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EDITORIAL

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What's next in gene therapy for Crigler-Najjar syndrome?

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1. Crigler-Najjar syndrome: background and current management

Crigler-Najjar syndrome (CN) is a recessively inherited error of bilirubin metabolism characterized by unconjugated hyperbilirubinemia, due to impaired function of uridine diphosphoglucuronosyl transferase 1A1 (UGT1A1) [1,2]. This enzyme deficiency restricts glucuronidation and subsequent elimination of unconjugated bilirubin (UCB) via bile. In patients with the most severe phenotype, where UGT1A1 activity is completely absent, UCB accumulates in the body to serum levels > 340 uM leading, without adequate treatment, to bilirubin-induced encephalopathy (kernicterus) and death [1,3].

Dependent on phototherapy (PT) for up to 14 hour a day, patients with severe CN can reach adulthood without neurological damage [4]. The evident impact of this burdensome therapy and the stigma that comes with chronic jaundice has a major impact on the quality of life in this patient population, although data to support this is scarce. Currently, liver transplantation is the only curative treatment available for CN. A donor liver fully restores hepatic UGT1A1 activity, normalizing serum bilirubin levels. With a 5-year survival rate of CN patients after liver transplantation in Europe of 92–95% the overall outcome is good [5]. It is mainly the lifetime burden of immunosuppressive therapy and the limited availability of donor livers that warrants the development of novel therapeutic strategies.

2. Gene addition therapy for Crigler-Najjar syndrome

Gene addition therapy aims to correct the dysfunction of a mutated gene by achieving durable expression of a functional copy of the affected gene. Efficient delivery of this so-called transgene to the hepatocyte is a critical step to provide efficient and sustained correction of the disorder in a clinical setting. So far this has only been achieved using viral vectors.

The most successful viral vectors for *in vivo* liver-directed gene therapy are derived from adeno-associated virus (AAV). Effective AAV-mediated gene therapy has been demonstrated in pre-clinical models and in a clinical setting for hemophilia A and B with positive results which led to the recent conditional approval given by EMA to Roctavian (BioMarin), an AAV5 gene therapy approach for Hemophilia A [6].

In both preclinical models for CN syndrome, a natural mutant rat, and a Ugt1a knockout mouse, AAV-mediated gene addition resulted in life-long correction of serum bilirubin [7–10]. Currently, this approach is being tested in adult CN patients (Anonymized) demonstrating prolonged correction of bilirubin to levels far below those causing neurotoxicity and allowing patients of the high-dose cohort to stop phototherapy (NCT03466463) [11].

3. Gene therapy for Crigler-Najjar disease and rare metabolic diseases in general: what's next?

The promising therapeutic correction seen after AAV-mediated gene transfer in CN patients supports further development of this treatment strategy. The next step is to overcome the remaining challenges that currently limits its application to pre-selected patients.

A major limitation is the humoral immune response toward AAV vectors. In CN patients, one third of the potential candidates had to be excluded because of the presence of neutralizing antibodies in serum possibly due to natural exposure to wild-type AAV in early childhood [12]. Even the presence of low neutralizing antibody (NAb) titers results in a dramatic reduction of transduction efficacy making this the major exclusion criterion. Depletion of anti-AAV antibodies from serum as well as capsid engineering appeared effective in circumventing preexisting humoral immunity although clinical demonstration is yet to be provided [13]. Recently, a different approach demonstrated feasibility *in vivo* to create a window of opportunity for AAV transduction in seropositive individuals. Treatment of non-human primates positive for NAb toward AAV with IdeS, a bacterial IgG-cleaving enzyme, prior to AAV administration, resulted in efficient liver transduction [14].

A second limitation to be addressed is the use of AAV-mediated gene therapy in neonates or children suffering from this disease. The rapid loss of episomal AAV vectors upon hepatocyte proliferation hampers long-term treatment efficacy in the fast-growing liver of neonatal and juvenile

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animals [10]. In addition, treatment with AAV vectors results in the formation of a strong, neutralizing antibody response, rendering subsequent hepatocyte transduction ineffective. This underscores that treatment early after birth may not provide long-term correction. In contrast to rodents, in which the liver growth occurs in a very limited period of 6 weeks, the slower liver growth in humans may lead to lower vector dilution. Interestingly, a recent report indicated persistent expression of the transgene in a 4-year-old MPS VI patient treated with an AAV8 vector expressing arylsulfatase B, suggesting that AAV treatment of young children may provide sustained correction [15].

As stated above, post-treatment humoral immunity also represents an important limitation as it precludes AAV vector re-administration in case of insufficient correction due to under-dosing or loss overtime. Transient immune suppression during the period of exposure of the vector to the immune system, prevented the induction of NAb in naïve Ugt1a1 deficient rats resulting in effective correction of serum bilirubin level upon re-administration of the vector [16].

4. Expert opinion

As the clinical development of gene addition therapy for CN syndrome progresses, preliminary data show safety and efficacy in treated patients. On the other hand, challenges have been identified that currently limits its use to pre-selected patients. Striving to make gene therapy available for all patients suffering from CN syndrome, and other inherited liver disorders alike, the following has to be addressed.

4.1. Limitations caused by neutralizing antibodies toward AAV

IdeS treatment represents the best option to allow effective treatment of CN patients now excluded because of the presence of anti-AAV NAb in serum. Blocking the induction of NAb to the vector capsid upon administration by immune suppression appeared effective in naïve rats but upon re-injection NAb were induced regardless of the immune suppression [16]. Due to prior exposure, most human subjects will not be naïve to AAV. Although immune suppression may not completely prevent NAbs, it can significantly reduce the NAb titers thus making the complete removal by plasmapheresis or by IdeS treatment feasible. However, the combination of IgG depletion and immune suppression may cause vulnerability to infections and the risk-benefit ratio of these combined approaches has to be taken into account.

4.2. Optimal age for of gene therapy

In the first two cohorts of the current gene therapy trial for CN only adult patients were included. Poor adherence to the PT treatment especially during adolescence may increase the risk for bilirubin-induced brain damage before adulthood. Lowering the inclusion age to younger patients in the next cohort therefore is very relevant. In several countries liver transplant at 8 or 9 year is the standard treatment for severe CN syndrome. Performing gene therapy at that age or earlier will improve the life quality of children having CN and their families. Little experience exists in liver directed gene transfer in pediatric populations. Although we cannot exclude the need to administer a higher vector dose to compensate for an eventual vector dilution, a single case report seems to indicate efficacy and stable expression overtime in a 4 year-old patient, supporting a direct translation of the adult treatment in the pediatric population.

4.3. Treating patients with a milder phenotype

Patients receiving a daily dose of PT of >6 hours are currently included. Upon demonstrating long-term safety and efficacy in the current trial, patients suffering from a milder form but dependent on PT may be included in the near future. Since these patients do have residual UGT1A1 activity, it is to be expected that the current vector will result in a more effective correction of serum bilirubin levels in the absence of phototherapy.

4.4. Cost effectiveness of gene therapy

Severely affected CN patients are initially treated by PT, a burdensome but inexpensive treatment. Most of them do need a liver transplant at some point in their life with an estimated cost of about €800.000, which increases rapidly when complications occur. Replacing OLT by AAV gene therapy can be cost effective. Some severely affected patients treated only with PT have reached adulthood without overt brain damage [3]. Although in these patients cost effectiveness will be questionable, it will allow them to have a more normal and productive life.

4.5. Demonstrating long-term efficacy

A single treatment has allowed CN patients to safely stop PT. It is too early to say if this correction will persist life-long but for instance, hemophilia B trials showed persistent correction for more than 10 years. Long-term data for the current ultimate treatment, a liver transplant, also show graft failure in about 20% of patients requiring a second OLT. In contrast, upon loss of correction, patients treated by gene therapy can restart PT to prevent toxic serum bilirubin levels. Most likely, due to the presence of residual UGT1A1 activity a lower PT dose may be sufficient initially.

4.6. Impact on quality of life

Life-long jaundice and the stigma that comes with it, combined with the burden of daily phototherapy has a major impact on the quality of life (QoL) of CN patients. So far, QoL in this patient population has been under-reported and deserves prompt recognition. Improvement of QoL, evaluated using appropriate questionnaires, will be a cornerstone efficacy endpoint in the development of any future treatment for CN.

5. Conclusion

The development of gene addition therapy for Crigler-Najjar syndrome is promising and under way. In the near future this treatment strategy will find its place alongside the curative option of liver transplantation or even replace it when its advantages exceed its limitations. Current efforts are focused on showing safety and efficacy of gene therapy in the first clinical trials as well as resolving challenges that limit its application in a part of the Crigler-Najjar patient population.

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Declaration of interest

G Ronzitti is author of patents related to the development of gene therapies for rare metabolic diseases and in particular, of one patent regarding AAV gene therapy for CN syndrome. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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