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Crigler-Najjar syndrome: Finally, light at the end of the tunnel!

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BASED ON ARTICLE

D'Antiga L, Beuers U, Ronzitti G, Brunetti-Pierri N, Baumann U, Di Giorgio A, Aronson S, Hubert A, Romano R, Junge N, Bosma P, Bortolussi G, Muro AF, Soumoudronga RF, Veron P, Collaud F, Knuchel-Legendre N, Labrune P, Mingozzi F. Gene Therapy in Patients with the Crigler-Najjar Syndrome. N Engl J Med. 2023 Aug 17;389(7):620-631. doi: 10.1056/NEJMoa2214084. PMID: 37585628.

SUMMARY

D'Antiga and colleagues report the results of the dose-escalation portion of a phase 1-2 study evaluating the safety and efficacy of a single intravenous infusion of an adeno-associated virus serotype 8 vector encoding UGT1A1 in patients with the Crigler-Najjar syndrome that was being treated with phototherapy or liver transplantation. Five patients received a single infusion of the gene construct (GNT0003): two received 2×1012 vector genomes (vg) per kilogram of body weight, and three received 5×1012 vg per kilogram. The primary end points were measures of safety and efficacy; efficacy was defined as a serum bilirubin level of 300 μmol per liter or lower measured at 17 weeks, 1 week after discontinuation of phototherapy. Alanine aminotransferase increased to levels above the upper limit of the normal range in four patients, a finding potentially related to an immune response against the infused vector; these patients were treated with a course of glucocorticoids. By week 16, serum bilirubin levels in patients who received the lower dose of GNT0003 exceeded 300 μmol per liter. The patients who received the higher dose had bilirubin levels below 300 μmol per liter in the absence of phototherapy at the end of follow-up (mean [±SD] baseline bilirubin level, 351±56 μmol per liter; mean level at the final follow-up visit [week 78 in two patients and week 80 in the other], 149±33 μmol per liter). No serious adverse events were reported. The most common adverse events were headache and alterations in liver-enzyme levels. The authors concluded that patients treated with the gene-therapy vector GNT0003 who received the higher dose had a decrease in bilirubin levels and were not receiving phototherapy at least 78 weeks after vector administration [1]

COMMENTARY

Changing the defective gene is the ultimate cure, a re-birth, a whole new person from a diseased one. The authors have made a landmark achievement in the possible cure of Crigler-Najjar syndrome with just 5 patients in their cohort. Rightly so, the article is published in New England Journal of Medicine, the top ranking journal in the field of medicine. Patients with the Crigler-Najjar syndrome, a monogenic defect

lack the enzyme uridine diphosphoglucuronate glucuronosyltransferase 1A1 (UGT1A1), the absence of which leads to severe unconjugated hyperbilirubinemia that can cause irreversible neurologic injury and death. The phototherapy regimen for the Crigler–Najjar syndrome is usually established empirically through observation of the response to treatment early in life; the severity of the disease varies considerably and is influenced by genotype and by levels of serum bilirubin. It is important that serum bilirubin levels do not exceed 350 to 400 μmol per liter; spikes in levels of unconjugated bilirubin in the serum affect quality of life and can cause neurologic damage [2]. Prolonged, daily phototherapy partially controls the jaundice, but so far the definitive cure was only a liver transplantation. Liver transplantation is easier said than done with potential hazards to donor-recipient, costs, graft rejection, drug toxicities and other complications. Therapeutic transplantation of allogeneic hepatocytes has been attempted, with limited and only short-term efficacy earlier. Auxiliary liver transplantation indicates that restoring 5 to 10% of UGT1A1 activity should be sufficient to decrease bilirubin levels by 30 to 40% while the patient is receiving phototherapy [3,4]. What better than to alter the problem at the source, which is a genetic defect, more so monogenic? Liver-directed gene therapy with adeno-associated virus (AAV) vectors holds the potential for long-lasting correction of a variety of diseases. The authors hypothesized that, on the basis of promising preclinical results earlier, serum bilirubin levels would be reduced by gene therapy with an AAV vector that includes UGT1A1 in patients with the Crigler–Najjar syndrome. Hence they conducted a multicenter, open-label, phase 1–2 study of gene therapy with an AAV serotype 8 vector (GNT0003) with dose escalation. Authors showed that GNT0003 at a dose of 5×1012 vg per kilogram reduced bilirubin levels to as low as 20 to 30% of baseline values after suspension of phototherapy. This finding suggests that the percentage of transduced hepatocytes in these patients was at least 5 to 10%. A vector dose of 2×1012 vg per kilogram elicited only a transient reduction in bilirubin levels. AAV vectors can trigger immune responses in humans; these responses usually can be managed with immunosuppression. The authors gave a prolonged course of sirolimus and steroids to counteract the rise in liver enzymes. Long term studies are required with larger numbers to validate and reproduce these findings. Sustained effect of the therapy is also a challenge in the long run.

What do we learn from this study? Determination, optimism and patience in research is the key. Crigler-Najjar syndrome is a potentially curable disease without liver transplantation. We are possibly, nearly there. There is light at the end of the tunnel, provided the train continues to steadily advance.

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