Liver/kidney Transplantation & HUS….Is there a place after complement inhibitors?

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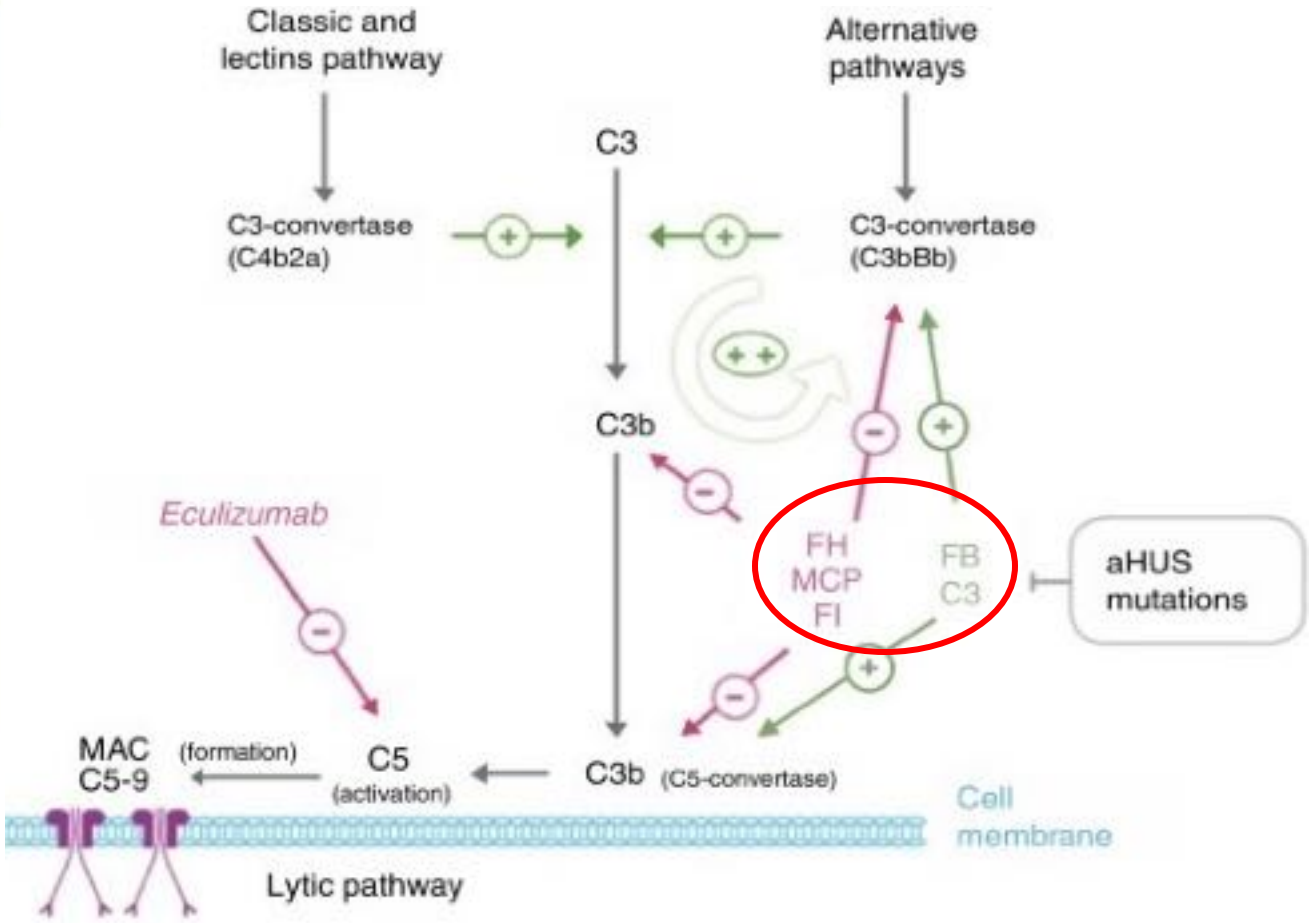
Source and location of complement-related proteins

Protein	Source	Location
Factor H	Liver	circulates
Factor I	Liver	circulates
C3	Liver, ?	circulates
Factor B	Liver, ?	circulates
MCP	Widespread	Membrane bound
Thrombomodulin	Liver, ?	Membrane bound - 5% circulates
Anti-FH-Ab	Lymphocyte	circulate

Jozsi et al. Blood 2008, Frémeaux-Bacchi V et al. Blood 2008, Goicoechea de Jorge 2007, Caprioli, et al Blood 2006, Kavanagh Curr Opin Nephrol Hypertens, 2007, Noris, NEJM 2009



Agenda

- Liver TX / combined liver kidney TX in HUS
- Complement inhibitors (eculizumab & rovulizumab)
- Eculizumab in ESKD….can it avoid need for TX?
- Prophylactic/ rescue eculizumab therapy in isolated KTX
- Eculizumab monitoring of effectiveness, duration, side effects
- Combined liver kidney TX & Eculizumab
- Combined liver kidney TX or Eculizumab

Combined liver kidney transplantation

With the exception of CD46 (MCP), the complement proteins implicated in the pathogenesis of aHUS (FH, FI, C3 and FB) are synthesized in the liver

Therefore liver TX in patients with mutations in one of these genes will restore normal complement control & considered curative option

Either liver TX (in patients with preserved kidney function) or combined liver kidney/TX is a potential treatment for aHUS

The need for liver Tx

- Organ shortage, which delays access to Tx
- Morbidity and mortality of liver Tx

Combined liver kidney transplantation

- The first experiences with LKT for treatment of aHUS were not-favourable
- Early acute liver failure probably resulted from intense intrahepatic complement activation with vascular injury
- Complement activation occurs in the graft organ during liver TX and triggers systemic complement activation

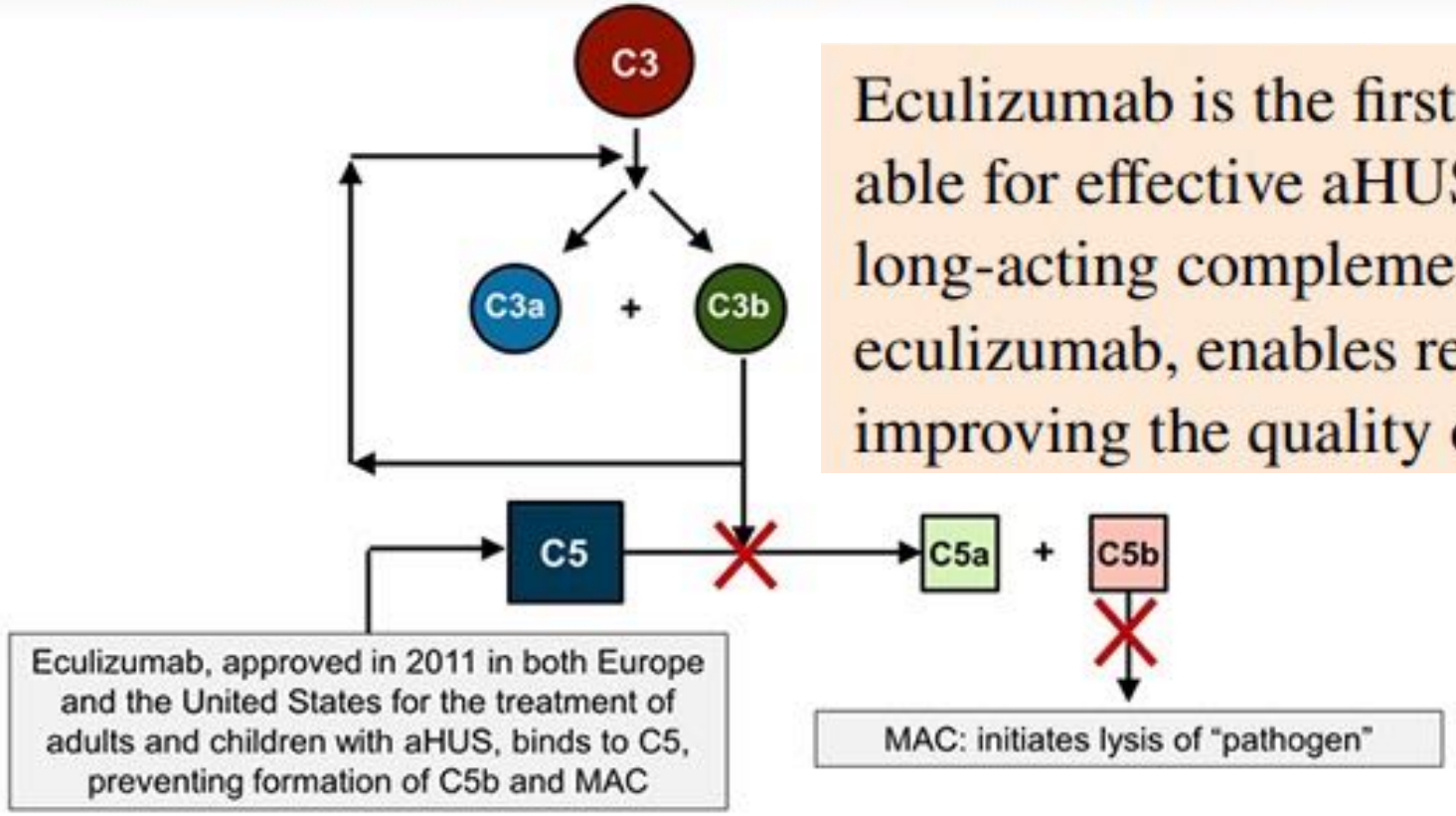
Am J Transplant 2005; 5: 1146–1150

More recent reports using prophylactic PE prior to surgery and anticoagulation have reported good outcomes

Clin J Am Soc Nephrol. 2009; 4(1): 201–206.

Complement inhibitors

Eculizumab
A Monoclonal, Humanized Antibody to C5



Eculizumab is the first complement inhibitor available for effective aHUS treatment. Ravulizumab, a long-acting complement inhibitor, re-engineered from eculizumab, enables reduction in dosing frequency and improving the quality of life in patients with aHUS.

Barbour T, et al. *Nephrol Dial Transplant*. 2012;27:2673-2685[5]; Zuber J, et al. *Nat Rev Nephrol*. 2012;8:643-657[23]; Schmidtko J, et al. *Am J Kidney Dis*. 2013;61:289-299.[25]

Complement Inhibitors

- Efficiently increase the chance of full recovery of renal function
- Prophylactic treatment markedly reduce risk of post-TX recurrence
- Except for meningococcal meningitis in 2/100 patients it is well tolerated

- Re-engineered from eculizumab by a two amino-acid substitution
- Targets the same epitope on C5 as eculizumab, but has a four times longer half-life
- Allow reduction in the dosing frequency and improving QOL

Pediatric Drugs (2023) 25:193–202

Eculizumab in ESKD…can it avoid need for TX?

Based on previous reports, eculizumab is expected to **improve CKD by more than 1 stage**

This effect of eculizumab is **time dependent**

N Engl J Med 2013;368: 2169-2181

More recently Eculizumab was proven to improve kidney function rapidly and stabilizes kidney function for a long duration

BMC Nephrol 2019;20:125

KDIGO recommended to **postpone TX for at least 6 months after starting eculizumab** therapy in ESKD HUS patient for possibility of delayed recovery of native kidney function with treatment

Kidney International (2017) 91, 539–551

Eculizumab in ESKD…can it avoid need for TX?

- Dialysis was discontinued in 4/5 patients (80%) who had required dialysis at the time of initiation of eculizumab

N Engl J Med. 2013;368(23):2169–81

- A case was reported of full kidney recovery with eculizumab treatment in a young woman with aHUS receiving long-term dialysis

Clin Nephrol. 2014;82(5):326–31

- A boy with aHUS and complete anuria receiving dialysis for 4.5 months weaned of dialysis after eculizumab therapy

Pediatr Nephrol. 2019;34(12):2601–4.

This highlights the importance of a treatment trial with eculizumab, even in patients already receiving long-term dialysis.

Prophylactic / rescue eculizumab therapy in isolated KTX

Options of eculizumab therapy in KTX

Prophylactic therapy

eculizumab start before kidney implantation and continue lifelong

Targeted rescue therapy

eculizumab start in patients who develop aHUS recurrence after TX

Evidence-based recommendations are lacking because of the absence of RCT

Variables that should affect decision making: **efficacy of rescue therapy, risks of lifelong exposure to eculizumab and costs**

Kidney Int Rep (2023) 8, 715–726

Prophylactic / rescue eculizumab therapy in isolated KTX

Rescue treatment is generally effective, with overall good outcome, provided treatment is started early after diagnosis

PLoS One. 2021;16:e0258319

On comparing 88 patients treated with eculizumab prophylaxis and 52 patients treated with rescue therapy, there was no significant difference in graft survival ……..However, eGFR at 2 year follow-up was markedly lower in patients who received eculizumab as rescue therapy

Kidney Int Rep. 2019;4: 434–446.

The prevelage of prophylaxis than rescue therapy may be related to long term rather than short term

Eculizumab monitoring of effectiveness, duration, side effects

Table 3 | Monitoring eculizumab therapy

CH50 (Total complement activity)	**Description** • Measures the combined activity of all of the complement pathways • Tests the functional capability of serum complement components to lyse 50% of sheep erythrocytes in a reaction mixture • Will be low in congenital complement deficiency (C1–8) or during complement blockade • Normal range is assay dependent **Recommended goal during therapeutic complement blockade** • <10% of normal
AH50 (Alternative pathway hemolytic activity)	**Description** • Measures the combined activity of the alternative and terminal complement pathways • Tests the functional capability of alternate or terminal pathway complement components to lyse 50% of rabbit erythrocytes in a Mg^{2+}-EGTA buffer • Will be low in congenital C3, FI, FB, properdin, FH, and FD deficiencies or during terminal complement blockade • Normal range is assay dependent **Recommended goal during therapeutic complement blockade** • <10% of normal
Eculizumab trough	**Description** • May be a free or bound level • ELISA-based assay using C5 coated plates, patient sera, and an anti-human IgG detection system • Not affected by complement deficiencies **Recommended trough level during therapeutic complement blockade** • 50–100μg/ml
Alternative assays	**The following assays are under investigation (or awaiting to be replicated in different laboratories)[62] as a means to monitor therapeutic complement blockade** • Free C5 • *in vitro* human microvascular endothelial cell test[62] • sC5b-9 (also referred to as sMAC and TCC) may remain detectable in aHUS patients in remission and therefore is not recommended as a monitoring tool

Kidney International (2017) 91, 539–551

Eculizumab monitoring of effectiveness, duration, side effects

Is it possible to discontinue eculizumab therapy?

Till now eculizumab is a life-long treatment of aHUS

There is increasing data about withdrawal of treatment, however **discontinuing eculizumab is associated with a risk of relapse** particularly in patients with pathogenic variants in CFH or has H/O of previous recurrence after TX

- The majority of aHUS recurrences occur in the first 3 mo after TX although recurrences have been reported yrs……Recommendations to treatment with eculizumab **for 6 mo post TX** to prevent early recurrence were adopted

https://www.atypicalhus.co.uk/wp-content

Eculizumab withdrawal in patients after TX is **associated with a higher relapse rate** than in patients with aHUS in native kidneys

Kidney Int Rep. 2022;8:91–102

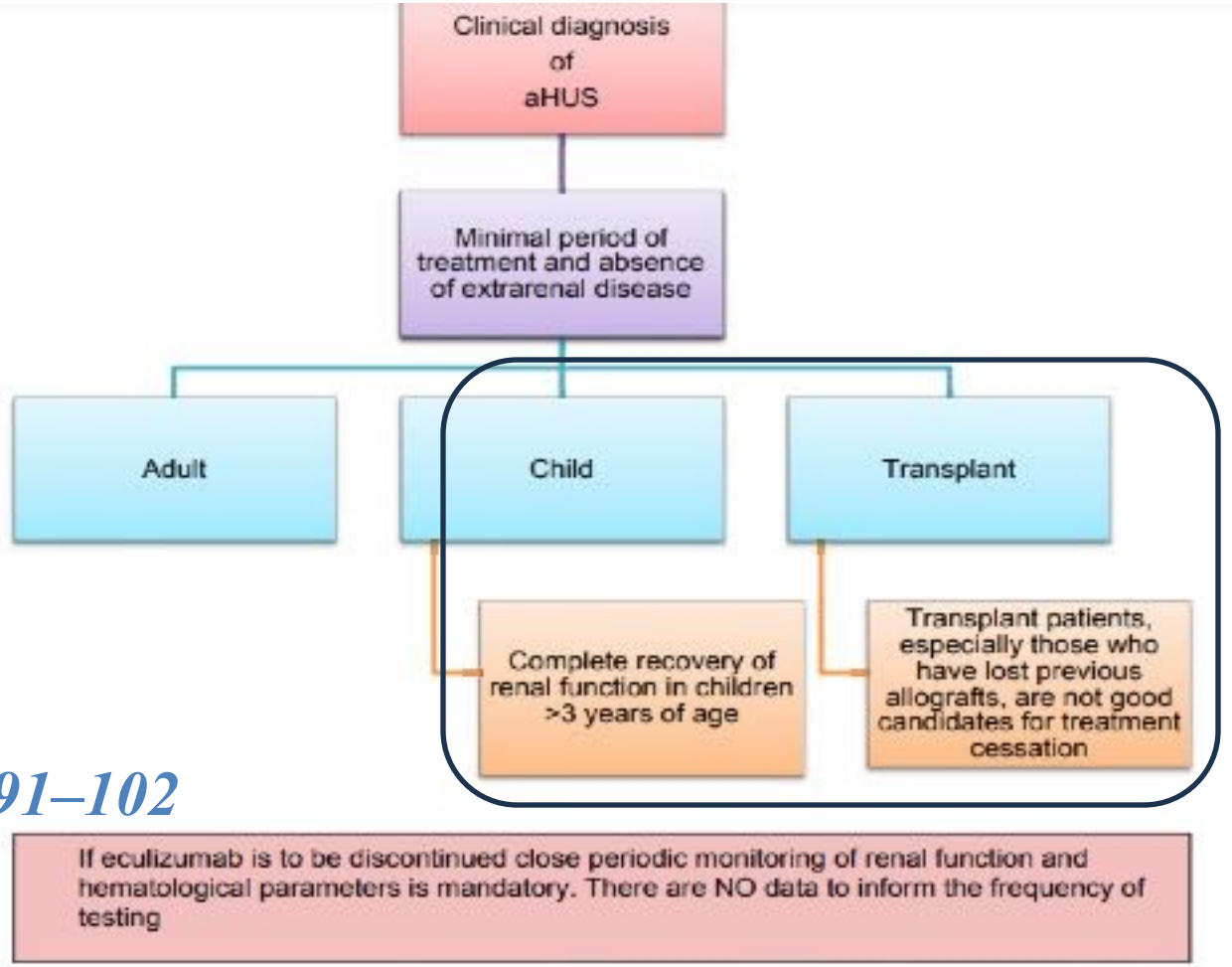


Figure 3 | Recommendations for cessation of treatment with complement inhibitors. There are no prospective controlled studies in patients with atypical hemolytic uremic syndrome (aHUS) to define criteria for discontinuation of eculizumab therapy. This flow diagram is based on expert opinion.[111–114] Discontinuation can be considered on a case-by-case basis in patients after at least 6 to 12 months of treatment and at least 3 months of normalization (or stabilization in the case of residual chronic kidney disease) of kidney function. Earlier cessation (at 3 months) may be considered in patients (especially children) with pathogenic variants in *MCP* if there has been rapid remission and recovery of renal function. In patients who have undergone dialysis, eculizumab should be maintained for at least 4 to 6 months before considering discontinuation. In this setting, the assessment of fibrotic changes in the kidney using a biopsy may be helpful. In patients who have undergone transplant, especially patients who have lost previous allografts, discontinuation is not recommended.

Kidney International (2017) 91, 539–551

Eculizumab monitoring of effectiveness, duration, side effects

Cost up to 500,000 $/year

Although safe & well tolerated
<u>However</u>
<u>Eculizumab treatment is not without risks</u>

- Susceptibility to infections with encapsulated bacteria, especially meningococcal
- A higher risk of infections can be expected in patients with aHUS after KTX
- The risk of developing human anti-human antibodies (HAHA) which could neutralize eculizumab
- Impact on hepatic affection ??????
- Long-term chronic sequalae of therapy are not yet fully comprehended

Pediatr Nephrol (2019) 34:2261–2277

Combined liver kidney TX & Eculizumab

Combined liver–kidney transplant is considered a curative treatment option for patients with defect in complement components synthesized by the liver

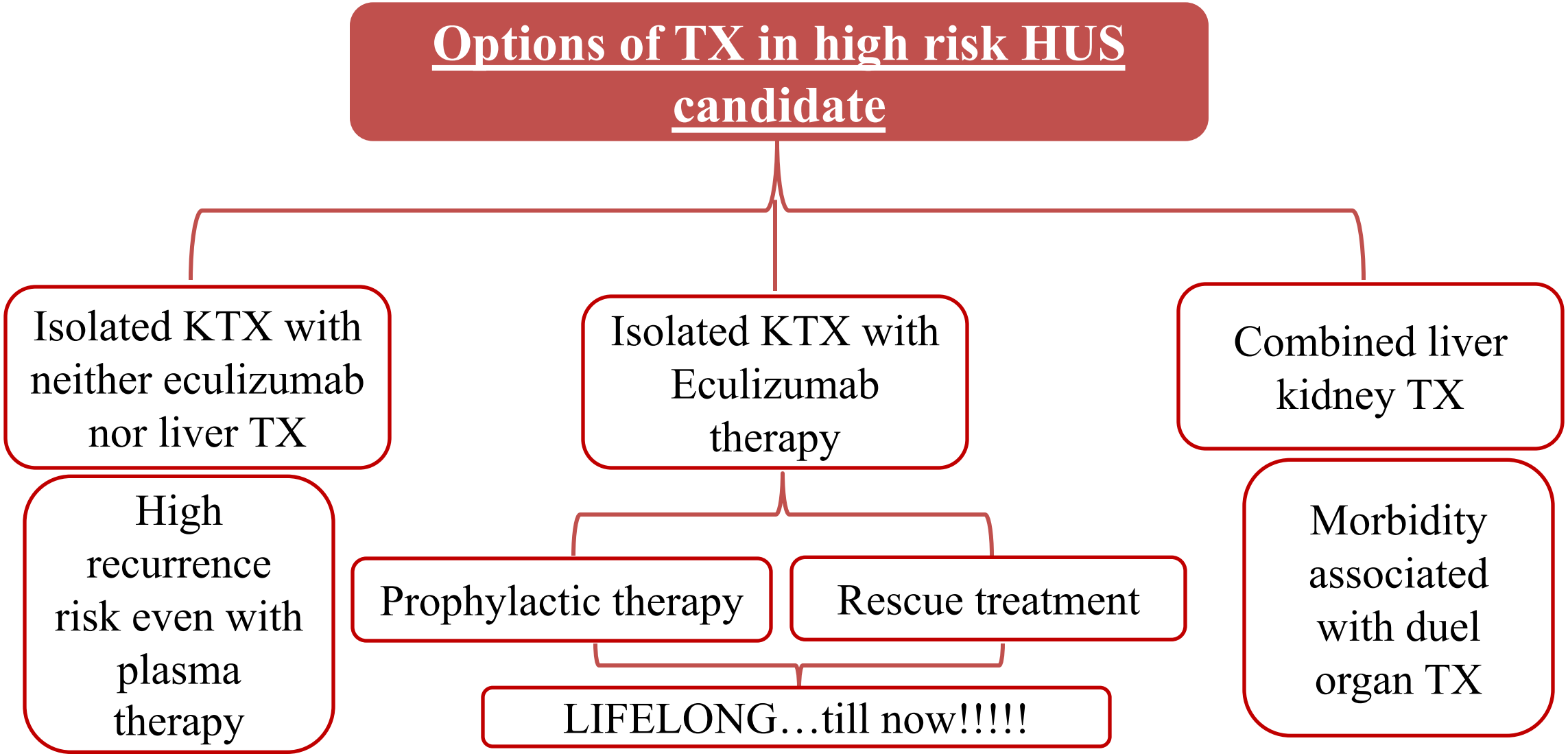
The complement system is one of the fastest responding defense mechanisms of the innate immune system.

One major unexpected risk includes liver failure secondary to uncontrolled complement activation

Perioperative use of eculizumab in conjunction with PE during simultaneous liver–kidney TX could optimize success by reducing the risk of graft thrombosis during the time of highest surgical stress while awaiting the liver graft to recover its synthetic function

Pediatr Nephrol (2014) 29:477–480

Combined liver kidney TX or Eculizumab



Pediatr Nephrol (2014) 29:329–332
DOI 10.1007/s00467-013-2722-2

EDITORIAL COMMENTARY

Liver–kidney transplantation to cure atypical HUS: still an option post-eculizumab?

Jeffrey Saland

Received: 19 November 2013 / Revised: 19 November 2013 / Accepted: 3 December 2013 / Published online: 22 December 2013

Abstract Patients with end-stage renal disease (ESRD) due to atypical HUS (aHUS) now have several potential options that can enable successful kidney transplantation. This editorial addresses these options by considering key factors that are important when making an individual treatment decision. advantages, and disadvantages of each, the most important issues being safety and efficacy. For clarification, this discussion concerns those individuals with dialysis-dependent ESRD due to aHUS who are considered for kidney transplant.

Pediatr Nephrol (2014) 29:329–332

Table 1 Comparison of transplant approaches

Isolated kidney with chronic eculizumab	Liver–kidney transplant
Lower short-term risk	Higher short-term mortality
Long-term outcomes yet to emerge	Long-term outcomes stable
Long-term dependence to prevent aHUS	aHUS recurrence unlikely
More "immunosuppressive"	Less immunosuppressive
Increased infection risk? Lower rejection risk?	Lower rejection risk
IV infusion every 2 weeks	Better lifestyle—no infusions
Limited availability worldwide	Lower monetary cost
Very high financial cost	More widely available
	Limited organ (liver) resource

aHUS atypical hemolytic uremic syndrome, *IV* intravenous

Pediatr Nephrol (2014) 29:329–332
DOI 10.1007/s00467-013-2722-2

EDITORIAL COMMENTARY

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Concluding opinion

While LKT remains the only "cure" for aHUS, eculizumab has rightly become the treatment of choice across all phases of the disease, including in the setting of transplantation following ESRD. However, eculizumab is not universally available and its use requires a commitment to chronic infusions that may not be possible or desired by individual patients. In such cases, LKT remains a reasonable option.

Home message

- The optimal treatment strategy of patients with aHUS after KTX is unknown
- With introduction of complement inhibitors; high risk patients and their treating physician have to choose between CLKT & chronic eculizumab therapy
- Eculizumab could improve kidney function even after regular dialysis initiation avoiding the need for even KTX
- Rescue eculizumab therapy after TX seems reasonable however long term outcomes are better with prophylaxis
- The possibility of discontinuation of eculizumab therapy safely has to be well studied as it will markedly impact its practical use

Thank you