Preemptive liver transplantation for primary hyperoxaluria type 1

P. Cochat & A. Liutkus

Centre de Référence des Maladies Rénales Héréditaires et Inserm U499, Hôpital Edouard-Herriot & Université Claude-Bernard, Lyon, France.

Hyperoxaluria may be either a secondary or a primary disease. Secondary hyperoxaluria is due to oxalate poisoning, i.e., accidental intoxication with precursors such as ethylene glycol, absorptive hyperoxaluria of bowel disease. Two distinct inherited enzyme defects have been related to type 1 and type 2 primary hyperoxalurias (PH), i.e., alanine : glyoxylate aminotransferase (AGT) and glyoxylate reductase/hydroxypyruvate reductase, respectively ; in addition non-PH1 non-PH2 patients have been reported.

Background

PH1 is one of the most challenging issues for nephrologists. This is an autosomal recessive disorder caused by the functional defect of the hepatic, peroxisomal, pyridoxal phosphate-dependent enzyme AGT leading to oxalate overproduction. The disease occurs because AGT activity is undetectable or because AGT is mistargeted to mitochondria which may explain enzymatic heterogeneity. Since calcium oxalate (CaOx) is insoluble in urine, PH1 usually presents with symptoms referable to the urinary tract. The median age at initial symptoms is 5 to 6 yrs and end-stage renal disease (ESRD) is reached between 25 and 40 yrs of age in half of patients. Along with progressive decline of GFR due to renal parenchymal involvement, continued overproduction of oxalate by the liver along with reduced oxalate excretion by the kidneys leads to a critical saturation point for plasma oxalate (Pox) so that oxalate deposition occurs in many organs, leading to systemic involvement (‘oxalosis’) and bone is the major compartment of the insoluble oxalate pool. The infantile form often presents as a life-threatening condition because of rapid progression to ESRD due to both early oxalate load and immature GFR : one-half of affected infants experience ESRD at the time of diagnosis and 80 % develop ESRD by the age of 3 yrs.

The aims of conservative therapeutic measures are to increase urinary solubility of CaOx and to decrease oxalate production. Such an aggressive supportive management should be started as soon as the diagnosis of PH1 has been considered that may significantly improve renal survival provided compliance is optimal. Conventional dialysis is unsuitable for patients who have reached ESRD because it cannot overcome the continuous excess production of oxalate.

Organ transplantation

Ideally, any kind of transplantation (Tx) should be a preemptive procedure. Further assessment of oxalate burden needs therefore to be predicted by monitoring sequential GFR, Pox, CaOx saturation and systemic involvement (bone mineral density, bone histology).

Kidney transplantation

Kidney Tx allows significant removal of soluble Pox. However, because the biochemical defect is in the liver, overproduction of oxalate and subsequent deposition in tissues continues unabated. The high rate of urinary oxalate excretion originates from both ongoing oxalate production from the native liver and oxalate deposits in tissues. Due to oxalate accumulation in the graft, isolated kidney Tx is no longer recommended, because recurrence leads to poor graft survival and patient quality of life. On the basis of recent genotype-phenotype studies, such a procedure might be proposed to pyridoxine responsive patients with Gly170Arg mutation but evidence of favorable long term outcome in kidney alone Tx in this subgroup of patients remains to be demonstrated.

Rationale for liver transplantation

Since the liver is the only organ responsible for glyoxylate detoxification by AGT, the excessive production of oxalate will continue as long as the native liver is left in place. Therefore any form of enzyme replacement will succeed only when the deficient host liver has been removed. Liver Tx is a form of gene therapy as well as enzyme replacement therapy as it will supply the missing enzyme in the correct organ, cell and intracellular compartment. The ultimate goal of organ replacement is to change a positive whole-body accretion rate into a negative one by reducing endogenous oxalate synthesis and providing good oxalate clearance via either native or transplanted kidney. However the current reason for enzyme replacement (liver Tx) is only to decrease oxalate, not to cure the disease.

Combined liver-kidney transplantation

In Europe, 6 to 7 combined liver-kidney Tx per year have been reported ; the results are encouraging, as

E-mail : pierre.cochat@chu-lyon.fr

Suggestions for transplantation strategies in pyridoxine resistant PH1 patients according to residual GFR, systemic involvement and local facilities (personal opinion)

GFR (mL/min per 1.73m²)	Estimated Oxalate load	*Proposed Tx strategy*	Comments
60-40	?	Preemptive CAD L-Tx?	Hazardous (hepatectomy, immunosuppression) Limited experience Ethical issues
< 40	+	Preemptive simultaneous (CAD) LK-Tx	HD only if post-Tx ATN/DFG Exposure to immunosuppression
ESRD	++	Simultaneous Tx procedure	Renal risk Pre/post-Tx HD often required
		2-step Tx procedure : 1. L-Tx 2. HD to clear oxalate 3. K-Tx	CAD : needs 2 different donors – loss of immunological benefit LRD : immunological benefit – increased risk for the donor

ATN, acute tubular necrosis
CAD, cadaver
DFG, delayed graft function
ESRD, end-stage renal disease
HD, hemodialysis
K, kidney
L, liver
LRD, living related donor
Tx, transplantation

patient survival approximates 80 % at 5 yrs and 69 % at 10 yrs. Comparable results have been reported from the United States Renal Data System, with a 76 % death-censored graft survival at 8 yrs post Tx. In addition, despite the potential risks for the grafted kidney due to oxalate release from the body stores, kidney survival is about 95 % three years post-Tx and the GFR ranges between 40 and 60 mL/min per 1.73m² after 5 to 10 yrs.

Isolated liver transplantation

Isolated liver Tx might be the first-choice treatment in selected patients before advanced chronic renal failure has occurred, i.e., at a GFR between 60 and 40 mL/min/1.73m². Such a strategy has a strong rationale but raises ethical controversies. Several patients have received an isolated liver transplant without uniformly accepted guidelines, since the course of the disease is unpredictable and a sustained improvement can follow a phase of rapid decrease in GFR.

Post-transplantation reversal of renal and extrarenal involvement

After combined Tx, Pox returns to normal before urine oxalate does, and oxaluria can remain elevated as long as several years. Therefore there is still a risk of recurrent nephrocalcinosis or renal calculi that might jeopardize graft function. Thus, independent of the Tx strategy, the kidney must be protected against the damage that can be induced by heavy oxalate load suddenly released from tissues. Forced fluid intake supported by the use of crystallization inhibitors is the most important approach. Pox, crystalluria and CaOx saturation are helpful tools in renal management after combined liver-kidney Tx. The benefit of daily (pre-) post-Tx hemodialysis is still debated ; it will provide a rapid drop in Pox with an increased risk of CaOx supersaturation in case of reduction in urine volume, and therefore should be limited to patients with significant systemic involvement.

Combined Tx should be planned when the GFR ranges between 20 and 40 mL/min per 1.73m² because, at this level, oxalate retention increases rapidly. In ESRD patients, vigorous hemodialysis should be started and urgent liver-kidney Tx should be performed. Even at these late stages, damaged organs do benefit from enzyme replacement, which results in an appreciable improvement in quality of life.

Donors for combined liver-kidney transplantation

The Tx strategy may be based either on immunological bases (i.e., using the same donor for both organs) or on biochemical rationale (i.e., using a two-step procedure according to oxalate body store) (Table). Indeed most publication currently report on the use of cadaver donors but a living related donor may be considered under certain conditions.

Conclusion

Patients with hyperoxaluria should be referred for diagnosis and management to reference centers with interest and experience in the conditions and access to the appropriate biochemical and molecular biological facilities. Indeed major advances in biochemistry, enzymology, genetics and management have been achieved during recent years. The understanding of genotype-phenotype relationship and underlying metabolic defects of PH is in progress. The ongoing analysis of

transplant strategies from multicentre database will improve individual enzyme replacement and subsequent patient survival and quality of life.

References

1. COCHAT. P., KOCH NOGUEIRA P.C., MAHMOUD A.M., JAMIESON N.V., SCHEINMAN J.I., ROLLAND M.O. Primary hyperoxaluria in infants : medical, ethical and economic issues. *J Pediatr*, 1999, **135** : 746-750.
2. MILLAN M.T., BERQUIST W.E., SO S.K., SARWAL M.M., WAYMAN K.I., COX K.L., FILLER G., SALVATIERRA O. JR, ESQUIVEL C.O. One hundred percent patient and kidney allograft survival with simultaneous liver and kidney transplantation in infants with primary hyperoxaluria : a single-center experience. *Transplantation*, 2003, **76** : 1458-1463.
3. VAN WOERDEN C.S., GROOTHOFF J.W., WIJBURG F.A., ANNINK C., WANDERS R.J., WATERHAM H.R. Clinical implications of mutation analysis in primary hyperoxaluria type 1. *Kidney Int*, 2004, **66** : 746-752.
4. JAMIESON N.V. A 20-year experience of combined liver/kidney transplantation for primary hyperoxaluria (PH1) : The European PH1 transplant registry experience 1984-2004. *Am J Nephrol*, 2005, **25** : 282-9.
5. GAGNADOUX M.F., LACAILLE F., NIAUDET P., REVILLON Y., JOUVET P., JAN D., GUEST G., CHARBIT M., BROYER M. Long term results of liver-kidney transplantation in children with primary hyperoxaluria. *Pediatr Nephrol*, 2001, **16** : 946-50.
6. ELLIS S.R., HULTON S.A., MCKIERNAN P.J., DE VILLE DE GOYET J., KELLY D.A. Combined liver-kidney transplantation for primary hyperoxaluria in young children. *Nephrol Dial Transplant*, 2001, **16** : 348-354.