephritis:

- Most patients with recurrent lupus nephritis: particularly those who have mild lesions on allograft biopsy
- ***do not require any change in the immunosuppressive regimen that they use to prevent rejection.***

SLE

Selected patients may require immunosuppressive therapy directed at recurrent lupus nephritis.

- who have a histologic diagnosis of recurrent lupus nephritis and rapid deterioration of kidney function.
- or who have proteinuria >500 mg/day accompanied by severe proliferative lesions on biopsy

SLE

- Increase the dose of mycophenolate mofetil to 2 to 3 g/day.
- Administer cyclophosphamide and discontinue the current antimetabolite (which is usually mycophenolate mofetil/sodium or azathiopri
- cyclophosphamide (0.5 to 1 g/m2 iv pulses monthly for six months)
- methylprednisolone 7 mg/kg/day (or 500 mg) iv for three days followed by a tapering oral glucocorticoid regimen.
- For patients who have failed treatment with both mycophenolate and cyclophosphamide:
- rituximab (1000 mg given on days 1 and 15)
- in addition to increasing mycophenolate to 3 g/day
- and increasing glucocorticoids (ie, methylprednisolone 7 mg/kg/day or 500 mg daily for three days followed by a tapering oral glucocorticoid regimen)

Fre ́de ́ric A. Houssiau

2002

SLE

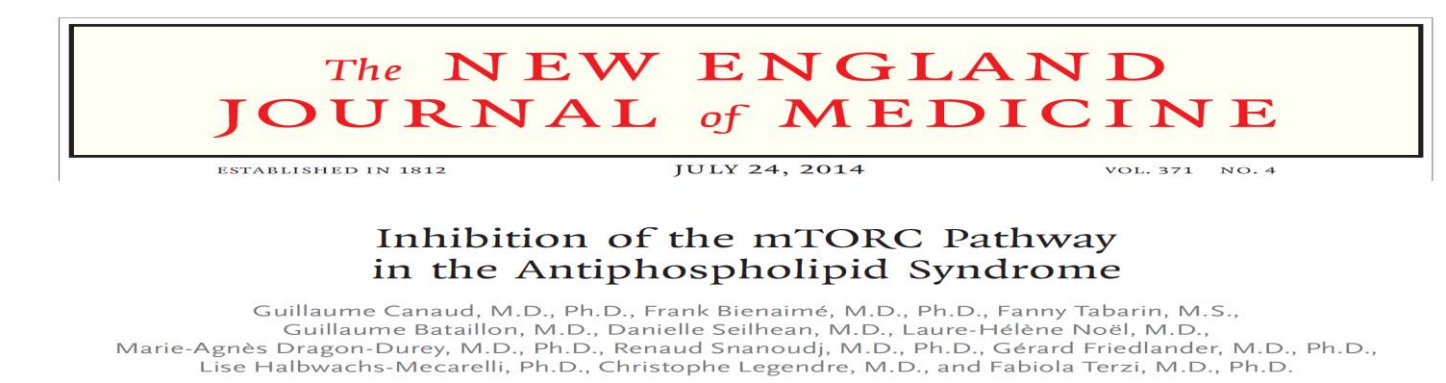
- **Renal prognosis**

The incidence of graft loss due to recurrent disease is low, being less than 2 to 4 percent over 5 to 10 years in most studies.

APS

Patients with systemic lupus erythematosus (SLE), a positive aPL, a history of thromboembolic events and lupus nephritis, as well as those with the APS

- may benefit from continued warfarin therapy after renal transplantation.
- The target INR for warfarin therapy was 2.0 to 2.5.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 24, 2014 VOL. 371 NO. 4

Inhibition of the mTORC Pathway in the Antiphospholipid Syndrome

Guillaume Canaud, M.D., Ph.D., Frank Bienaimé, M.D., Ph.D., Fanny Tabarin, M.S., Guillaume Bataillon, M.D., Danielle Seilhean, M.D., Laure-Hélène Noël, M.D., Marie-Agnès Dragon-Durey, M.D., Ph.D., Renaud Snanoudj, M.D., Ph.D., Gérard Friedlander, M.D., Ph.D., Lise Halbwachs-Mecarelli, Ph.D., Christophe Legendre, M.D., and Fabiola Terzi, M.D., Ph.D.

- Inhibitors of the mammalian target of rapamycin (mTOR) may decrease the recurrence of APS-associated vascular lesions among kidney transplant recipients.

In the study by JohnW.Eikelboom
2014

- 10 patients +APS+sirolimus

✓decreased hyperplasia of endothelial cells
✓allograft function appeared to be better

- 27 patients+APS -sirolimus

TMA

- The recurrence rate after KTX is between 25 and 50 percent .
- Recurrence is uncommon among patients who had infection-related TMA.
- Adults have recurrence more than children with HUS .
- recurrence : 50 to 100 percent among patients with mutations (CFH or CFI) .
- 15 to 20 percent among patients with mutations (MCP) .

Clin J Am Soc Nephrol 1: 811–819, 2006

TMA

Other risk factors that have been associated with recurrent TMA in the renal allograft include

- short duration between disease onset and ESRD or transplantation
- receiving a living-related donor kidney
- and use of calcineurin inhibitors

Patients with recurrent TMA usually present within one year after transplantation and often within days to weeks (3m)

TMA

aHUS recurrence and PT-TMA are clinically and pathologically indistinguishable:

- a personal and family history of aHUS
- an abrupt onset
- and a complete and systemic TMA are suggestive of aHUS recurrence

Extrarenal manifestations of aHUS apart from hemolytic anemia are frequent in aHUS recurrence, but they are rarely observed in de novo PT-TMA .

Ana Ávila

2021

TMA

- In transplant patients suspected of having TMA, a renal allograft biopsy is not required to confirm the diagnosis of TMA

- genetic mutation associated with complement-mediated TMA can confirm the diagnosis.

TMA

Avoid using a living-related donor kidney for patients with TMA attributed to a genetic mutation.because:

- some patients have more than one mutation,
- one-third of patients with TMA have complement mutations presently unidentified.
- nephrectomy may trigger complement-mediated TMA in the genetically susceptible donor.

TMA

Prophylactic therapy with eculizumab

- initiate eculizumab (an antibody that targets the complement component C5) prior to transplantation in all patients with complement-mediated TMA due to a genetic deficiency or dysfunction of CFH or CFI.

TMA

In patients who are receiving a **living-unrelated donor** kidney:

- administer eculizumabn at 900 mg iv 24 hours prior to transplantation and on days 7, 14, and 21 following transplantation, followed by 1200 mg every 2weeks thereafter.
- Supplemental doses (900 mg or 1200 mg) may need to be administered in settings where complement activation is known to occur, such as following **surgery** or when there is **infection**

In patients who are receiving a **deceased-donor** kidney:

- administer eculizumab at 900 mg iv on postoperative day 3 (after completion of antithymocyte globulin induction) and continue 900 mg weekly for 3 additional doses, followed by 1200 mg every 2weeks thereafter.

TMA

Combined kidney-liver transplantation

- In patients with ESRD due to TMA related to mutations of complement factors that are produced by the liver (eg, CFH), combined kidney-liver transplant has been used to correct the ESRD along with the underlying etiology of TMA.

TMA

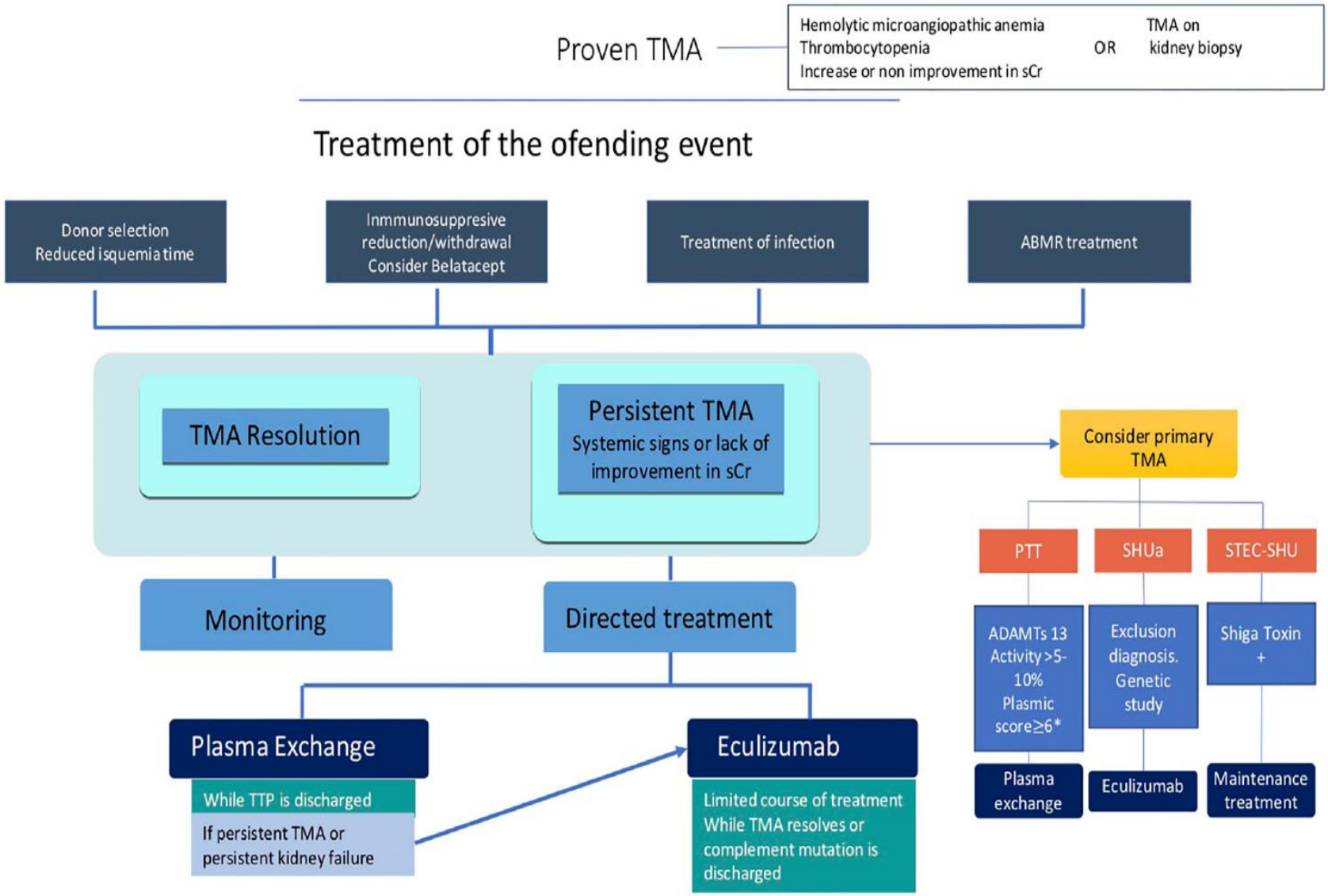
TREATMENT:

All patients with recurrent TMA with eculizumab, 900 mg iv administered weekly for 4 weeks followed by 1200 mg every 2weeks thereafter

In patients with recurrentTMA, plasmapheresis is generally reserved for patients who have TMA associated with (CFH) antibodies or

used as a temporizing measure in patients awaiting the availability of eculizumab therapy.

Post-transplant TMA management



TMA

Prophylaxis against meningococcal infection

- Treatment with eculizumab is associated with life-threatening and fatal meningococcal infections.
- Patients should receive meningococcal vaccination at least two weeks prior to initiation of eculizumab .

patients listed for transplant with atypical hemolytic uremic syndrome (HUS) are vaccinated against meningococcus prior to transplant.

- children should be vaccinated for *S. pneumoniae and Haemophilus influenza type B (Hib) as they are at risk of developing*

serious infections due to these bacterial species

TMA

Monitoring during eculizumab therapy

- Among patients treated with eculizumab, monitor:
- hemoglobin, platelet count, lactate dehydrogenase (LDH)

daily while patients are hospitalized and then at each subsequent clinic visit.

- To assess the effectiveness of complement blockade, measure (CH50) prior to each dose of eculizumab for the first four doses; patients with complete suppression should have a CH50 of <10 percent.
- trough serum eculizumab levels (if available) can be measured with a target level of >100 mcg/mL .

THANKS FOR ATTENTION