Towards Therapy in Genetic Kidney Diseases: Hopes and Uncertainties

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The finding of drusen-like lesions beneath the retina in patients with membranoproliferative (or mesangiocapillary) glomerulonephritis (MPGN) type II, with or without partial lipodystrophy, was first reported in 1989. This was confirmed subsequently and has not been reported in other types of glomerulonephritis. These drusen develop at an early age, often in the second decade of life. Some authors have suggested a correlation between the development of eye changes and the duration of renal disease. Many patients do not develop visual impairment, but some may lose vision as a result of development of choroidal neovascularization (CNV) or central serous retinopathy.

D’souza et al. studied four patients who had MPGN type II and these eye changes and were followed up during 14 to 37 yr. Three of them received a kidney transplant. There was no progression of retinopathy during 10 yr in any patient. None developed CNV or central serous retinopathy.

Type II MPGN (also called dense-deposit disease [DDD]) is associated in 70% of the cases with an IgG autoantibody named C3 nephritic factor (C3NeF) and low C3 serum level, as a result of uncontrolled alternative pathway C3 activation. This C3NeF is also found in 30% of patients with MPGN type I. The principle function of complement function H is to downregulate alternative pathway complement activation. Regulation of fluid-phase C3 activation requires the N-terminal five short consensus repeat domains of the protein. In contrast, targeting of the protein to cell surfaces (surface recognition function) is mediated by C-terminal domains. Various factor H defects were detected in the whole spectrum of MPGN, with or without C3NeF, called “C3 glomerulopathy” by Pickering and Cook in their excellent review (1). This group included DDD, atypical DDD, and other forms MPGN-like diseases.
gans, including the brain, kidneys, and lungs. Renal angiomyolipomas are multiple and bilateral. These tumors are rich in fat, muscle, and blood vessels that can hemorrhage or infiltrate the kidney, leading to renal failure. They develop in approximately 80% of patients with tuberous sclerosis. Renal lesions also encompass cysts and more rarely renal cell carcinoma. Lymphangioleiomyomatosis (LAM) is the major pulmonary manifestation in women with or without tuberous sclerosis. It is a progressive and severe lung disease characterized by infiltration of smooth muscle cells and formation of parenchymal cysts; it affects probably 1 to 3% of people with tuberous sclerosis (1).

Tuberous sclerosis has a birth rate of 1 in 6000. It is caused by mutations in the tuberin gene (TSC2) or the hamartin gene (TSC1). Two thirds of the patients have sporadic mutations. The overall mutation detection rate is approximately 85 to 90%. Mutations of TSC1 account for 15 to 30% of the families. Preponderance of TSC2 mutations is even higher in sporadic cases. Individuals with TSC2 mutations have, on the whole, more severe symptoms than those with mutations in TSC1. Most tuberous sclerosis–associated cases of pulmonary LAM are caused by mutations in TSC2 (1).

The hamartin-tuberin complex regulates signaling through the mammalian target of rapamycin (mTOR) pathway to control processes such as growth, cell-cycle progression, apoptosis, and autophagy. Constitutive activation of mTOR and its downstream targets occurs in tuberous sclerosis complex, suggesting that mTOR inhibition might be potentially targeted therapies in affected individuals. Anecdotal cases have reported shrinkage of renal angiomyolipomas and cerebral astrocytomas and more recently dramatic reduction of facial angiofibroma in a renal transplant patient in response to administration of the mTOR inhibitor sirolimus (2).

The study by Bissler et al. is a 24-mo, nonrandomized, open-label trial of 14 patients with the tuberous sclerosis complex and of six with sporadic LAM. Sirolimus was administered for the first 12 mo only, at an initial dosage of 0.25 mg/m² body surface area, and adjusted to achieve a blood level between 1 and 5 ng/ml. The dosage was subsequently increased according to the response to treatment evaluated from serial magnetic resonance imaging of kidneys and brain, lung computed tomography scan, and pulmonary function tests. The mean reduction of renal angiomyolipoma volume at 12 mo was 53.2%. At 24 mo, only five patients had a persistent reduction in the angiomyolipoma volume of ≥30%. Of note, 14 patients (all female) with pulmonary LAM were included in the active phase of the study. Some of them had improvement in spirometric measurements and gas trapping that persisted after treatment. No changes in the size of the cerebral tubers were observed.

These encouraging results were in part confirmed by the interim report of another study involving 13 patients. Shrinkage of angiomyolipomas was seen in all patients; the mean reduction of the longest diameters at 12 mo was 26.1%, but no clear improvement in lung function was observed in the four patients with pulmonary involvement (3).

A word of caution comes from the adverse events while receiving sirolimus. In the study by Bissler et al., five patients had six serious adverse events, including stomatitis, respiratory involvement, diarrhea, and urinary tract infection. Five patients were hospitalized for adverse events. In the other series, all patients had grade 1 or 2 adverse events (3). The study by Zuber et al. (4) draws attention to another potential adverse effect of sirolimus. That retrospective study was performed in 43 male renal transplant recipients who received sirolimus. From sperm counts and fathered pregnancy rates, the authors concluded that sirolimus (and probably everolimus) may reduce fertility in male renal transplant recipients.

It should be remembered that other means, such as arterial embolization, radiofrequency ablation, or surgery, can be used in the treatment of large renal angiomyolipomas; however, these treatments cannot be considered in some patients with tuberous sclerosis and a high number of angiomyolipomas (and cysts) infiltrating both kidneys. These patients are at risk for progressing to ESRD, necessitating renal replacement therapy. Lung transplantation is also a mode of treatment of severe lymphangioleiomyomatosis. A retrospective study was performed of 44 patients (all women) with a mean age of 41 yr at transplantation (34 single-lung transplantation and 11 bilateral transplants, including one retransplantation). Intraoperative cardiopulmonary bypass was required in 13 cases. The mean length of mechanical ventilation was 7.5 d. The 10-yr survival rate was 52.4%. There were two cases of recurrence of LAM (5).

Neurologic involvement accounts for the most disabling clinical problems in tuberous sclerosis, including epilepsy, often refractory to therapy, autism, and mental retardation (1). Mice with conditional inactivation of the TSC1 gene primarily in glia develop glial proliferation, progressive epilepsy, and premature death. Early or later treatment with rapamycin prevented or suppressed seizures and prolonged survival in these mice (6). These results open new avenues for basic and clinical research in tuberous sclerosis.

References

Treatment of Fabry disease: Outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg. PloS One 2: e598, 2007


The availability of enzyme replacement therapy (ERT) has stimulated research in Fabry disease, an X-linked storage disorder characterized by a deficiency of the lysosomal enzyme (α-Gal A) leading to accumulation of globotriaosylceramide (GL-3 or Gb 3) in endothelial cells and other cell types in the body. Currently, two different enzyme preparations (which have only minor differences) are available for the treatment of patients with Fabry disease: Agalsidase alfa and agalsidase beta. Only the latter preparation is available in United States. The authorized dosages are 0.2 mg/kg for agalsidase alfa and 1.0 mg/kg for agalsidase beta every 2 wk. Previous studies established the efficacy of ERT and showed that early treatment is the best option for patients with Fabry disease to profit from ERT (1).

Several points remain to be clarified, and these questions have been addressed in the past months: What is really detrimental in Fabry tissues (Gb3 or lyso-Gb3)? Why different dosing regimens of the two agalsidases? What are the consequences of α-Gal A antibodies on plasma and urinary GL-3?

Various findings suggest that Gb3 elevation and clinical manifestations do not necessarily correlate in Fabry disease; for example, plasma or urinary levels of Gb3 in neither hemizygotes nor heterozygotes correlate with the severity of disease manifestations; prominent Gb3 accumulation occurs in hemizygotes long before any clinical symptoms develop; plasma Gb3 concentrations in some symptomatic boys may exceed those in asymptomatic adult hemizygotes. Aerts et al. (2) found that decacylated Gb3, globotriaosylsphingosine (or lyso-Gb3), and a minor additional metabolite are dramatically increased in plasma of classically affected male patients with Fabry disease. Lyso-Gb3 is an inhibitor of α-Gal A activity. Exposure of smooth muscle cells but not fibroblasts to lyso-Gb3 at concentrations observed in plasma of patients promote proliferation. Very high lyso-Gb3 levels were detected in plasma specimens of all classically affected Fabry hemizygotes, including young boys; however, no correlation was found between plasma lyso-Gb3 with regard to age or Mainz Severity Score Index. Measurement of circulating lyso-Gb3 might be useful in the future to monitor Fabry disease and may contribute to better understanding of its pathophysiology.

Vedder et al. compared the two enzyme preparations at identical dosages (0.2 mg/kg biweekly) in a randomized, controlled, open-label trial. Treatment efficacy was assessed at 12 and 24 mo. Thirty-four patients (18 male, 16 female) were initially included. The median ages at baseline were 44 and 47 yr for agalsidase alfa and beta, respectively. There was no difference in treatment efficacy (reduction in left ventricular mass and estimated GFR or other parameters) with either agalsidase alfa or beta. Treatment failure (progression of renal or cardiac disease, new cerebrovascular accident (CVA)) occurred in eight of 34 patients. Four of these eight patients were ≥50 yr of age. This shows again that ERT when initiated late in life does not protect completely from vascular complications (3).

The occurrence of treatment failure did not differ between the two treatment groups.

In a more recent study, Vedder et al. focused on α-Gal A antibodies and their consequences on plasma and urinary GL-3 (28 male and 24 female). The composition of this group is atypical (46% of the patients were female, in whom the disease is less severe) and heterogeneous (this was not a prospective study; seven male patients had been switched from 0.2 to 1 mg/kg treatment because of treatment failure in the previously analyzed study). Follow-up was short (12 mo).

α-Gal A antibodies were detected in 18 male patients after 6 mo of therapy: Four of 10 agalsidase alfa 0.2, six of eight agalsidase beta 0.2, and eight of 10 agalsidase beta 1.0 mg/kg. Antibodies were seen more frequently in patients who received agalsidase beta 1.0 than in those who received agalsidase alfa 0.2 mg/kg. There was however no significant difference in the occurrence of antibodies between the two groups treated with 0.2 mg/kg. None of the female patients developed antibodies. In vitro neutralizing activity of the antibodies was present in 17 of 18 male patients.

Plasma GL-3 levels decreased after 12 mo of treatment in all of the groups, irrespective of treatment regimen or presence of antibodies. In contrast, neutralizing antibodies significantly interfered with urinary GL-3 excretion. After 12 mo of 0.2 mg/kg treatment, there was a reduction in antibody-negative patients, whereas there was an increase in antibody-positive patients. In 18 antibody-positive patients, treatment with 0.2 mg/kg resulted in an increase of urinary GL-3, whereas treatment with 1.0 mg/kg caused a significant reduction. Curiously, baseline urinary GL-3 levels were higher in patients who subsequently developed antibodies. Urinary GL-3 levels are believed to derive from accumulation of glycolipid in epithelial cells shed by the distal tubules of the patients. The link between antibodies and urinary GL-3 excretion is not well delineated by the authors. This study confirms the results reported by the same group of investigators in 2004 (4). Several studies have indicated that long-term effects of ERT are maintained despite the presence of antibodies (5).

Corrections of interpretation of plasma Gb3 (or GL-3) and lyso-Gb3 and of urinary Gb3 excretion is still lacking. Clinical consequences of antibodies are still a matter of debate.

References


