RNA therapeutics for rare diseases: hyperoxaluria and beyond

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Rare diseases in nephrology have peculiar characteristics that challenge both patients and physicians. There is currently no consensus on the definition of rare diseases since the prevalence threshold varies across the globe. The majority of these diseases have a genetic origin and there are currently over 150 defined disorders related to genetic kidney diseases. The recent advances in genetic testing and understanding of the molecular and pathophysiological basis of these disorders uncovered potential new therapeutic targets.

RNA interference (RNAi) is a therapeutic strategy targeting messenger RNA (mRNA) that was first described by Nobel laureates Andrew Fire and Craig Mello in the late 1990s. However, the synthesis of RNAi therapeutics required sophisticated technology to create anti-sense oligonucleotides that complement specific mRNA sequences. The first RNAi therapies were developed for amyloidosis, porphyria and haemophilia, followed by the more prevalent diseases. Currently, RNAi therapies are limited to targeting diseases with underlying pathophysiology in the liver, specifically hepatocytes, where they create a blockade against the over-production of deleterious proteins. Initially, RNAi therapies were administered intravenously using lipid nanoparticles as a delivery vehicle that protected the oligonucleotides from degradation in the bloodstream. However, the subcutaneous application using N-Acetylgalactosamine (GalNAc), which binds to a specific receptor on hepatocytes, is more effective. To prolong the time between injections, advanced techniques, such as fluoridation, have been employed to protect and stabilize the drug, enabling administration every 3 to 6 months.

The late endo/lysosome effect is a cellular biology concept that underlies RNA interference (RNAi) therapy. The introduction of the GalNAc enabled specific targeting of hepatocytes by binding asialoglycoprotein receptor 1, which leads to increased stability due to chemical modifications. This ultimately resulted in the RNAi therapy reaching the nucleus, cytoplasm, and the RISC-loading complex (RLC), specifically targeting the intended mRNA rapidly and intensely.

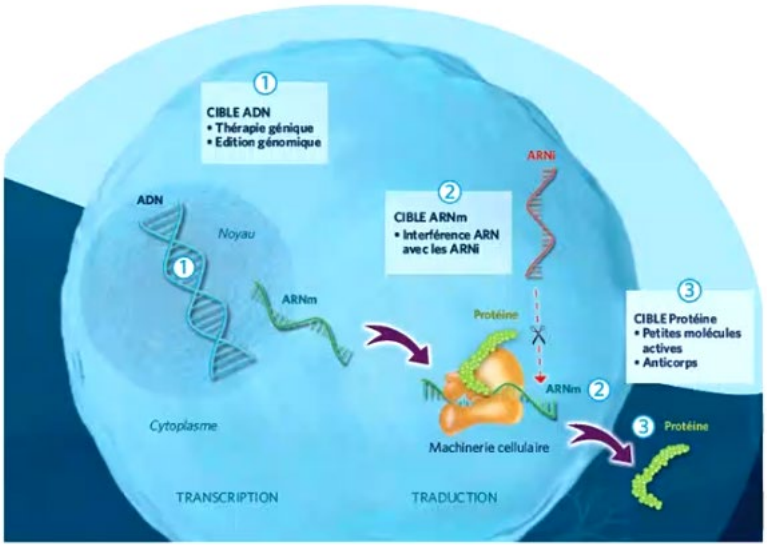

Figure 1. RNA therapies - a novel therapeutic group targeting mRNA

Primary hyperoxaluria

Primary hyperoxaluria (PH) is an extremely rare and severe disease that manifests in three genetic forms: PH1, PH2, and PH3. Clinical presentation varies widely, particularly in the PH1 subgroup, which ranges from the neonatal onset with progression to end-stage kidney disease (ESKD) within the first months of life to adult nephrolithiasis. Additionally, PH1 can be diagnosed in patients who relapse after receiving a renal graft for ESKD of unknown origin. With a risk of ESKD reaching nearly 100% of cases, PH1 is the most severe form of primary hyperoxaluria, requiring recurring liver and kidney transplantation. PH2 and PH3 are less severe, with a 25% risk of ESKD in PH2 and chronic kidney disease (CKD) in 50% of PH3 cases.

Patients with PH1 may exhibit one or more clinical manifestations, including bilateral or recurrent lithiasis, nephrocalcinosis, or progressive kidney function decline. Since PH1 is an autosomal recessive condition, the typical manifestations are juvenile kidney stones and failure to thrive in infancy. The risk also rises in the presence of consanguinity or a family history of stones. In PH1 individuals with normal renal function plasma oxalate levels are preserved, thus warranting verification of hyperoxaluria. Plasma oxalate will tend to increase in PH1 individuals as renal function declines below the estimated glomerular filtration rate (eGFR) of 45 ml/min/1.73 m^2. From this point, PH1 will also cause systemic oxalosis besides renal derangements, manifested by calcium oxalates depositing in the bones, heart, blood vessels and eyes. This results in significant deterioration of quality of life and increases mortality. Furthermore, patients with PH1 experience a vicious cycle during hemodialysis. Endogenous liver oxalate production ranges from 4 to 7 mmol/1.73 m^2/day, but only 1-2 mmol/1.73 m^2 and 3 to 4 mmol/1.73 m^2 can be removed daily in adults and children respectively, even with intensive dialysis strategies. This leads to progressive oxalate accumulation and worsening of systemic oxalosis even with the most intensive dialysis management.

Table 2. Features and Treatment of the Inherited Primary Hyperoxalurias.

Feature	Type 1	Type 2	Type 3
Chromosomal location	2q37.3	9p13.2	10q24.2
Age at onset	All ages, although mostly in childhood	All ages	All ages
Presentation	Calcium oxalate renal stones, nephrocalcinosis, renal failure	Calcium oxalate renal stones	Calcium oxalate renal stones
Treatment			
Supportive treatment	Hydration, citrate, pyridoxine	Hydration, citrate	Hydration, citrate
Transplantation	Liver and kidney	Kidney	Not required — no reported cases of renal failure to date

Figure 2. Primary hyperoxaluria(s)

There are two possible targets for RNAi therapies in PH1. Since the original defect is in the hepatocytes, it is possible to target the upstream enzyme - glycolate oxidase and alter the complex oxalate pathway in the hepatocytes into a non-toxic glycolate pathway. Namely, decreasing the hepatic oxalate synthesis increases the synthesis of glycolate. In 2017, Liebow et al. conducted a study on mice, which demonstrated that RNA interference (RNAi) therapies could effectively reduce urinary oxalate levels by inhibiting the enzyme glycolate oxidase. Concurrently, this led to a significant increase in urinary glycolate thus raising concerns as to whether blocking oxalate pathways and increasing glycolate levels would lead to a new disease. McGregor et al. addressed this issue in a paper where they identified a young female patient with a lifelong, complete knockout of the glycolate oxidase gene HAO1. Interestingly, the patient's plasma glycolate levels were twelve times above the upper normal limit, while her urinary glycolate levels were six times the upper normal limit but with no clinical manifestations.

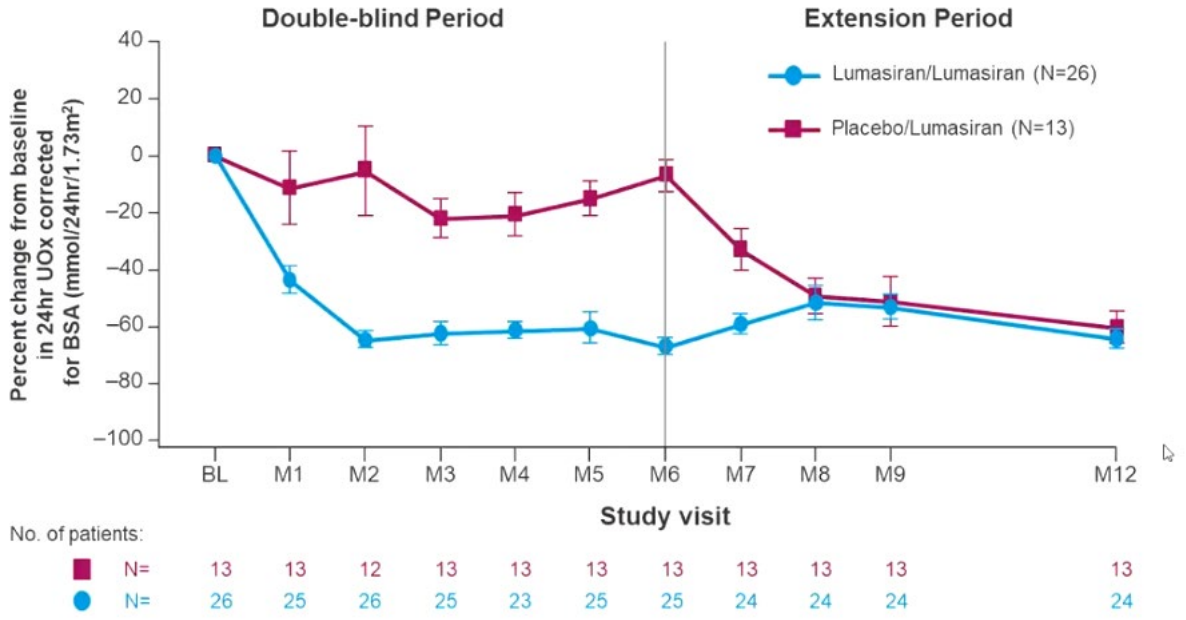

Figure 3. Illuminate A at 1 year

Lumasiran and other RNA therapeutics for PH1

Lumasiran was the first RNAi therapeutic agent approved for the treatment of PH1 acting through targeting glycolate oxidase to reduce hepatic oxalate production. The Illuminate A study, which was the first randomized, placebo-controlled trial on lumasiran, enrolled 26 patients who received lumasiran and 13 patients in the control group. The patients were over six years of age, had an eGFR above 30ml/min/1.73m^2 and exhibited significant hyperoxaluria. The results revealed a significant and sustained reduction in urinary and plasma oxalate levels with lumasiran. After six months of follow-up, the control group was switched to lumasiran and showed a decrease in urinary oxalate as well. The Illuminate B study was a phase 3 single-arm open-label study that evaluated lumasiran in children under six years of age with PH1 and eGFR above 45 ml/min/1.73 m^2. This trial showed a significant decrease in urinary oxalate in all patients. The most recent Illuminate C study was an open-label, single-arm phase 3 trial that involved patients of all ages with PH1 and CKD stage 3b-5D and plasma oxalate ≥20 µmol/L at screening, with or without systemic oxalosis. The freshly published results acknowledged a significant decrease in plasma and urine oxalate levels, with an acceptable safety profile.

Nedosiran is a novel RNAi therapy intended to prevent the final common pathway of oxalate metabolism by inhibiting the production of hepatic lactate dehydrogenase (LDH). It is aimed at treating PH1, PH2 and PH3, but clinical trials are still ongoing. The PHYOX trial on nedosiran has demonstrated a significant reduction in urinary oxalate.

An interesting point which is also being addressed is whether patients on RNAi therapy could benefit from isolated renal transplantation instead of a combined kidney-liver transplant. A research team in Paris observed a 39-year-old woman with PH1 who had undergone three years of conventional dialysis, one year of intensive dialysis, and seven months of lumasiran therapy before receiving an isolated kidney transplant. Despite hyperhydration, alkalization, pyridoxine, and a low oxalate diet, the patient experienced severe rejection at three weeks post-transplantation, with oxalate deposits in the biopsy. Nevertheless, the results showed a significant reduction in plasma and urinary oxalate levels, proving the initial hypothesis.

Key points

1. RNA interference (RNAi) therapy is a promising new approach to treating primary hyperoxaluria (PH) by targeting the underlying genetic defect in the liver.
2. Lumasiran is the first RNAi therapy approved for the treatment of PH1. In clinical trials, lumasiran has significantly reduced urinary oxalate levels and improved kidney function in patients with PH1.
3. While the long-term safety and efficacy of RNAi therapy for PH are still being studied, early results are promising and suggest that this approach could provide a much-needed treatment option.

Further reading

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